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# Allergic Disorders at a Venerable Age: A Mini-Review

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**Key Words**
Elderly · Allergic disorders · Asthma · Allergic rhinitis · Allergic dermatitis · Immunosenescence · Inflammation · Comorbidity

**Abstract**
This review focuses on 3 allergic disorders of persons coming up against venerable age: asthma, allergic rhinitis, and atopic dermatitis. The prevalence of allergic diseases in the elderly ranges from 5 to 10% and appears to be rising. A gradual decline in immune function, termed immunosenescence, and age-related changes in tissue structure influence the development of these disorders. Common complications are comorbidities, polypharmacy, and adverse effects of drugs. The elderly have difficulty mounting protective immune responses against newly encountered antigens. The integrity of epithelial barriers is compromised, leading to a chronic, subclinical inflammatory state and an enhanced Th2 (allergic) immune response. Undiagnosed asthma is frequent in elderly persons (about 8%) and still more commonplace in those with respiratory symptoms. Poorly controlled asthma in the elderly undermines their functional status and leads to a loss of autonomy and social isolation that may delay seeking medical services. Aggravation of allergic rhinitis coincides with exacerbation of asthma, whereas treatment of nasal inflammation improves control of the asthma. Atopic dermatitis is a chronically relapsing inflammatory skin disease often associated with respiratory allergy.



## Introduction

Allergic, or atopic, disorders are most common in children, but they also afflict adults and often persist into old age. The prevalence of allergic diseases in the elderly ranges from 5 to 10% and appears to be rising [1]. A gradual decline in immune function, termed immunosenescence, and age-related changes in tissue structure shape the manifestations of these disorders complicated markedly by comorbidities, polypharmacy, and adverse effects of drugs.

The elderly have notable difficulty mounting protective immune responses against newly encountered antigens. Such responses depend on short-lived, naive T and B cells. In the young, the bone marrow continually replenishes these cells. In the elderly, a lifetime of sustained antigenic stress typically leads to immunosenescence characterized by depletion of naive T cells [2]. Antigen-experienced cells, such as memory CD4+ and CD8+ T cells and memory B cells with an immunogenic repertoire

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constrained by the individual's past exposures, take over the peripheral lymphoid compartments. Aged individuals are less able to generate adequate immunity against newly encountered infections or to respond effectively to unfamiliar vaccinations. Fewer than half of older recipients of influenza or hepatitis B vaccines produce protective antibody titers [3]. Because viral upper respiratory infections trigger the majority of asthma exacerbations, the age-related decline in antiviral responses bears upon associated morbidity and mortality.

T cells in the lungs of the elderly exhibit activation with increased expression of HLA-DR and CD69, and elevated plasma levels of inflammatory cytokines, including interleukin (IL)-6, IL-1β, and TNFα, have been detected in the serum of elderly individuals free of allergic disease [4]. Thymic involution begins soon after birth, and by the time an individual reaches the age of 60 years, his thymus has become completely replaced by fatty tissue. Reduction in Th1 immune vigor contributes to the skewed immune response toward the proallergenic Th2 because IFN-γ, a Th1 cytokine, and T-bet, the master Th1 transcription factor, inhibit Th2 immune responses. The shift from Th1 to Th2 cytokine profiles enhances Th2 immune responses and allergic sensitization. Yet Th1 inflammation triggered by respiratory infection, superantigens, and IL-17 is a possible mechanism for nonallergic asthma.

Findings related to the aging in myeloid cells are at variance. An increase in neutrophils in bronchoalveolar lavage fluid has been observed in the elderly even in absence of disease. However, neutrophil functions, including the ability to kill phagocytosed organisms and the reduction in reactive oxygen species decline in older individuals. Further, neutrophils of the elderly are more susceptible to apoptosis. Mathur [1] showed that airway eosinophilia is similar in young and elderly asthmatic patients, but that eosinophil degranulation in response to IL-5 stimulation is significantly decreased in the elderly. Studies of mast cells have differed in their findings of age-related changes in the numbers of mast cells in tissues [5], but the sensitivity of the skin prick test, a reflection of mast cell function in the skin, has been shown to decrease in the elderly.

