



## Atopic dermatitis epidemiology and unmet need in the United Kingdom

Michael J. Cork, Simon G. Danby & Graham S. Ogg

To cite this article: Michael J. Cork, Simon G. Danby & Graham S. Ogg (2019): Atopic dermatitis epidemiology and unmet need in the United Kingdom, Journal of Dermatological Treatment, DOI: [10.1080/09546634.2019.1655137](https://doi.org/10.1080/09546634.2019.1655137)

To link to this article: <https://doi.org/10.1080/09546634.2019.1655137>



© 2019 The Author(s). Published with license by Taylor & Francis Group, LLC.



Published online: 21 Oct 2019.



Submit your article to this journal [↗](#)



Article views: 326



View related articles [↗](#)



View Crossmark data [↗](#)

REVIEW ARTICLE



## Atopic dermatitis epidemiology and unmet need in the United Kingdom

Michael J. Cork<sup>a,b</sup>, Simon G. Danby<sup>a,b</sup> and Graham S. Ogg<sup>c</sup>

<sup>a</sup>Sheffield Dermatology Research, Department of Infection, Immunity & Cardiovascular Disease, Faculty of Medicine, Dentistry & Health, The University of Sheffield, Sheffield, UK; <sup>b</sup>Sheffield Children's Hospital and Sheffield Teaching Hospitals Clinical Research Facilities, Sheffield, UK; <sup>c</sup>MRC Human Immunology Unit, NIHR Biomedical Research Centre, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK

### ABSTRACT

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin condition associated with a significant health-related and socioeconomic burden, and is characterized by intense itch, disruption of the skin barrier, and upregulation of type 2-mediated immune responses. The United Kingdom (UK) has a high prevalence of AD, affecting 11–20% of children and 5–10% of adults. Approximately 2% of all cases of childhood AD in the UK are severe. Despite this, most AD treatments are performed at home, with little contact with healthcare providers or services. Here, we discuss the course of AD, treatment practices, and unmet need in the UK. Although the underlying etiology of the disease is still emerging, AD is currently attributed to skin barrier dysfunction and altered inflammatory responses. Management of AD focuses on avoiding triggers, improving skin hydration, managing exacerbating factors, and reducing inflammation through topical and systemic immunosuppressants. However, there is a significant unmet need to improve the overall management of AD and help patients gain control of their disease through safe and effective treatments. Approaches that target individual inflammatory pathways (e.g. dupilumab, anti-interleukin (IL)-4 receptor  $\alpha$ ) are emerging and likely to provide further therapeutic opportunities for patient benefit.

### ARTICLE HISTORY

Received 16 July 2019  
Accepted 31 July 2019

### KEYWORDS

Atopic dermatitis; disease burden; financial cost; unmet need

### Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin condition associated with epithelial, immune, and environmental factors. It is characterized by intense itch, disruption of the skin barrier, and upregulation of type 2-mediated immune responses in the skin (1–4).

As a disease, AD is characterized by early age of onset, with approximately 60% of AD cases in the UK diagnosed in the first year of life (5). Prevalence of AD decreases with age, with 30% of 4-year-olds, 11–20% of school-aged children, and 5–10% of adults diagnosed with AD (6,7). Data from the International Study of Asthma and Allergies in Childhood (ISAAC) and other studies (8–10) showed that among children within a general practitioner (GP) setting or within the general population, the annual AD prevalence varies between age groups, and highlighted differences between self-reported prevalence of AD in the open population compared with physician-diagnosed disease in general practice (10).

Severity of AD can be assessed objectively in a standardized manner using the SCORing AD (SCORAD) index. Higher numbers indicate greater severity, and the scale ranges from 0 to 103 (11). Approximately 18% of all cases of childhood AD in the UK are moderate (as defined by Ben-Gashir et al., SCORAD = 16–40) and 2% severe (SCORAD  $\geq$  40) (4). The odds of having severe AD are twice as great for children with AD onset during the first year of life (4). Moderate-to-severe AD can not only impact a child's physical development but can also have psychological sequelae,

placing a substantial burden on parents and carers (12,13). Fortunately, diagnosis of AD is typically accurate in secondary care – a review of dermatology cases over a 25-year period in Scotland identified AD with 97% accuracy (14). However, given that most treatments are performed at home with little GP or hospital services involvement, there remain significant challenges with associated health-related and socioeconomic burdens (12,13).

### The individual financial cost for AD

A recent study in the United States of America (USA) investigated the costs, stratified by severity, for adults with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable (15). The average lifetime cost for usual care was 271,356 USD for patients with moderate AD and 271,579 USD for patients with severe AD (15). Because of the differences between healthcare systems in the UK and USA, however, it is difficult to correlate these lifetime costs with the financial burden in the UK.

