REVIEW ARTICLE

BJD
British Journal of Dermatology

Atopic dermatitis in the elderly: a review of clinical and pathophysiological hallmarks*

S. Williamson, J. Merritt and A. De Benedetto

Department of Dermatology, College of Medicine, University of Florida, Gainesville, FL, U.S.A.

Linked Comment: Szegedi. Br J Dermatol 2020; **182**:9–10.

Correspondence
Anna De Benedetto.
E-mail: adebenedetto@ufl.edu

Accepted for publication
15 March 2019

Funding sources
S.W. was supported by the Medical Student Summer Research Program at the University of Florida, College of Medicine.

Conflicts of interest
A.D.B. served as consultant for Regeneron and Sanofi Genzyme. All authors have read the manuscript and have approved submission.

*Plain language summary available online

DOI 10.1111/bjd.17896

Summary

Background Atopic dermatitis (AD) is a multifactorial and complex disease, characterized by an impaired skin barrier function and abnormal immune response. Many elderly patients present with pruritus and xerosis to dermatology, allergy and primary care clinics, and there is a lack of information available to clinicians regarding the proper diagnosis and management of these patients. Although the elderly are described as having a distinct presentation of AD and important comorbidities, most investigations and clinical care guidelines pertaining to AD do not include patients aged 60 years and older as a separate group from younger adults.

Objectives To summarize current information on pathophysiology, diagnosis and management of AD in the elderly population and identify areas of insufficient information to be explored in future investigations.

Methods We carried out a systematic review of published literature, which assessed changes in the skin barrier and immune function with ageing and current information available for physicians to use in the diagnosis and treatment of AD in elderly patients.

Results Many age-related changes overlap with key hallmarks observed in AD, most notably a decline in skin barrier function, dysregulation of the innate immune system, and skewing of adaptive immunity to a type-2 T helper cell response, in addition to increased *Staphylococcus aureus* infection.

Conclusions While general physiological alterations with ageing overlap with key features of AD, a research gap exists regarding specific ageing-related changes in AD disease development. More knowledge about AD in the elderly is needed to establish firm diagnostic and treatment methodologies.

What's already known about this topic?

- Atopic dermatitis (AD) is a common inflammatory skin disease that causes significant burden worldwide.
- Recently, elderly patients have been considered a subgroup of patients with distinct AD manifestation.
- Limited studies have characterized the clinical presentation and role of IgE-mediated allergy in elderly patients with AD.

What does this study add?

- This review offers a summary of age-related skin and immune alterations that correspond to pathogenic changes noted in patients with AD.
- The role of itch, environmental factors and skin microbiota in AD disease presentation in ageing patients is explored.

Atopic dermatitis (AD) is the most common chronic inflammatory skin condition and leading cause of disease burden among nonlethal skin conditions.[1,2] AD is characterized by eczematous rash, diffuse xerosis, intense pruritus and recurrent *Staphylococcus aureus* infection.[3] Patients with AD often have atopy, including asthma, allergic rhinitis, and environmental and food allergies.[4] The clinical manifestations of AD tend to vary with age.[5] Three groups of patients with AD have been well established based on appearance and localization of eczematous lesions at different ages, i.e. infantile type, childhood type, and adolescent and adult type.[6] In infants (infantile type), AD typically presents as acute eczematous crusting plaques on the face, and scales on the scalp.[5] Childhood-type AD is characterized by acute and chronic lesions often involving the flexural aspects of limbs and around the mouth, nose and eyes,[5] while adult-type AD tends to present with diffuse lichenified plaques at the flexural surfaces, head and neck.[5] Elderly-type AD has recently been considered a fourth separate group, presenting more commonly with the reverse sign of lichenified eczema at the antecubital and popliteal fossae than with lesions localized to the creases of the folds, as is typical of adult-type AD.[5,7] Patients with elderly-type AD can be further subdivided by disease onset, i.e. infancy or childhood onset with recurrence or continuation of AD at age ≥ 60 years; initial onset in adolescence or adulthood with recurrence or continuation of AD at age ≥ 60 years; and primary onset of AD at age ≥ 60 years.[8]

This review presents the current information available regarding ageing-related AD pathophysiology, which is an evolving field of knowledge, as few articles have characterized AD in the elderly population.[7,9–12]

Epidemiology

More than 230 million people worldwide have a diagnosis of AD,[1] a disease with high prevalence in children (15–30%) and adults (2–10%),[6] but there is limited prevalence data for the elderly. In Saarland, Germany, the prevalence of AD in patients aged 60–69 years was ~4%.[13] In Poland, AD prevalence was 2% for the elderly population (≥ 60 years),[10] compared with ~5% of children (6–7 years),[14] ~4% of adolescents (13–14 years)[14] and ~3% of adults (20–44 years).[14] Similarly, ~3% of elderly patients ≥ 60 years[15] and ~4% of adults (30–39 years)[15] who visited a Tokyo hospital had AD, compared with ~19% of children (7–9 years)[16] in Otsu, Japan. A multicentre cross-sectional study produced in France reported a high prevalence of xerosis in the elderly (~56% of patients aged ≥ 65 years) and found that a history of atopy, especially AD, is associated with significantly increased risk of xerosis in elderly patients.[17]