Integrity of epithelial barriers in the skin, lung, and gut is compromised in the elderly. The impaired first line of defense may lead to a chronic, subclinical inflammatory state that contributes to the susceptibility to infections. Further, the leaky epithelial barrier promotes Th2 immune responses by allowing allergens to penetrate into tissues. The infiltrating allergens are processed by keratinocytes and presented to T cells. Allergen-exposed keratinocytes produce thymic stromal lymphopoietin, which incites Th2 immune responses [6]. A recent publication proposed that decreased digestive capacity of the stomach in the elderly caused by atrophic gastritis or anti-ulcer medication is a risk factor for food allergies [7]. Significantly, gastric proteolysis reduces IgE reactivity against celery proteins in aged allergic patients [8].

This review will focus on three allergic disorders of the elderly – asthma, allergic rhinitis (AR), and atopic dermatitis (AD). Their clinical presentation arises from the interaction of allergic inflammation and structural cells – constriction of airway smooth muscle and airway remodeling associated with asthma; vasodilatation, nasal obstruction and discharge in AR; disruption of the epithelial barrier in AD [9, 10]. Significantly, not one single cell or mediator is responsible for all the elements of allergic disease [9]. The inflammatory pathways are redundant and, for that reason, a magic bullet to treat allergic disorders has thus far evaded discovery. Current pharmacological remedies for allergic disorders, although reasonably safe and effective, do not alter the course of disease and provide relief only as long as they are adhered to. Most patients with allergic disorders benefit from avoiding offending agents and taking anti-inflammatory medications for the long term [11].

## Asthma and Its Differential Diagnosis in the Elderly

Poorly controlled asthma in the elderly undermines their functional status and leads to loss of autonomy and social isolation that may delay seeking medical services [12]. The elderly are high users of medical resources for the treatment of asthma. Assessment of asthma epidemiology in the elderly is complicated by history of cigarette smoking and heart disease. Older asthmatic patients are more likely to be underdiagnosed and undertreated [13]. In 2004, in the US the prevalence of asthma in those 65 years or older was 7%, with 1,088,000 reporting an asthma attack in the previous 12 months [13]. Individuals over 65 years old account for 13% of the population in the US and for 23% of asthma hospitalizations. They also have the highest death rate (51.3 per million persons). While the mortality related to asthma in younger patients is caused by asthma in itself, in older patients comorbid conditions are partly responsible. The presence of comorbid chronic obstructive pulmonary disease (COPD) increases the risk of an asthma-related hospitalization in Medicare patients 3.6-fold, respiratory medical costs almost 6-fold, and total medical costs 2-fold [14].

Asthma is best described by its clinical features – airway inflammation with hypersecretion of mucus and reversible airflow limitation. Patients experience episodic exacerbations that may be severe and life-threatening. Long-standing asthma and chronic inflammation are likely to lead to airway remodeling – increased airway wall thickness involving both smooth muscle and collagen tissues, increased mucous glands and mucus production and increased vascularity [14]. These structural changes result in reduced lung function. The diagnosis of asthma may be overlooked because of the mistaken belief that asthma is rare in older patients and that dyspnea is merely a symptom of aging [15, 16]. Wheezing, breathlessness and cough exacerbating with exercise or at night are the typical symptoms of asthma but also occur with COPD. The same symptoms associated with orthopnea caused by congestive heart failure may be diagnosed as cardiac asthma. The latter is not a true form of asthma caused by inflammation of the airways, but rather by heart failure mimicking asthma. Thus, asthma may be confused with COPD or congestive heart failure, or may be comorbid with either or both. Vocal cord dysfunction (VCD) is another condition that frequently mimics or confounds asthma. It is characterized by a paradoxical adduction of the vocal cords on inspiration. The apposition of the vocal cords produces airflow obstruction sufficient to cause wheezing, chest tightness, shortness of breath, and cough. The clinical presentation is often dramatic and its misdiagnosis as asthma has led to inappropriate treatment, most notably with high-dose corticosteroids [17]. Because of improved treatment of asthma, VCD is now seen almost routinely among patients referred for consultation. Its prevalence is unknown, but it may be present in as many as 40% of patients seeking evaluation of asthma that fails to respond to aggressive therapy [17]. Gastroesophageal reflux disease (GERD) may aggravate asthma and VCD and should be addressed in the older patient. GERD has been reported in as many as 80% of patients with asthma but may not manifest the typical digestive symptoms in 50% of them [18]. Obesity is associated with increased prevalence and severity of asthma, and weight reduction has been shown to improve asthma symptoms [18].