A study comprised of adults with AD from nine different European countries including the UK found that out-of-pocket costs accounted for about 900 EUR (~800 GBP) per year, including moisturizers and emollients, medications, travel expenses, and other costs. Additionally, many patients had extra costs related to everyday expenses, such as the purchase of extra or special cleaning products or washing powder (laundry detergent), bedding, or clothing that otherwise would not be purchased (16).

**CONTACT** Michael J. Cork ✉ [m.j.cork@sheffield.ac.uk](mailto:m.j.cork@sheffield.ac.uk) Sheffield Dermatology Research, Faculty of Medicine, Dentistry & Health, The University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK

© 2019 The Author(s). Published with license by Taylor & Francis Group, LLC.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

On top of direct costs, indirect costs associated with AD include disruption of employment (time off work, reduction in employment, and loss of productivity). In the European study, 26% of patients missed 6–10 days at work within the last year due to their AD, and over half missed 1–5 days. Patients with moderate-to-severe AD were more likely to miss work (16). In addition to patients themselves, indirect costs affect carers as well. For example, mothers of children with AD were found to be less likely to take up outside employment or to pursue leisure activities compared with mothers of children without AD (13,17,18).

It is unclear how the financial burden of AD impacts treatment compliance in patients (19–22). The large-scale International Study of Life with Atopic Eczema (ISOLATE) investigated the effect of AD on patients' lives and society; it examined how patients and their carers coped with AD and how well they believed their disease was being controlled. Most of the patients in the study were prescribed reactive topical corticosteroid (TCS)-based AD therapies (20). Although effective, concerns over TCSs led to compliance issues and treatment delays or restrictions, resulting in 39% of participants using TCSs less frequently and for shorter periods than was recommended, and 66% using TCSs only as a last resort. The results of ISOLATE highlight AD as an undertreated disease, which, despite the availability of effective therapies, has considerable, yet often avoidable, adverse effects on patients, their carers, and society – including socioeconomic costs (e.g. unemployment, lost productivity, and an impact on schoolwork, learning, and academic performance among younger patients) (20).

An audit commissioned by the British Association of Dermatologists provided data on the national service outcomes of 235 patients with AD in secondary care in the UK (23). The audit gathered information from patients using pre- and post-consultation questionnaires in 29 hospital dermatology departments randomly selected from 187 centers. The outcomes measured were quality of life (QoL), sleep improvement, improvement in the worst aspect of AD, and the ability to return to work or school (23), and were based on audit standards established by the British Association of Dermatologists and the Research Unit of the Royal College of Physicians (24).

An improvement in QoL (>25%) was reported in 49% of adults and 44% of children, and improved sleep was reported in 44% of adults and 47% of children; however, these results fell short of the working standards of 60% for QoL and 70% for improved sleep. Further, an improvement in the worst aspect of AD was reported in 61% of adults and 59% of children, but that too fell short of the working standard of 80%. Although 87.5% of children returned to school within 6 weeks and met the working standard of 80%, only 70% of adults returned to work, again falling short of the working standard (23). It should be taken into account that only a small percentage of AD patients are referred to dermatologists for care in the UK (4% of children aged 1–5) (19) therefore poor outcomes may reflect selection bias for patients with severe and recalcitrant disease. Nevertheless, these studies demonstrate a significant need to improve the management of AD and help patients gain control of their disease.

### Pathogenesis and course of AD

Although the underlying etiology of AD is not fully known, it is believed to be attributable to complex, yet interrelated, biologic pathways, including dysfunction of the skin barrier and altered innate or adaptive immune responses (25). There is increasing

evidence that disruption of the skin barrier function and atopy affect one another reciprocally, 'driving' the progress of AD (26–28).