Pathophysiology

The pathogenesis of AD is complex and multifactorial (as described by Weidinger *et al.* in their comprehensive review).[1] Hallmarks of the disease are an impaired skin barrier and abnormal T helper (Th)2-skewed immune response to environmental antigens and allergens. Traditionally, the following two hypotheses have been proposed: (i) *inside out*, in which a primary immune system defect drives skin damage and dermatitis, and (ii) *outside in*, in which the primary skin barrier defect is thought to determine the aberrant immune response.[18] A growing body of evidence now suggests that in either case, there is active crosstalk between skin barrier and immune system; once one arm is perturbed, it can affect the other, feeding a vicious cycle that likely supports disease chronicity.

Bacterial colonization and recurrent skin infection are two important factors associated with disease severity. In addition, itch is a key feature of AD lesions. These components are negatively correlated with quality of life and need to be considered essential elements in the disease pathogenesis. The hypothesis of AD pathogenesis is developing to include age as a subphenotype, which contributes to different mechanisms of disease development and clinical presentation.[5] Well-established skin barrier and immune system changes associated with ageing likely contribute to this process (summary in Fig. 1 and Table 1).

Physical skin barrier

Ageing skin is classically associated with reduced physical barrier function,[19–24] which contributes to AD exacerbation in older patients. Ageing skin is thinner, more translucent, and undergoes elastosis, rendering it more physically fragile.[19–24] Epidermal stem cells at the dermoepidermal interface regularly replenish keratinocytes.[25] As skin ages, a normal number of these stem cells are still present, but their ability to migrate

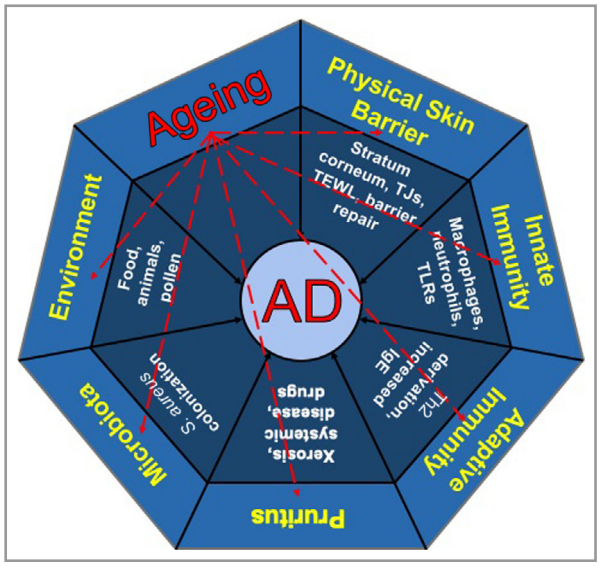

Fig 1. The impact of ageing on factors contributing to the pathogenesis of atopic dermatitis (AD). TEWL, transepidermal water loss; Th2, T helper cell type 2; TJ, tight junction; TLR, Toll-like receptor.

Table 1 Summary of ageing-related changes in skin barrier and immune system and overlap with known abnormalities in atopic dermatitis (AD)

Age-related changes	Hallmarks in AD
Skin barrier	
Filaggrin is downregulated	Filaggrin *null* mutations are a strong genetic risk factor for AD
Claudin-1 and occludin proteins are downregulated	Reduced expression of claudin-1, -4 and -23 noted in nonlesional AD skin
Decreased barrier repair occurs after irritation (based on increased TEWL)	Increased TEWL occurs at baseline and after tape stripping in nonlesional skin
Innate immunity	
PRRs decline in function	PRR expression and function are impaired in cDCs and skin
Phagocytic function of PMNs decreases	Phagocytic capacity of PMNs in skin declines
Adaptive immunity	
Possible Th2 shift occurs	Th2 (+ Th17/T22) skewed immune infiltrate noted in acute lesions, with Th1 cells also detected in chronic lesions
IgE+ CD1a+ DCs and mast cells are increased in skin	Increased FcεRI on CD1a+ epidermal DCs and FcεRI and FcεRII on monocytes detected in peripheral blood samples

TEWL, transepidermal water loss; PRR, pattern recognition receptor; cDC, conventional dendritic cell; PMN, polymorphonuclear leucocyte; Th2, T helper cell type 2; DC, dendritic cell; FcεRI, high-affinity IgE receptor; FcεRII, low-affinity IgE receptor.

and respond to proliferative signals declines.[26] The rate of new keratinocyte production in the epidermis decreases with ageing,[25] and collagen fibres comprising the dermal extracellular matrix become fragmented and disordered.[27]

The stratum corneum (SC) serves as the primary component of the skin barrier.[19] The epidermal cornified envelope composition differs considerably as skin ages, contributing to decreased barrier function.[28,29] The cornified envelope is composed of a keratin and filaggrin protein network stabilized by cross-linking transglutaminases and surrounded by a lipid layer.[28] With ageing, certain cornified envelope proteins are upregulated and others (i.e. filaggrin) are downregulated.[29] *FLG* null mutations are a major predisposing factor to AD development,[1] and while genetic mutations are likely noncontributory in the pathogenesis of new-onset AD in elderly patients, age-related decline in filaggrin production may be a contributing factor.