The patients' medications, inhaler technique and adherence must be reviewed at every visit. Agents used to treat such common conditions of the aged as congestive heart failure, joint pains, and glaucoma may exacerbate asthma. Nonselective β-blockers still used for hypertension or coronary artery disease block $\beta_2$-receptors and cause constriction of airway smooth muscle. Similar agents used as eye drops in the treatment of glaucoma are known to produce asthma attacks. Some patients with asthma are sensitive to aspirin and NSAIDs [18]. Confusion about medications is magnified by the complexity of asthma regimens and visual or cognitive impairment [19].

Asthma is a highly heterogeneous disease. Characteristics of the disease and drug response in the elderly asthmatic patient stand apart from those of younger patients [9]. The elderly have higher rates of bronchial hyperreactivity and more severe asthma; however, the association between sensitization and markers of asthma control do not differ between asthma patients over 55 and under 40 years old. Significantly, respiratory symptoms of elderly asthmatics are more difficult to control with drug therapy, and their disease is more likely to be resistant to corticosteroids. For these patients, leukotriene receptor antagonists may be a suitable alternative, although the response to these agents may be deficient as well [14].

Undiagnosed airway obstruction is common in elderly persons (about 8%), and still more common in elderly patients with respiratory symptoms. Although not all older persons are able to perform spirometry, it should be attempted for all those with a history of dyspnea, cough or wheezing in order to exclude or confirm and assess airway obstruction [15]. The most commonly used measurement of lung function at home is peak expiratory flow rate, and in the office it is spirometry with the determination of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). The lungs exhibit continued loss of function with advancing age. FEV1 and FVC both decrease between 25 and 30 ml every year after the age of 20 [20]. This decline is 3–4 times greater in patients with asthma. Bronchodilator response measured to determine airway reversibility characteristic of asthma is often impaired in the elderly. Its opposite, bronchial hyperreactivity measured by histamine or methacholine challenge, has been reported to increase with advancing age. Bronchial hyperreactivity is detectable as an exaggerated airway narrowing in response to many stimuli. The degree of bronchial hyperreactivity relates to asthma symptoms. Inflammation of the airways increases bronchial hyperreactivity. Diffusing capacity of the lung for carbon monoxide (DLCO) is a measurement of the transfer of CO molecules from alveolar gas to the red cell hemoglobin in the pulmonary circulation. The DLCO is preserved in asthma but reduced in interstitial lung diseases and COPD. Imaging techniques and measures of lung function not requiring effort such as forced oscillation should be used to extend our knowledge about lung structure-function relationships in the elderly [14].

In a recent study of age-related differences in asthma outcomes in the United States, adults with physician-diagnosed asthma were divided into 2 age groups: younger adults (17–54 years of age) and older adults (55 years or older). The older group had more hospitalizations in the past year, more comorbidities, and poorer lung function ($p < 0.05$ for each). During a median follow-up of 15 years, significant baseline predictors of higher all-cause mortality included older age (≥55 vs. <55 years old: adjusted hazard ratio, HR, 6.77; 95% confidence interval, CI, 3.15–14.54), poor health status (fair and poor vs. excellent health status: adjusted HR, 10.07; 95% CI, 3.75–27.01), and vitamin D deficiency (vitamin D level <30 vs. ≥50 nmol/l: adjusted HR, 2.19; 95% CI, 1.05–4.58) [21].