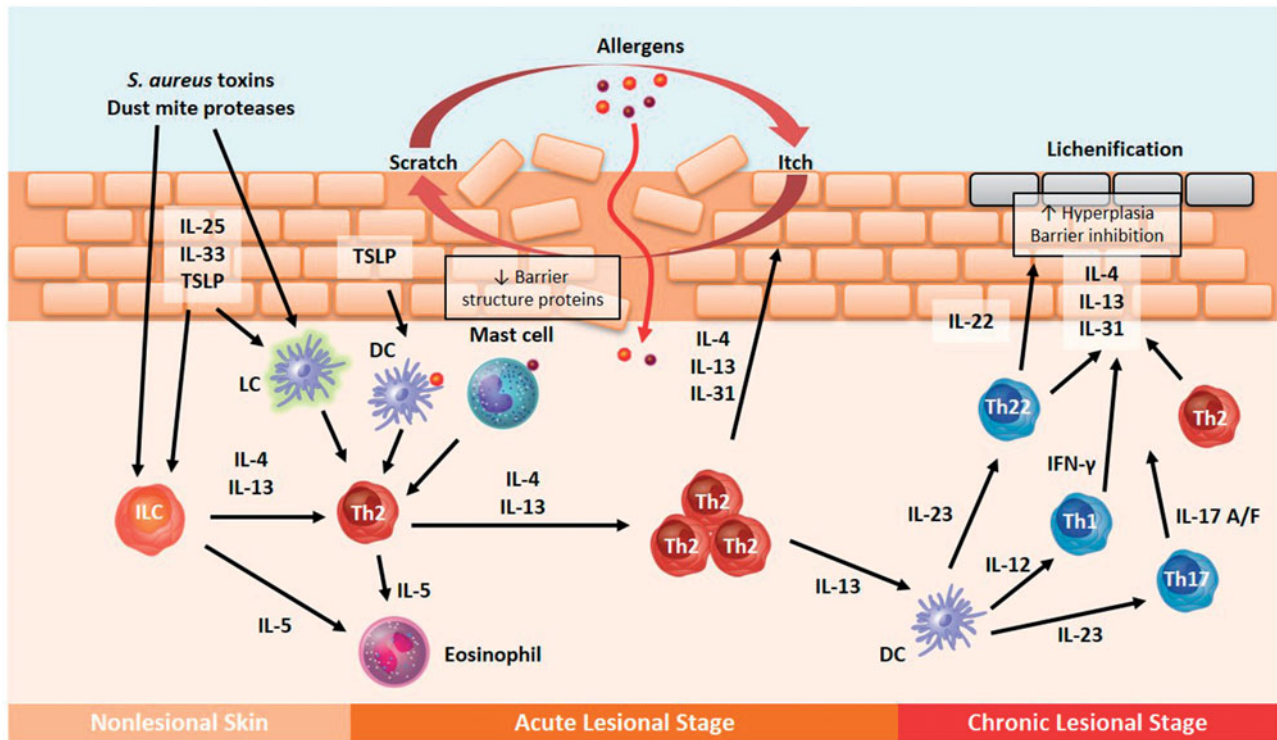
The stratum corneum (SC) is composed of corneocytes, terminally differentiated enucleated keratinocytes that are densely packed with lipids and proteins (29). Filaggrin contributes to SC function through many roles, including keratin cross-linking, hydration, and pH modulation (30–34). Filaggrin is naturally broken down in the SC into several compounds that are the constituents of natural moisturizing factor (NMF) (31,33,35). NMF is essential for optimal SC hydration, desquamation, plasticity, and acidity, and it provides the optimal environment for commensal microorganisms colonizing the skin (32,33,35,36). Disruption of the healthy epidermal microbiome can be associated with skin disorders or infections by potentially pathogenic bacteria such as *Staphylococcus aureus* (37–39).

Many genetic factors influence the integrity of the skin in AD, including mutations in genes encoding structural proteins, such as filaggrin (25,40). Loss-of-function mutations in the gene encoding filaggrin (*FLG*) have been associated with early-onset, severe, and long-lasting AD, and are considered to be the most significant genetic risk factor for developing the disease (25,26). Mutations in proteases and protease inhibitors also play an important role in AD, leading to altered desquamation and defects in the skin barrier (40–42). These and other immunological genetic factors (43–45) are thought to provide the underlying susceptibility that may predispose individuals to develop AD (25,41,42,46–48).

Environmental trigger factors are believed to play an important role in the progression of disease and development of AD (49). Data obtained (at age 7, 11, and 16 years) from 828 children born in 1958 showed a marked and statistically significant geographical variation in AD prevalence. The highest risk was associated with London and the South-East, North Midlands, Eastern, and Southern regions of the UK (49). In other studies, urban areas have been shown to have a higher risk of severe disease than rural areas (4,50). These regions may be associated with environmental factors such as temperature and humidity, allergen exposure, microbial exposure, pollution, and lifestyle factors (51,52). Itch is a key symptom of AD and promotes physical disruption of the skin barrier (53), which can promote the penetration of allergens such as the house dust mite *Dermatophagoides* protease (Der p1). Such proteases have been linked directly to the degradation of the skin barrier (54–56). Other environmental factors known to impact AD include water hardness and contaminants in water (57), soaps and detergents (58,59), and prolonged use of TCSs (60,61).