Tight junctions (TJs) are cell–cell connections located under the SC, which contribute to epidermal barrier integrity.[30–32] Epithelial TJs are composed of proteins including claudin (CLDN), occludin and zonula occludens.[30,31] CLDN1 is integral to TJ functionality in the skin barrier.[31,33] CLDN1 mutations are associated with skin xerosis, pruritus and AD development.[31,32] Jin *et al.* demonstrated changes in epidermal TJ protein constituents in older skin (from patients aged ≥ 75 years) compared with younger skin, suggesting that TJ dysregulation could play a role in AD pathogenesis in the elderly.[31] Intrinsically aged skin was characterized by downregulation of CLDN1 and occludin proteins. In the same patients, photoaged skin sampled from the forearm displayed decreased CLDN1 expression compared with intrinsically aged skin from the buttock.[31]

Transepidermal water loss (TEWL) is a well-established method used to measure skin barrier integrity *in vivo*.[34] While one could speculate that the aforementioned age-related deterioration of the skin barrier would consistently result in higher TEWL, some discrepancies exist among the analyses of the relationship between ageing and TEWL. Roskos *et al.* determined that there was no difference in baseline TEWL rates, measured using the ServoMed EPIC unventilated evaporimeter (ServoMed, Stockholm, Sweden), between individuals aged < 43 years and > 68 years. However, after occlusion of skin that mimicked a stressed condition, TEWL rates were higher and returned to baseline levels more slowly in the elderly group,[35] suggesting impaired barrier recovery function. A meta-analysis of studies measuring TEWL across age groups reported lower TEWL in people aged over 65 years,[34] which contrasted with another study reporting similar baseline TEWL in the elderly and younger adults.[35]

The ability to repair the skin barrier after irritation is diminished in elderly individuals.[36] Barrier recovery after insult by tape stripping or acetone application, determined by measuring TEWL values at various time intervals after insult, was deficient in the elderly (aged > 80 years) compared with young (aged < 30 years) volunteers.[37] Following insult, the decreased TEWL took longer to increase to baseline levels in older participants, demonstrating that barrier recovery is appreciably slower in aged skin.[37]

Altogether, strong evidence suggests that physical or environmental irritation, in combination with a defective aged epidermal barrier, may contribute to AD development in the elderly.

Immune system

The immune system becomes dysregulated with age and is characterized by chronic inflammation – a concept referred to as 'inflammageing'.[38,39] Inflammageing is thought to be a consequence of a remodelling of the innate and adaptive immune system, resulting in chronic inflammatory cytokine

production. Notably, some of the age-related changes in the immune system are analogous to defects observed in patients with AD. However, it is important to disclose that similarities do not mean that these changes, if present, are mechanistically involved in elderly AD pathogenesis. Specific studies are needed to provide further confirmation of causality for the changes in elderly AD.

Innate immunity

The innate immune system decline with age includes changes in cell number and function in addition to changes in the expression of pattern recognition receptors (PRRs) and their involved signalling pathways.[38] Based on studies of peripheral blood, expression and function of Toll-like receptors (TLRs) in dendritic cells (DCs), polymorphonuclear (PMN) leucocytes, and monocytes decrease with age, causing innate immune cells to be less capable of killing bacteria.[40,41] Skin macrophages produce less tumour necrosis factor and fewer neutrophils are recruited, leading to impaired wound healing.[38] Decreased neutrophil and eosinophil functional ability contributes to weaker defences against bacteria and microorganisms.[38,42] In older people, neutrophils have impaired pathogen-killing ability owing to declining phagocytic function such as opsonization and production of reactive oxygen species.[38]

A variety of defects have been identified in the innate immune system in AD including dysfunction in PRRs and diminished recruitment of innate immune cells (e.g. PMNs and plasmacytoid DCs) to the skin (De Benedetto *et al.*,[43] McGirt and Beck[44] and Wollenberg *et al.* have reviewed this topic).[45] Skin biopsies of patients with AD have been found to lack PMNs, notably even with *S. aureus* infection or skin scratching.[44] PMNs are observed to display functional impairment in AD, including defective chemotactic activity and impaired phagocytic capacity,[43,44] similar to changes with ageing. Overall, the effectiveness of the immune system to defend the body against pathogens declines with age,[38] rendering the elderly more susceptible to severe and chronic infections.[40] The irreversible decline in innate immune cell function may contribute to the difficulty in the treatment and cure of elderly patients with AD.