### The Goals of Asthma Treatment

Since 1991, national and international expert panels have issued guidelines in response to growing concern over underdiagnosis, undertreatment and suboptimal treatment of asthma [22, 23]. The current goals are to achieve and maintain clinical control. Assessment of asthma control includes clinical manifestations (symptoms, nocturnal awakening, use of reliever medications, limitation of activities, lung function) and also the expected future risk to the patient (exacerbations, accelerated decline in lung function, and side effects of treatment). In planning a medical regimen, it is essential to bear in mind these issues as well as possible drug interactions, the patient's ability to use inhalers, and nonadherence, defined as not taking medication in the way that was agreed upon [11, 22, 24]. The medical literature is immense in reports of clinical trials in asthma, but to their discredit these trials routinely exclude the elderly, smokers and patients with concomitant COPD or congestive heart failure. Guidelines based on such evidence may not relate fully to older patients [25].

In accordance with expert guidelines issued by the Global Initiative for Asthma and the National Institutes of Health, treatment protocols for asthma use step-care pharmacologic therapy based on the intensity of asthma symptoms and the response to these interventions [22, 23]. As symptoms and lung function worsen, step-up or add-on therapy is given. As symptoms improve, therapy can be stepped down. Special attention must be given to the potential adverse effects of commonly used medications (see above). Medications to treat asthma can be classified as relievers or controllers. Relievers are quick-acting medications to be used on an as-needed basis to reverse airway obstruction and relieve symptoms. Both physicians and patients must be aware that overreliance on relievers and underuse of controllers, especially corticosteroids, increase the risk of life-threatening exacerbations. Relievers include rapid-acting inhaled $\beta_2$-agonists, inhaled anticholinergics, and short-acting theophylline. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. They include inhaled and systemic corticosteroids, leukotriene modifiers, long-acting inhaled $\beta_2$-agonists (LABA) in combination with inhaled corticosteroids (ICS), sustained-release theophylline, chromones, and anti-IgE [22].

Corticosteroids reduce airway inflammation. Many studies have shown that ICS are safe and effective for persistent asthma, but data for the elderly population are scarce. ICS are considered the most potent and consistently effective long-term control medications for asthma. Significantly, adherence to ICS treatment has historically been problematic, with adherence rates often below 50% [24, 26]. If the initial treatment with low-dose ICS does not establish control in a patient who does not have a condition mimicking asthma, increasing the dose of ICS or adding LABA is recommended. It is important to note that elderly asthmatics and smokers, 2 groups with considerable overlap, have increased neutrophil counts in their airways, a finding associated with steroid resistance [27]. A recent publication reported that adding theophylline to an ICS-LABA preparation significantly reduced asthma exacerbations, improved small airway function and decreased sputum eosinophils in a parallel group study of 325 adults with asthma [28].

Long-term use of ICS has been associated with acceptable safety, but doses higher than 1,000 μg/day may cause suppression of the hypothalamic-pituitary-adrenal axis. Local adverse effects, such as hoarseness, dysphonia, cough, and oral candidiasis can usually be prevented by proper inhaler technique and by rinsing the mouth after use. Oral corticosteroids should be avoided if possible because they place the patient at risk for bone fracture and increased likelihood of cataracts, muscle weakness, back pain, bruising, and oral candidiasis [22]. Additional controller medications may be added if control is not established. Patients considered for high daily doses of ICS or multiple controller medications should be referred to a specialist. Leukotriene-modifying agents (LTMs) are also asthma controllers. Studies of their use in the elderly are limited, but they are generally less effective than low-dose ICS. However, LTMs may reduce asthma exacerbation rates and the need for steroid bursts. Anticholinergics,

such as inhaled ipratropium, a short-acting bronchodilator, and tiotropium, a bronchodilator with 24-hour action, have an excellent safety profile in the elderly. They should be considered when additional bronchodilator therapy is necessary; however, their role in long-term maintenance of asthma in the elderly has not been established. Theophylline is an effective bronchodilator that has some anti-inflammatory properties. However, the use of theophylline is limited by its narrow therapeutic range, pharmacokinetics altered by concomitant illnesses, and drug interactions that affect its clearance. It is essential to monitor blood theophylline levels in older patients.