AD is a product of interplay between such environmental factors and genetic susceptibility. The loss-of-function *FLG* mutation results in decreased levels of filaggrin and, consequently, reduced NMF. Low levels of NMF increase transepidermal water loss and elevate SC pH levels (33,35). This altered skin environment can lead to *S. aureus* infection (62,63), which in turn leads to skin inflammation and systemic immunoglobulin (Ig) E sensitization (64–66). *S. aureus* can damage the skin barrier directly and secrete exotoxins that can activate an immune response to allergens penetrating the skin barrier (64,65,67–69). For example, one *S. aureus* exotoxin functions as an adjuvant to promote the inflammatory response to Der p1 (70).

The penetration of allergens through the defective skin barrier results in interaction with local immune cells and in the release of AD-related pro-inflammatory cytokines (27,54,71–78).



**Figure 1.** Skin barrier dysfunction and immune response in atopic dermatitis (AD). DC: dendritic cell; IFN- $\gamma$ : interferon gamma; ILC: innate lymphoid cell; IL: interleukin; IL-17 A/F: IL-17 A/F homodimer or heterodimer; LC: Langerhans cell; Th1: T helper type 1 cell; Th17: T helper type 17 cell; Th2: T helper type 2 cell; Th22: T helper type 22 cell; TSLP: thymic stromal lymphopoietin.

During the initial or acute phase of AD, a type 2 (including innate lymphoid cells [ILCs] and T helper type 2 cells [Th2]) immune response characterized by interleukin (IL)-4, IL-13, and IL-5 predominates (Figure 1) (79–81). This may, in part, be related to the release from keratinocytes of type 2-driving alarmins (IL-25, IL-33, and thymic stromal lymphopoietin [TSLP]). In the chronic phase, a mixed response involving Th1, Th17, and Th22 immune cells can be observed (74–78,82,83).

Lesional skin biopsies from patients with acute and chronic AD are enriched for the type 2 cytokines IL-4, IL-5, IL-13, IL-31, and IL-33 (75,79–81). The IL-4 and IL-13 cytokines are critical for further type 2 polarization and the development of AD (80,84–87). IL-5 is produced by Th2 cells and other cells and promotes eosinophilic inflammation in atopic diseases (88). IL-31, primarily produced by Th2 cells and mast cells in response to antimicrobial peptides, is significantly increased in AD, and it has been implicated in the regulation of itch (53,89). IL-33 activates Th2 cells, ILCs, mast cells, neutrophils, and eosinophils in response to allergen or *S. aureus* exotoxin exposure and other triggers (77,78,90). Recently, it was shown that house dust mite-derived phospholipases act on the skin to produce antigenic neolipids that are presented by CD1a for recognition by T cells. The production of type 2 cytokines by ILCs, peptide-specific major histocompatibility complex-restricted T cells, and lipid-specific CD1a-reactive T cells supports the generation of allergen-specific IgE (28,91). Type 2 cytokines have also been shown to contribute to the skin barrier dysfunction by modulating the expression of structural proteins and antimicrobial peptides – key to maintaining the skin integrity – and thereby facilitating allergen penetration through the skin (Figure 1) (27,92). Both increased allergen-specific IgE presentation and allergen penetration through the skin barrier potentiate the inflammatory response.

The generation of IgE antibodies and skin-derived TSLP is associated with the development of other atopic disorders, including asthma, allergic rhinitis, and/or food allergies (93–97). Additionally, AD has recently been shown to be associated with non-atopic disorders, including cardiovascular disease (98,99) and some forms of cancer (100). The relation of localized skin disorders with systemic disease represents one of the largest challenges for treating AD and associated morbidity (101). Early and effective management of AD may therefore have effects beyond the skin.

### AD treatment in the UK

The aim of the guidance and information available on skin conditions provided by the UK's National Health Service (NHS) is to facilitate a whole system-integrated approach for people with AD that ensures timely access, high-quality care (close to home, where applicable), and value for money (102). In England and Wales, the NHS directive uses the standards set for patient care by the National Institute for Health and Care Excellence (NICE). The NICE guidelines cover the diagnosis and management of AD in children and adults to improve care and QoL, and to decrease the physical severity of their disease (103,104).

The management of AD in the UK occurs predominantly in the primary care setting, and current treatment options include approaches intended to protect the skin barrier (e.g. emollients [leave-on and wash], medicated bandages) or reduce inflammation (TCSs, topical calcineurin inhibitors [TCIs], broad immunosuppressants, biologics). Also significant in the management of AD is the identification, avoidance, and treatment of exacerbating environmental factors. As discussed above, disruptions in the skin barrier result in greater exposure to allergens, and avoiding such allergens can play a role in the management of AD. For children



**Table 1.** Holistic assessment of atopic dermatitis (AD) and treatment options for children under the age of 12 years (103).