Adaptive immunity

Ageing is associated with profound change in the adaptive immune system. As people age, naive Th0 cells become less functional and produce less interleukin (IL)-2, while Th1 and Th2 cells increase cytokine production.[46] IL-3, IL-4 and interferon (IFN)-γ play an important role in cellular and humoral immunity, but inconsistent data have been found regarding their expression in the elderly. An increased production of IL-5 and IL-10 has been more consistently observed, favouring a shift towards the Th2-type immune response.[47]

Two cytokines produced by the Th2 inflammatory response, namely IL-4 and IL-13, have a key role in the pathogenesis of AD.[48] The presence of IL-4 and IL-13 during keratinocyte differentiation leads to a weakened physical skin barrier resulting from reduced production of structural epidermal protein components including filaggrin, loricrin and involucrin.[48] IL-4 and IL-13 also prevent production of antimicrobial peptides and downregulate Th1- and Th17-dependent immune responses in the skin, leading to increased susceptibility to *S. aureus* infection.[48] Another cytokine associated with Th2 inflammation, namely IL-31, contributes to itch and has been implicated in AD and noted to be elevated in the ageing population.[49–52] Elevated levels of IL-31 and IL-31-producing T cells have been detected in AD skin lesions.[51,53] *S. aureus* superantigen was shown to induce IL-31 expression and T-cell recruitment, and mediate pruritus in patients with AD.[53] AD tends to be very itchy in elderly patients; it remains to be determined whether this is associated with increased expression of IL-31 or its receptors in elderly AD skin.

Patients presenting with AD at age 60 years or older often have very high levels of IgE, which is considered a marker of Th2 inflammation.[5] While serum IgE decreases with age in patients with allergic rhinitis and asthma, no significant decrease is shown with age in patients with AD.[54] Elderly patients with AD can be classified into IgE-allergic type (60–80% of patients, namely extrinsic AD) and non-IgE allergic type (20–30% of patients, namely intrinsic AD), according to total serum IgE and allergen-specific IgE levels.[7,10] Elderly patients with IgE-allergic AD have a Th2-dominant cytokine profile in peripheral blood including IL-4, IL-5 and IL-13, whereas elderly patients with non-IgE-allergic AD are skewed towards a Th1-dominant profile including IL-2 and IFN-γ.[7] Chronic lichenified lesions of elderly patients with IgE-allergic type AD were noted to have infiltrating IgE+ CD1a+ DCs in the epidermis, CD11c+ DCs in the epidermis and upper dermis, and IgE+ mast cells in the upper dermis,[8] while in comparison, the chronic lesion of an elderly patient with asteatotic (nonatopic) dermatitis contained only CD11c+ DCs.[8] This result is similar to those of other studies performed across age groups. IgE-allergic type AD lesions of patients not being treated with local or systemic glucocorticoids had significantly increased levels of high-affinity IgE receptor (FcεRI) on CD1a+ epidermal DCs compared with both normal control skin and non-IgE-allergic AD skin lesions.[55] Peripheral blood of patients with nonglucocorticoid-treated IgE-allergic AD was shown to have monocytes with significantly higher levels of FcεRI and FcεRII compared with that of nonatopic control patients, and significantly increased levels of FcεRI compared with monocytes in the peripheral blood of patients with non-IgE-allergic AD.[56] These cell types implicated in IgE-allergic type AD can lead to cutaneous hypersensitivity reactions owing to the accumulation of IgE and allergen complexes in upper skin layers.[7]

In summary, age-related changes in the immune system align with defects typically observed in AD, and it remains to be determined whether those changes are directly involved in AD pathogenesis.

Pruritus

Pruritus has complex and varied pathomechanisms[57] in AD involving histamine- and nonhistamine-responsive afferent sensory C-fibres that relay signals regarding cutaneous itch to the central nervous system.[58,59] Pruritus is a common and distressing symptom affecting one-quarter of patients over the age of 65 years seen annually in U.S. outpatient clinics[60] and affects a significant proportion of patients in other regions. Pruritus in the elderly is most often secondary to xerosis and is commonly associated with other dermatological conditions, including AD.[57,61] Whether pruritus plays a direct role in the pathogenesis of AD in the elderly has not yet been investigated.