In 2005, the US Federal Drug Authority (FDA) expressed concern over the safety of LABA. This was based on the Salmeterol Multicenter Asthma Research Trial (SMART) study in which a small (<1%), but significant increase in respiratory-related deaths and asthma-related deaths occurred in patients, predominantly African-Americans, who received salmeterol [29]. In 2010, the FDA issued a safety warning that recommended the use of a LABA only for patients not well controlled with an ICS, and the discontinuation of LABA after control has been reestablished [30]. The FDA also mandated several large randomized, blinded studies of ICS versus ICS/LABA [31]. Analysis of more than 23,000 patients in 42 clinical trials with formoterol and non-LABA treatment arms found no increased risk for asthma-related death or hospitalization in patients using formoterol with or without ICS [32]. Substantively, the results of a recent meta-analysis showed that patients whose asthma had been well controlled by the addition of a LABA to ICS did worse when LABA was withdrawn. Outcome measures included control of asthma, quality of life, and the use of short-acting rescue bronchodilators [33].

The engineering of monoclonal antibodies is a promising approach to block the effects of cellular and molecular components of TH2 response. Numerous targets have been identified, and ongoing investigation persists. Anti-IgE (omalizumab) is a recombinant humanized monoclonal antibody that binds to free IgE. It decreases free IgE in circulation and markedly reduces the amount of IgE binding to both high-affinity (FcεRI) and low-affinity (FcεRII) IgE receptors, resulting in a suppression of allergic reactions [34]. In a recent retrospective study of 17 veterans with a median age of 60 years, anti-IgE therapy was associated with a significant reduction in acute asthma exacerbations requiring prednisone treatment ($p < 0.01$), a significant improvement in FEV1 ($p < 0.01$), and significantly higher asthma control test (ACT) scores at 3 ($p = 0.043$), 6 ($p = 0.039$), and 12 months of therapy ($p < 0.01$) [35]. The mean lifetime discounted costs and quality-adjusted survival were USD 83,400 and 13.87 for usual care and USD 174,500 and 14.19 for omalizumab plus usual care. The incremental cost-effectiveness ratio was USD 172,300/QALY, where a year of life lived in perfect health is worth 1 QALY [36]. Another recombinant humanized monoclonal antibody, one that targets the binding of IL-5, the cytokine that incites eosinophil maturation and survival, has been found to reduce exacerbation rates in patients with severe asthma and eosinophilic airway inflammation despite corticosteroid treatment [37].

We have a need for specific instruments to evaluate asthma control in the elderly as well as measures of self-management and adherence to improve disease control [38]. All elderly patients with asthma should receive an annual influenza vaccination. It may be beneficial to administer their pneumococcal vaccination more frequently than every 5–10 years. There is little enthusiasm for specific allergen immunotherapy administered by subcutaneous injection to elderly patients with asthma [11]. One retrospective study reports that sublingual allergen-specific immunotherapy reduces symptoms, drug consumption and disease progression in elderly subjects with mild bronchial asthma who are allergic to house-dust mites [39].

### AR in the Elderly

AR is a common and vexing condition of the elderly, its symptoms frequently ignored or wrongly ascribed to respiratory infections. The 2005 National Center for Health Statistics Report noted the prevalence of AR as 10.7% in individuals aged 45–64 years, 7.8% in those 65–75 years old, and 5.4% in those older than 75 [40]. AR is an inflammatory disorder of the nasal mucosa characterized by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival irritation. Nasal congestion predisposes to sleep disturbance and apnea. Symptoms such as fatigue, drowsiness (due to the disease or to medications) and malaise lead to impaired work performance, missed workdays, and traffic accidents. More than 40% of patients with AR also have asthma, and up to 80% of patients with asthma experience nasal symptoms [41]. Individuals with AR often have related sinusitis, and AD. The significance of AR as an illness stems from its high prevalence, detrimental effects on quality of life, and comorbidities. Inexplicably, little attention is paid to AR in the general medical literature.

AR is classified as 'intermittent' or 'persistent' disease, its severity as 'mild' or 'moderate/severe' [42]. Allergic

inflammation of the mucous membranes in AR, as in asthma, arises from a complex interaction of inflammatory mediators triggered by an IgE-mediated response to an extrinsic protein. AR is most often associated with the indoor allergens: house dust mites, animal danders, mice, and cockroaches. Cat and dog allergies are of major importance in the US. The allergens from the saliva and sebaceous secretions may remain airborne for a prolonged time. The ubiquitous major cat allergen, Fel d 1, may be carried on cat owners' clothing into such cat-free surroundings as homes without pets and hospitals.