	Skin/physical severity	Impact on quality of life and psychosocial well-being	Stepped approach to treatment
Clear	Normal skin, no evidence of active eczema	No impact on quality of life	
Mild	Areas of dry skin, infrequent itching (with/without redness)	Little impact on everyday activities, sleep, and psychosocial well-being	Emollients, mild potency topical corticosteroids (TCSs)
Moderate	Areas of dry skin, frequent itching, redness (with/without excoriation and localized skin thickening)	Moderate impact on everyday activities and psychosocial well-being, frequently disturbed sleep	Emollients, moderate potency TCSs, topical calcineurin inhibitors (TCIs), bandages and dressings
Severe	Widespread areas of dry skin, incessant itching (with/without excoriation, extensive skin thickening, bleeding, oozing, cracking, alteration of pigmentation)	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep	Emollients, potent TCSs, TCIs, bandages and dressings, phototherapy, systemic therapy

Adapted from NICE, 2007 (103).

under the age of 12 years, a stepwise approach should be taken to manage the disease, with the potency of the medications adapted to the severity of the disease and the anatomical site of application (Table 1) (103).

According to the NICE guidelines, the treatment options for children with AD should be tailored to meet the needs of the patient. Emollients such as creams, ointments, sprays, lotions, gels, and bath additives are considered first-line therapies and are selected by the patient (103,105). Emollients are products that contain various moisturizing components that improve symptoms, including humectants (hygroscopic substances that attract water) and non-physiologic lipids. The lipids provide an artificial protective layer over the surface of the skin that aids water retention and transiently improves skin barrier function. Emollients can help soften skin texture and help relieve the pruritus (itch) caused by excessive dryness (106), and some may even reduce the need for TCSs (107). Simple emollients are tolerated in children as young as 6 months (103,108).

The accepted best practice for emollient therapy recommends consistent and liberal use of emollients and skin protectants. Recent evidence suggests that not all emollients for the protection and maintenance of the skin barrier are the same, with some displaying additional physiological effects on the skin and others having adverse effects (109–112). For example, some emollients contain surfactants and emulsifying agents (such as sodium lauryl sulfate) that not only disrupt the epidermal barrier function (113,114) but can also irritate the skin and induce an immune response (58,115). In contrast, other emollients appear to delay the onset of flares and may even help prevent the primary emergence of AD (116,117). As such, many uncertainties still remain regarding the use of emollients, including which emollient to use and how much (118).

Bathing, by soaking in lukewarm water with emollients (and possibly short-term/intermittent antimicrobials), offers an opportunity to improve skin hydration, provides symptomatic relief of AD symptoms, and has an antipruritic effect (103,106). However, bathing can also cause dryness, especially if a harsh detergent is used. Therefore, non-soap-based cleansers and mild synthetic detergents (pH of 5.5–6.0) that protect the skin's acid mantle are recommended for patients with AD (105).

While treating flares with TCSs can offer rapid and effective relief from symptoms, their long-term use carries potential safety concerns, such as cutaneous adverse events and possible systemic side effects (119). Over the years, however, these concerns have escalated into phobias (120), particularly among parents of pediatric AD patients (121–123). These phobias led to treatment non-compliance (120) and ultimately reduced disease control, which increased morbidity and the burden of the disease. 'Corticophobia' might also explain, at least partially, why patients

often delay treatment of flares, resulting in the disease needlessly going untreated for extended periods. The introduction of a non-steroidal treatment option for patients with AD – TCIs (or topical immunomodulators) – is thus intended to complement the existing treatment choices and overcome the negatives associated with TCS therapy (103,124).

TCSs have been the mainstay of AD treatment for over 40 years. When a patient with AD first applies one of the more potent variants, the benefit is often rapid and apparent. However, increasing the potency of the preparation in response to tachyphylaxis (drug tolerance) (125) may lead to local adverse events. Furthermore, the side effects of persistent daily applications of a potent TCS can be unfavorable. As discussed above, prolonged use of TCSs can potentially damage the skin barrier, resulting in thinning of the skin, telangiectasia, or striae distensae (60,61,125). The potency of a TCS is partly determined by the amount of vasoconstriction produced and the degree to which it inhibits inflammation. Thus, a mild TCS can be used to treat a mild AD flare. The TCIs, tacrolimus and pimecrolimus, are not recommended as first-line therapy for AD in England and Wales (103,104). TCIs do not damage the skin barrier and are therefore particularly useful on skin sites with a thin skin barrier such as the face and flexures, which are most vulnerable to the adverse effects of TCSs (126). TCIs should be used only in the absence of clinical infections. For the use of both TCSs and TCIs, maintenance treatment twice per week can be helpful in reducing the frequency and severity of flares, although TCIs are preferable because of their positive effects on the skin barrier (103,126). The correct use of all topical therapies should be demonstrated by specialist dermatology nurses and care plans should be provided as part of an intensive educational package (103,104). Phototherapy may also be used in patients whose medical, physical, and/or psychological states are greatly affected by their AD (103). Narrowband ultraviolet B (UVB) light is the most common form of phototherapy because of its relative efficacy, availability, and provider comfort level. Though there are few risks associated with narrowband UVB (127), there is a potential risk of skin cancer from using psoralen and ultraviolet A (PUVA) (128). The risk of skin cancer from narrowband UVB is not well established, as a systematic review found no increased risk compared with PUVA (129) and another review found insufficient evidence of risk (130). Phototherapy is not appropriate for young children, and, for all patients, the need to attend treatment sessions three times per week can impact adversely on school, work, or other commitments.