Skin microbiota

Patients with AD are susceptible to bacterial skin infections owing to physical skin breakdown, dysregulated skin antimicrobial immunity, and bacterial colonization.[62,63] Patients with AD have less heterogeneous colonizing skin bacteria and an increased presence of *S. aureus*.[9,63] More severe AD flares are associated with decreased skin bacterial diversity.[64] A high prevalence of *S. aureus* colonization has been noted in the elderly population. In Swedish nursing homes, 48% of patients aged ≥ 60 years were found to have *S. aureus* colonization in the nares,[65] compared with a prevalence of ~32% in people aged 4–19 years reported throughout Sweden.[66]

There is a diversity that has been observed when the skin microbiome of younger people has been compared with that of older individuals. Older Thai men (51–57 years) were found to have a predominance of *Rhizobiales* order, *Sphingomonas* and *Pseudoalteromonas* bacteria on the cheek and forehead, whereas the skin of young adult men (19–24 years) was skewed towards *Propionibacterium* and *Staphylococcus epidermidis* bacteria.[67] A study comparing Japanese women of various ages noted increased alpha diversity in forearm, forehead and cheek skin, and increased beta diversity of the forearm and scalp in elderly women (60–76 years) compared with younger adults (21–37 years).[68] Gut bacterial populations in elderly individuals are characterized by reduced bacterial diversity and a decrease in beneficial microorganisms, linked to diet and lifestyle.[69,70]

Further investigation into the effect of ageing on the microbiome and the role of the skin microbiome in AD pathogenesis is needed. Increased AD severity in the elderly may be related to greater *S. aureus* colonization and infection because of its role in AD development in the general population.

Environmental factors

Patients with AD are often hyperresponsive to environmental irritants and more likely to develop other atopic conditions.[36,71] These patients often have high IgE levels specific to common allergens.[36] Certain foods such as milk, eggs and wheat, and environmental allergens including animal dander, grasses and pollens can trigger AD. Food allergy plays a more significant role in inducing AD symptoms in children than in older patients, and adult and elderly patients with AD who have moderate-to-severe disease tend to have greater sensitization to food allergens compared with patients who have milder AD.[9] Elderly patients with AD are most sensitive to dust mites and pollens, measured by increased serum IgE levels specific to these allergens,[9] and less allergic to foods, animal dander and fungi.[7] However, elderly patients with more severe AD, in particular, display allergic sensitivity to various allergens.[9] Elderly patients most often have hypersensitivity to fragrance mixes including balsam of Peru and metals including nickel and cobalt.[72–74]

In summary, this pathophysiology section reports evidence of common changes observed with ageing that may constitute risk factors for triggering or worsening AD in the elderly population (summary in Fig. 1 and Table 1). While general physiological alterations with ageing overlap with key features of AD, a research gap exists regarding specific ageing-related changes in AD disease development. It must be noted that the majority of people diagnosed with AD experience disease resolution before adulthood, and most infants with AD have complete remission before age 2 years.[5] Why certain individuals outgrow AD while others develop more persistent endotypes or late-onset AD remains to be understood. It is tempting to propose the hypothesis that in order to reach a level of disease state in predisposed patients, a certain 'threshold' of skin barrier impairment and/or immunological abnormalities needs to be achieved. While some of these defects that present early in life might be compensated for in childhood, others might be worsened later in life as part of the physiological ageing process. Future studies are needed to provide greater clarity regarding the factors contributing to both AD progression and resolution.

Diagnosis and management

There is a lack of specific guidelines available for physicians to distinguish AD from other pruritic skin conditions in the elderly. Compared with other age groups, the elderly tend to have more comorbidities and medications that can cause pruritus and xerosis, rendering the diagnosis of AD more difficult.[7] Currently, older patients are diagnosed with AD after at least 6 months[7] of symptom assessment and exclusion of other conditions,[7] including cutaneous T-cell lymphoma,[75] allergic contact dermatitis,[5] drug reactions,[7] and chronic idiopathic or secondary erythroderma.[7] Bieber *et al.* recently stated that AD in the elderly has not been well characterized as a specific phenotype of AD and that clearer criteria for diagnosis are necessary.[5]

There is a lack of information regarding AD treatment specifically for the elderly. Tanei and Hasewaga stated that elderly patients should currently be treated according to the standardized guidelines for general AD treatment.[7] From a practical point of view, the treatment of elderly patients with AD is complicated by several age-dependent factors and

comorbidities that the physician must consider. For example, high blood pressure and reduced kidney function might limit the use of ciclosporin, whereas diabetes, high blood pressure and osteoporosis raise concerns for initiating systemic steroid treatment. An increased propensity for infection in the elderly can restrict the use of systemic immunosuppressant medications. Thinning of the skin with diffuse photoageing might even limit the use of topical steroids. Decreased physical mobility of elderly patients may further reduce the ability to moisturize the skin properly and apply topical treatments.