The symptoms of AR are magnified by anatomic and physiological changes in the nose that arise with age. A significant correlation exists between aging and nasal airway resistance. Dehydration common in older patients predisposes to nasal irritation, thickened mucus and crusting. Submucosal vessels become blocked and ineffective at humidifying and warming inspired air. Postmenopausal women may suffer from mucosal atrophy, impaired mucociliary clearance, and cough secondary to hormonal changes. Elderly men suffer from 'old man's drip', a watery nasal discharge related to low testosterone. Structural changes, such as retraction of the nasal columella and a loss of support of the nasal tip, initiate and enhance nasal obstruction [11].

Evaluation of AR calls for a thorough history, including details of the patient's environment and diet and family history of allergic conditions, physical examination, and laboratory evaluation. First onset of symptoms in an elderly patient raises the suspicion that nonallergic rhinitis is the primary diagnosis or contributes significantly to the symptoms. Many nonallergic triggers induce nasal symptoms that mimic AR. These include drugs such as aspirin and other nonsteroidal anti-inflammatory agents, occupational and chemical agents, physical and emotional factors, and viral infections. Symptoms that include sneezing, rhinorrhea, nasal itching, and congestion and the laboratory findings of elevated IgE, specific IgE antibodies, and positive allergy skin tests typify AR. Nonallergic rhinitides cause sporadic symptoms. Their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils, but without elevated IgE antibodies, imitates AR in its presentation and response to treatment. Vasomotor rhinitis is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions mimic AR such as infectious rhinitis, structural problems including nasal polyps and septal deviation, rhinitis medicamentosa (most often due to the overuse of topical vasoconstrictors), hormonal rhinitis associated with pregnancy or hypothyroidism, neoplasms, vasculitides, and granulomatous disorders.

AR is frequently associated with complications and comorbid conditions. Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation improves the control of asthma. Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but more often the main findings are marked mucosal thickening and sinus opacification, sometimes with polyposis and inflammation but with negative bacterial cultures. The sinusitis of triad asthma (asthma, sinusitis with nasal polyposis, and aspirin sensitivity) often responds poorly to therapy. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Rhinitis is linked to sleep abnormalities and subsequent daytime fatigue.

An accurate assessment of the morbidity of AR cannot be obtained without asking about the effects on the patient's quality of life. The physician should inquire about symptoms such as fatigue, malaise, drowsiness (that may be related to medication), and headache, and investigate functional status and sleep quality. Quality of life indices have been developed to assess the effects of the disease and of therapeutic interventions.

Epicutaneous skin tests provide the best method for detection of allergen-specific IgE (positive predictive value of 48.7% for the epidemiologic diagnosis of AR). Serum immunoassays for IgE to allergens provide a suitable alternative (positive predictive value 43.5%) for patients with dermatographism or extensive dermatitis, patients taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in the nasal smear supports the diagnosis of AR, and that of neutrophils of infectious rhinitis.

Safe and effective prevention or relief of symptoms is the goal of treatment. An important aim is to moisten the nasal mucosa. Medications generally well tolerated by the elderly are second-generation antihistamines, nasal ICS, leukotriene modifiers and ipratropium nasal spray [43]. Specific measures to reduce indoor allergen exposure likely reduce the symptoms of allergic respiratory disease, although existing studies report contradictory results.

Specific allergen immunotherapy administered by subcutaneous injection should be considered for patients in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Sublingual allergen-specific immunotherapy in elderly patients al-

lergic to the dust mites *Dermatophagoides pteronyssinus* and *D. farinae* generated significant clinical improvement [44]. Anti-IgE reduces allergic responses in the nose. Treatment strategies that incorporate both anti-IgE and specific allergen immunotherapy hold promise for the future.