Systemic therapy using oral immunosuppressants can only be used in severe, non-responsive cases of AD. It is essential to ensure that topical therapies have been used to their maximum potential by giving comprehensive and repeated education and demonstration (103,104,131). Oral cyclosporine, azathioprine, and

methotrexate are all effective systemic treatments (132–136). While the effect of cyclosporine is rapid, azathioprine- and methotrexate-induced improvements tend to emerge later. Immunosuppressant use, however, is associated with significant side effects and requires careful monitoring (133–136).

## Discussion

Despite common worldwide principles and protocols in dermatology, significant differences in global treatment methods and approaches exist. For example, systemic immunosuppressants are used more frequently in the UK and the USA than in Japan (137). Furthermore, their use differs across European countries, as reported by the European Treatment of Severe Atopic Eczema in Children Taskforce (TREAT) survey (138). Azathioprine, for instance, is used more often as a first- or second-line systemic treatment option in the UK than in other European countries, whereas oral corticosteroids are used less frequently in the UK than in Italy, the Netherlands, Spain, or Sweden. Such variations in treatment habits and approaches are not surprising in the pediatric population given the scarcity of randomized controlled AD trials and the absence of any licensed therapies.

Several new targeted approaches are emerging, which may enhance the safe and effective management of patients with AD. Dupilumab is a fully human monoclonal antibody directed against the shared IL-4 receptor  $\alpha$  subunit that inhibits IL-4 and IL-13, which are key drivers of type 2/Th2-mediated inflammation. Dupilumab is approved for subcutaneous administration for the treatment of patients aged  $\geq 12$  years in the USA with moderate-to-severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable (139), for the treatment of adult AD patients not adequately controlled with existing therapies in Japan and for use in patients aged  $\geq 12$  years with moderate-to-severe AD who are candidates for systemic therapy in the European Union (140).

Through a combination of appropriate access to services, appropriate diagnosis, and appropriate use of existing approaches, we can make a significant contribution to patient benefit. However, we are entering an exciting phase of development where the number of available treatments for patients is likely to increase, offering enhanced potential to treat them safely and effectively, and to address a significant unmet need.

## Disclosure statement

M.J. Cork is an investigator and consultant for Astellas, Boots, Galapagos, Galderma, Hyphens, Johnson & Johnson, LEO Pharma, L'Oreal, Menlo, Novartis, Oxagen, Pfizer, Procter & Gamble, Perrigo, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme, and consultant to AbbVie, Galderma, Dermavant, and Reckitt Benckiser. S.G. Danby received research grants, participated in advisory boards, or has consulted with Almirall, Astellas Pharma, Bayer, Harvey Water Softeners, Johnson & Johnson, MSD, and Stiefel-GSK. G.S. Ogg received research grants, participated in advisory boards and clinical trials, or has consulted with AnaptysBio, Atopix, Celgene, Grünenthal, Johnson & Johnson, Novartis, Orbit Discovery, Regeneron Pharmaceuticals, Inc., Roche, Sanofi, and UCB.

## Funding

Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. Medical writing/editorial assistance provided by Ravi

Subramanian, PhD and Lauren D. Van Wassenhove, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc. Graham Ogg receives support from the Medical Research Council, (grant number CF00.G3) and the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC), (grant number CFR00800). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