This is an exciting time for developments in the treatment of AD as the first biological medication (dupilumab) has been approved by the U.S. Food and Drug Administration, and more biological and small molecule medications are in the pipeline.[76–78] However, adult clinical trials traditionally enrol only patients aged 18–65 years, thus excluding a large proportion of the elderly. Further studies and clearer guidelines for treating AD in the elderly need to be developed. Elderly patients with AD rarely achieve complete disease remission, and many affected patients eventually die with the condition.[7]

Conclusions

Studies estimate that 2–3% of the elderly population is affected by AD, yet despite its prevalence, there is a knowledge gap hindering diagnosis and treatment. Many prior AD studies have not isolated this population from other age groups, though doing so reveals important differences in disease manifestation. Factors rendering the elderly susceptible to AD include innate physiological changes of ageing, notably decline in skin barrier function, dysregulation of innate immune cells, and skewing of adaptive immunity to a Th2 response. As the number of elderly people increases worldwide, the disease burden of this relatively undescribed condition can be anticipated to increase in both personal and societal cost. The pruritus, painful broken skin, and infections associated with AD contribute to a decline in quality of life and an increased financial and public health burden. More knowledge about elderly AD is needed to establish firm diagnostic and treatment methodologies. Prompt and adequate care that achieves remission could ensure a robust quality of life and allay the higher healthcare costs associated with hospitalization for severe AD. Detailed studies of the integumentary and immune systems of elderly patients with AD are necessary so that treatment regimens can be tailored for these patients and their care can be standardized more effectively.

References

1 Weidinger S, Beck LA, Bieber T *et al.* Atopic dermatitis. *Nat Rev Dis Primers* 2018; **4**:1.
2 Hay RJ, Johns NE, Williams HC *et al.* The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014; **134**:1527–34.
3 Wollenberg A, Bieber T. Atopic dermatitis: from the genes to skin lesions. *Allergy* 2000; **55**:205–13.
4 Habif T. *Clinical Dermatology: a Color Guide to Diagnosis and Therapy*, 6th edn. Amsterdam: Elsevier Inc., 2016.
5 Bieber T, D'Erme AM, Akdis CA *et al.* Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? *J Allergy Clin Immunol* 2017; **139**:S58–64.
6 Bieber T. Atopic dermatitis. *N Engl J Med* 2008; **358**:1483–94.
7 Tanei R, Hasegawa Y. Atopic dermatitis in older adults: a viewpoint from geriatric dermatology. *Geriatr Gerontol Int* 2016; **16** (Suppl. 1):75–86.
8 Tanei R, Hasegawa Y, Sawabe M. Abundant immunoglobulin E-positive cells in skin lesions support an allergic etiology of atopic dermatitis in the elderly. *J Eur Acad Dermatol Venereol* 2013; **27**:952–60.
9 Katsarou A, Armenaka M. Atopic dermatitis in older patients: particular points. *J Eur Acad Dermatol Venereol* 2011; **25**:12–18.
10 Bozek A, Fisher A, Filipowska B *et al.* Clinical features and immunological markers of atopic dermatitis in elderly patients. *Int Arch Allergy Immunol* 2012; **157**:372–8.
11 Tanei R. [Atopic dermatitis in the elderly]. *Arerugi* 2015; **64**:918–25 (in Japanese).
12 Tanei R, Katsuoka K. Clinical analyses of atopic dermatitis in the aged. *J Dermatol* 2008; **35**:562–9.
13 Wolkewitz M, Rothenbacher D, Löw M *et al.* Lifetime prevalence of self-reported atopic diseases in a population-based sample of elderly subjects: results of the ESTHER study. *Br J Dermatol* 2007; **156**:693–7.
14 Sybilski AJ, Raciborski F, Lipiec A *et al.* Epidemiology of atopic dermatitis in Poland according to the Epidemiology of Allergic Disorders in Poland (ECAP) study. *J Dermatol* 2015; **42**:140–7.
15 Muto T, Hsieh SD, Sakurai Y *et al.* Prevalence of atopic dermatitis in Japanese adults. *Br J Dermatol* 2003; **148**:117–21.
16 Sugiura H, Umemoto N, Deguchi H *et al.* Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: comparison with the disease frequency examined 20 years ago. *Acta Derm Venereol* 1998; **78**:293–4.
17 Paul C, Maumus-Robert S, Mazereeuw-Hautier J *et al.* Prevalence and risk factors for xerosis in the elderly: a cross-sectional epidemiological study in primary care. *Dermatology* 2011; **223**:260–5.
18 Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis–part I: clinical and pathologic concepts. *J Allergy Clin Immunol* 2011; **127**:1110–18.
19 Boireau-Adamezyk E, Baillet-Guffroy A, Stamatas GN. Age-dependent changes in stratum corneum barrier function. *Skin Res Technol* 2014; **20**:409–15.
20 Luebberding S, Krueger N, Kerscher M. Age-related changes in skin barrier function - quantitative evaluation of 150 female subjects. *Int J Cosmet Sci* 2013; **35**:183–90.
21 Fenske NA, Lober CW. Structural and functional changes of normal aging skin. *J Am Acad Dermatol* 1986; **15**:571–85.
22 Gilchrest BA. Skin aging and photoaging: an overview. *J Am Acad Dermatol* 1989; **21**:610–13.
23 Biniek K, Kaczvinsky J, Matts P, Dauskardt RH. Understanding age-induced alterations to the biomechanical barrier function of human stratum corneum. *J Dermatol Sci* 2015; **80**:94–101.
24 Ramos-e-Silva M, Boza JC, Cestari TF. Effects of age (neonates and elderly) on skin barrier function. *Clin Dermatol* 2012; **30**:274–6.
25 Rinnerthaler M, Streubel MK, Bischof J, Richter K. Skin aging, gene expression and calcium. *Exp Gerontol* 2015; **68**:59–65.
26 Zouboulis CC, Adjaye J, Akamatsu H *et al.* Human skin stem cells and the ageing process. *Exp Gerontol* 2008; **43**:986–97.
27 Quan T, Fisher GJ. Role of age-associated alterations of the dermal extracellular matrix microenvironment in human skin aging: a mini-review. *Gerontology* 2015; **61**:427–34.