Therapy with nonsedating antihistamines and intranasal corticosteroids significantly improves health-related quality of life measures in patients of all ages with AR, provided that they continue to take their medications. Prospects for the future are bright. They comprise measures to prevent atopy, induce immune tolerance, and hold back the expression of the allergic phenotype. Pharmacotherapy will target cells and cytokines involved in inflammation and treat allergy as a systemic process.

## AD in the Elderly

AD is a chronically relapsing inflammatory skin disease often associated with respiratory allergy. Multiple gene-gene and gene-environment interactions play a pivotal role [45]. Gene-gene interactions are borne out when mutations in two or more genes produce a phenotype often unpredictable from each mutation's individual effects. Gene-environment interactions are similar occurrences involving genes and exposures. Current insights into the genetics and pathophysiology of AD point to an important role of structural abnormalities in the epidermis as well as immune dysregulation [10]. Many patients with AD have a mutation in the gene encoding the filaggrin protein, a component of the cornified cell envelope produced by differentiating keratinocytes [46]. The skin of patients with AD is deficient in ceramides, leading to transepidermal water loss [47]. In a recent review, de Benedetto et al. [48] called attention to the interaction between the epidermis and the immune system and presented evidence that epidermal cytokines (thymic stromal lymphopoietin, IL-25, and IL-33) direct the Th2 immune response when the skin barrier is compromised.

Skin changes are the most conspicuous sign of aging. Intense pruritus is the main symptom of AD, although elderly persons without AD also endure this vexation. Pruritus results from a variety of etiologies, dry skin (xerosis) the most common among them. Other skin changes in advanced age that contribute to itch include decreased skin surface lipids and impaired clearance of transepidermally absorbed materials from the dermis, reduced sweat and sebum production, and diminished barrier repair. The skin becomes thinner, more fragile, and the protective subcutaneous fat layer is lost. Patients with AD have a reduced threshold for craving to scratch. Their itch worsens with allergen exposures, dry air, sweating, local irritation, and emotional stress. Skin lesions range from erythema to severe lichenification. Common triggers include foods (milk, eggs, soy, wheat, peanuts, fish, vegetables, most notably celery [49]), aeroallergens (dust mites, molds, dander), staphylococcal colonization of the skin, and topical products, mainly cosmetics.

Serum IgE concentrations of patients with AD may be greatly elevated, often exceeding 1,000 IU/ml. The skin contains large numbers of dendritic cells that control the initiation and inhibition of immune responses [50]. Allergen-induced IgE synthesis and Th2-like cell expansion, mast cell degranulation, and cell injury all contribute to chronic skin inflammation in AD. In acute exacerbations, the rash becomes oozing and crusted. Patients with AD are predisposed to colonization and infection by microbial organisms, most notably *Staphylococcus aureus* and herpes simplex virus [10]. The carriage rate of *S. aureus* is 76% for uninvolved skin, and 93% for lesions. Toxin-producing *S. aureus* intensifies the inflammation in AD by secreting superantigens that activate T cells and macrophages. AD patients make specific IgE antibodies against the staphylococcal toxins on their skin. Methicillin-resistant *S. aureus* has become endemic in recent years. The main complications of AD are secondary bacterial and viral infections, regional lymphadenitis, and exfoliative dermatitis.

Present treatment consists of hydration, topical corticosteroids, oral antihistamines, avoidance of offending foods and, when necessary, antibiotics for bacterial superinfection with attention paid to antibiotic resistance. Treatment with low doses of cyclosporine has been beneficial. Topical tacrolimus, its mode of action similar to cyclosporine, has been shown to be effective, and is most useful for treating the face. Most patients improve markedly in less than 3 weeks. Patients who do not improve at home frequently achieve gratifying results in the course of a brief hospitalization. The future holds promise for subclassification of patients with AD that will lead to individualized treatment approaches targeting specific pathways [51].

## Conclusion

Our challenge is to promote healthy aging. Allergic disorders of the elderly are often underdiagnosed and difficult to treat. Specific instruments to evaluate asthma

control in the elderly as well as measures of self-management and adherence are needed. Better understanding of the mechanisms of inflammation will most certainly lead to improved therapy. But optimal treatment of all patients, most especially the elderly, requires an alliance between the patient and the physician. Caring sets the foundation of healthcare.

## Disclosure Statement

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