## References

- Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130:1344–1354.
- Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)*. 1980;92:44–47.
- Jungersted JM, Scheer H, Mempel M, et al. Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema. *Allergy*. 2010;65:911–918.
- Ben-Gashir MA, Seed PT, Hay RJ. Predictors of atopic dermatitis severity over time. *J Am Acad Dermatol*. 2004;50:349–356.
- Kay J, Gawkrödger DJ, Mortimer MJ, et al. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol*. 1994;30:35–39.
- Prescott-Clarke P, Primatesta P. The health survey for England 1996. London: The Stationery Office; 1998.
- Simpson CR, Newton J, Hippisley-Cox J, et al. Trends in the epidemiology and prescribing of medication for eczema in England. *J R Soc Med*. 2009;102:108–117.
- Asher MI, Montefort S, Björkstén S, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368:733–743.
- Deckers IA, McLean S, Linssen S, et al. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. *PLoS One*. 2012;7:e39803.
- Pols DH, Wartna JB, Moed H, et al. Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: a systematic review. *Scand J Prim Health Care*. 2016;34:143–150.
- Severity scoring of atopic dermatitis: The SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186:23–31.
- Fennessy M, Coupland S, Popay J, et al. The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. *J Epidemiol Community Health*. 2000;54:581–589.
- Su JC, Kemp AS, Varigos GA, et al. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child*. 1997;76:159–162.
- Benton EC, Kerr OA, Fisher A, et al. The changing face of dermatological practice: 25 years' experience. *Br J Dermatol*. 2008;159:413–418.
- Zimmermann M, Rind D, Chapman R, et al. Economic evaluation of dupilumab for moderate-to-severe atopic dermatitis: a cost-utility analysis. *J Drugs Dermatol*. 2018;17:750–756.

16. Zink A, Arents B, Fink-Wagner A, et al. Out-of-pocket costs for individuals with atopic eczema: a cross-sectional study in nine European countries. *Acta Derm Venereol.* 2019;99: 263–267.
17. Daud LR, Garralda ME, David TJ. Psychosocial adjustment in preschool children with atopic eczema. *Arch Dis Child.* 1993;69:670–676.
18. Elliott BE, Luker K. The experiences of mothers caring for a child with severe atopic eczema. *J Clin Nurs.* 1997;6: 241–247.
19. Emerson RM, Williams HC, Allen BR. What is the cost of atopic dermatitis in preschool children? *Br J Dermatol.* 2001;144:514–522.
20. Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol.* 2006;118:226–232.
21. Eckert L, Gupta S, Amand C, et al. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: an analysis using the National Health and Wellness Survey. *J Am Acad Dermatol.* 2017;77: 274–279.
22. Silverberg JL. Health care utilization, patient costs, and access to care in US adults with eczema: a population-based study. *JAMA Dermatol.* 2015;151:743–752.
23. Shum KW, Lawton S, Williams HC, et al. The British Association of Dermatologists audit of atopic eczema management in secondary care. Phase 3: audit of service outcome. *Br J Dermatol.* 2000;142:721–727.
24. Shum KW, Lawton S, Williams HC, et al. The British Association of Dermatologists audit of atopic eczema management in secondary care. Phase 1: audit of service structure. *Br J Dermatol.* 1999;141:430–437.
25. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38:441–446.
26. Baurecht H, Irvine AD, Novak N, et al. Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol.* 2007;120: 1406–1412.
27. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol.* 2007;120:150–155.
28. Jarrett R, Salio M, Lloyd-Lavery A, et al. Filaggrin inhibits generation of CD1a neolipid antigens by house dust mite-derived phospholipase. *Sci Transl Med.* 2016;8:325ra18.
29. Lavker RM, Matoltsy AG. Formation of horny cells: the fate of cell organelles and differentiation products in ruminal epithelium. *J Cell Biol.* 1970;44:501–512.
30. Denecker G, Hoste E, Gilbert B, et al. Caspase-14 protects against epidermal UVB photodamage and water loss. *Nat Cell Biol.* 2007;9:666–674.
31. Riethmuller C, McAleer MA, Koppes SA, et al. Filaggrin breakdown products determine corneocyte conformation in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2015;136:1573–1580.
32. Jang H, Matsuda A, Jung K, et al. Skin pH is the master switch of kallikrein 5-mediated skin barrier destruction in a murine atopic dermatitis model. *J Invest Dermatol.* 2016; 136:127–135.
33. Kezic S, O'Regan GM, Lutter R, et al. Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol.* 2012;129:1031–1039.e1.
34. Steinert PM, Marekov LN. The proteins elafin, filaggrin, keratin intermediate filaments, loricrin, and small proline-rich proteins 1 and 2 are isopeptide cross-linked components of the human epidermal cornified cell envelope. *J Biol Chem.* 1995;270:17702–17711.
35. Kezic S, Kemperman PM, Koster ES, et al. Loss-of-function mutations in the filaggrin gene lead to reduced level of natural moisturizing factor in the stratum corneum. *J Invest Dermatol.* 2008;128:2117–2119.
36. Bibel DJ, Aly R, Lahti L, et al. Microbial adherence to vulvar epithelial cells. *J Med Microbiol.* 1987;23:75–82.
37. 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;22:850–859.
38. 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 pii: eaah4680. DOI:10.1126/scitranslmed.aah4680
39. Oh J, Conlan S, Polley EC, et al. Shifts in human skin and nares microbiota of healthy children and adults. *Genome Med.* 2012;4:77.
40. Winge MC, Hoppe T, Berne B, et al. Filaggrin genotype determines functional and molecular alterations in skin of patients with atopic dermatitis and ichthyosis vulgaris. *PLoS One.* 2011;6:e28254.
41. Vasilopoulos Y, Cork MJ, Teare D, et al. A nonsynonymous substitution of cystatin A, a cysteine protease inhibitor of house dust mite protease, leads to decreased mRNA stability and shows a significant association with atopic dermatitis. *Allergy.* 2007;62:514–519.
42. Vasilopoulos Y, Cork MJ, Murphy R, et al. Genetic association between an AACC insertion in the 3'UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. *J Invest Dermatol.* 2004;123:62–66.
43. He JQ, Chan-Yeung M, Becker AB, et al. Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. *Genes Immun.* 2003;4:385–389.
44. Lesiak A, Kuna P, Zakrzewski M, et al. Combined occurrence of filaggrin mutations and IL-10 or IL-13 polymorphisms predisposes to atopic dermatitis. *Exp Dermatol.* 2011;20:491–495.
45. Namkung JH, Lee JE, Kim E, et al. Association of polymorphisms in genes encoding IL-4, IL-13 and their receptors with atopic dermatitis in a Korean population. *Exp Dermatol.* 2011;20:915–919.
46. Paternoster L, Standl M, Waage J, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet.* 2015;47:1449–1456.
47. Walley AJ, Chavanas S, Moffatt MF, et al. Gene polymorphism in Netherton and common atopic disease. *Nat Genet.* 2001;29:175–178.
48. Yousef GM, Scorilas A, Magklara A, et al. The KLK7 (PRSS6) gene, encoding for the stratum corneum chymotryptic enzyme is a new member of the human kallikrein gene family – genomic characterization, mapping, tissue expression and hormonal regulation. *Gene.* 2000;254:119–128.
49. McNally NJ, Williams HC, Phillips DR, et al. Is there a geographical variation in eczema prevalence in the UK?