28 Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. *Nat Rev Mol Cell Biol* 2005; **6**:328–40.

29 Rinnerthaler M, Duschl J, Steinbacher P *et al.* Age-related changes in the composition of the cornified envelope in human skin. *Exp Dermatol* 2013; **22**:329–35.

30 Niessen CM. Tight junctions/adherens junctions: basic structure and function. *J Invest Dermatol* 2007; **127**:2525–32.

31 Jin SP, Han SB, Kim YK *et al.* Changes in tight junction protein expression in intrinsic aging and photoaging in human skin *in vivo*. *J Dermatol Sci* 2016; **84**:99–101.

32 De Benedetto A, Rafaels NM, McGirt LY *et al.* Tight junction defects in patients with atopic dermatitis. *J Allergy Clin Immunol* 2011; **127**:773–86.e1–7.

33 Sugawara T, Iwamoto N, Akashi M *et al.* Tight junction dysfunction in the stratum granulosum leads to aberrant stratum corneum barrier function in claudin-1-deficient mice. *J Dermatol Sci* 2013; **70**:12–18.

34 Kottner J, Lichterfeld A, Blume-Peytavi U. Transepidermal water loss in young and aged healthy humans: a systematic review and meta-analysis. *Arch Dermatol Res* 2013; **305**:315–23.

35 Roskos KV, Guy RH. Assessment of skin barrier function using transepidermal water loss: effect of age. *Pharm Res* 1989; **6**:949–53.

36 Cork MJ, Robinson DA, Vasilopoulos Y *et al.* New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol* 2006; **118**:3–21; quiz 22–3.

37 Ghadially R, Brown BE, Sequeira-Martin SM *et al.* The aged epidermal permeability barrier. Structural, functional, and lipid biochemical abnormalities in humans and a senescent murine model. *J Clin Invest* 1995; **95**:2281–90.

38 Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nat Rev Immunol* 2013; **13**:875–87.

39 Licastro F, Candore G, Lio D *et al.* Innate immunity and inflammation in ageing: a key for understanding age-related diseases. *Immun Ageing* 2005; **2**:8.

40 Kollmann TR, Levy O, Montgomery RR, Goriely S. Innate immune function by Toll-like receptors: distinct responses in newborns and the elderly. *Immunity* 2012; **37**:771–83.

41 Montgomery RR, Shaw AC. Paradoxical changes in innate immunity in aging: recent progress and new directions. *J Leukoc Biol* 2015; **98**:937–43.

42 Gomez CR, Nomellini V, Faunce DE, Kovacs EJ. Innate immunity and aging. *Exp Gerontol* 2008; **43**:718–28.

43 De Benedetto A, Agnihothri R, McGirt LY *et al.* Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol* 2009; **129**:14–30.

44 McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol* 2006; **118**:202–8.

45 Wollenberg A, Räwer HC, Schauber J. Innate immunity in atopic dermatitis. *Clin Rev Allergy Immunol* 2011; **41**:272–81.

46 Hakim FT, Gress RE. Immunosenescence: deficits in adaptive immunity in the elderly. *Tissue Antigens* 2007; **70**:179–89.

47 Boren E, Gershwin ME. Inflamm-aging: autoimmunity, and the immune-risk phenotype. *Autoimmun Rev* 2004; **3**:401–6.

48 Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017; **139**:S65–76.

49 Nobbe S, Dziunycz P, Mühleisen B *et al.* IL-31 expression by inflammatory cells is preferentially elevated in atopic dermatitis. *Acta Derm Venereol* 2012; **92**:24–8.

50 Raap U, Weissmantel S, Gehring M *et al.* IL-31 significantly correlates with disease activity and Th2 cytokine levels in children with atopic dermatitis. *Pediatr Allergy Immunol* 2012; **23**:285–8.

51 Szegedi K, Kremer AE, Kezic S *et al.* Increased frequencies of IL-31-producing T cells are found in chronic atopic dermatitis skin. *Exp Dermatol* 2012; **21**:431–6.

52 Ginaldi L, De Martinis M, Ciccarelli F *et al.* Increased levels of interleukin 31 (IL-31) in osteoporosis. *BMC Immunol* 2015; **16**:60.

53 Sonkoly E, Muller A, Lauerma AI *et al.* IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; **117**:411–17.

54 Mediaty A, Neuber K. Total and specific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis. *Immun Ageing* 2005; **2**:9.

55 Oppel T, Schuller E, Gunther S *et al.* Phenotyping of epidermal dendritic cells allows the differentiation between extrinsic and intrinsic forms of atopic dermatitis. *Br J Dermatol* 2000; **143**:1193–8.

56 Novak N, Kruse S, Kraft S *et al.* Dichotomic nature of atopic dermatitis reflected by combined analysis of monocyte immunophenotyping and single nucleotide polymorphisms of the interleukin-4/interleukin-13 receptor gene: the dichotomy of extrinsic and intrinsic atopic dermatitis. *J Invest Dermatol* 2002; **119**:870–5.

57 Reich A, Ständer S, Szepietowski JC. Pruritus in the elderly. *Clin Dermatol* 2011; **29**:15–23.

58 Schmelz M, Schmidt R, Bickel A *et al.* Specific C-receptors for itch in human skin. *J Neurosci* 1997; **17**:8003–8.

59 Potenzieri C, Undem BJ. Basic Mechanisms of itch. *Clin Exp Allergy* 2012; **42**:8–19.

60 Berger TG, Shive M, Harper GM. Pruritus in the older patient: a clinical review. *JAMA* 2013; **310**:2443–50.

61 Norman RA. Xerosis and pruritus in the elderly: recognition and management. *Dermatol Ther* 2003; **16**:254–9.

62 Nakatsuji T, Chen TH, Narala S *et al.* Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med* 2017; **9**: eaah4680.

63 Nakatsuji T, Chen TH, Two AM *et al.* *Staphylococcus aureus* exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. *J Invest Dermatol* 2016; **136**:2192–200.

64 Kong HH, Oh J, Deming C *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; **22**:850–9.

65 Stark L, Olofsson M, Löfgren S *et al.* Prevalence and molecular epidemiology of *Staphylococcus aureus* in Swedish nursing homes – as revealed in the SHADES study. *Epidemiol Infect* 2014; **142**:1310–6.

66 den Heijer CDJ, van Bijnen EME, Paget WJ *et al.* Prevalence and resistance of commensal *Staphylococcus aureus*, including meticillin-resistant *S. aureus*, in nine European countries: a cross-sectional study. *Lancet Infect Dis* 2013; **13**:409–15.

67 Wilantho A, Deekaew P, Srisuttiyakorn C *et al.* Diversity of bacterial communities on the facial skin of different age-group Thai males. *PeerJ* 2017; **5**:e4084.

68 Shibagaki N, Suda W, Clavaud C *et al.* Aging-related changes in the diversity of women's skin microbiomes associated with oral bacteria. *Sci Rep* 2017; **7**:10567.

69 Salazar N, Valdes-Varela L, Gonzalez S *et al.* Nutrition and the gut microbiome in the elderly. *Gut Microbes* 2017; **8**:82–97.

70 Zapata HJ, Quagliarello VJ. The microbiota and microbiome in aging: potential implications in health and age-related diseases. *J Am Geriatr Soc* 2015; **63**:776–81.

71 Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res* 2011; **3**:67–73.

72 Wöhrl S, Hemmer W, Focke M *et al*. Patch testing in children, adults, and the elderly: influence of age and sex on sensitization patterns. *Pediatr Dermatol* 2003; **20**:119–23.
73 Wantke F, Hemmer W, Jarisch R, Götz M. Patch test reactions in children, adults and the elderly. A comparative study in patients with suspected allergic contact dermatitis. *Contact Dermatitis* 1996; **34**:316–19.
74 Arcanjo LC. Reactivity of the contact tests (patch test) in elderly patients compared to non-elderly at the allergy clinic of the Policlínica Geral do Rio de Janeiro. *World Allergy Organ J* 2015; **8** (Suppl. 1):A202.
75 Miyagaki T, Sugaya M, Suga H *et al*. IL-22, but not IL-17, dominant environment in cutaneous T-cell lymphoma. *Clin Cancer Res* 2011; **17**:7529–38.
76 Hajar T, Gontijo JRV, Hanifin JM. New and developing therapies for atopic dermatitis. *An Bras Dermatol* 2018; **93**:104–7.
77 Wang D, Beck LA. Immunologic targets in atopic dermatitis and emerging therapies: an update. *Am J Clin Dermatol* 2016; **17**:425–43.
78 Guttman-Yassky E, Dhingra N, Leung DYM. New era of biologic therapeutics in atopic dermatitis. *Expert Opin Biol Ther* 2013; **13**:549–61.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Powerpoint S1 Journal Club Slide Set.