- Evidence from the 1958 British Birth Cohort Study. *Br J Dermatol.* 2000;142:712–720.
50. Schäfer T, Vieluf D, Behrendt H, et al. Atopic eczema and other manifestations of atopy: results of a study in East and West Germany. *Allergy.* 1996;51:532–539.
  51. Arlian LG, Bernstein D, Bernstein IL, et al. Prevalence of dust mites in the homes of people with asthma living in eight different geographic areas of the United States. *J Allergy Clin Immunol.* 1992;90:292–300.
  52. Molloy HF, LaMont-Gregory E, Idzikowski C, et al. Overheating in bed as an important factor in many common dermatoses. *Int J Dermatol.* 1993;32:668–672.
  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;117:411–417.
  54. Comoy EE, Pestel J, Duez C, et al. The house dust mite allergen, *Dermatophagoides pteronyssinus*, promotes type 2 responses by modulating the balance between IL-4 and IFN-gamma. *J Immunol.* 1998;160:2456–2462.
  55. Tan BB, Weald D, Strickland I, et al. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet.* 1996;347:15–18.
  56. Wan H, Winton HL, Soeller C, et al. Der p 1 facilitates trans-epithelial allergen delivery by disruption of tight junctions. *J Clin Invest.* 1999;104:123–133.
  57. McNally NJ, Williams HC, Phillips DR, et al. Atopic eczema and domestic water hardness. *Lancet.* 1998;352:527–531.
  58. Danby SG, Brown K, Wigley AM, et al. The effect of water hardness on surfactant deposition following washing and subsequent skin irritation in atopic dermatitis patients and healthy controls. *J Invest Dermatol.* 2018;138:68–77.
  59. White MI, Jenkinson DM, Lloyd DH. The effect of washing on the thickness of the stratum corneum in normal and atopic individuals. *Br J Dermatol.* 1987;116:525–530.
  60. Kao JS, Fluhr JW, Man MQ, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. *J Invest Dermatol.* 2003;120:456–464.
  61. Sheu HM, Lee JY, Chai CY, et al. Depletion of stratum corneum intercellular lipid lamellae and barrier function abnormalities after long-term topical corticosteroids. *Br J Dermatol.* 1997;136:884–890.
  62. Gong JQ, Lin L, Lin T, et al. Skin colonization by *Staphylococcus aureus* in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. *Br J Dermatol.* 2006;155:680–687.
  63. Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br J Dermatol.* 1974;90:525–530.
  64. Brauweiler AM, Goleva E, Leung DYM. Th2 cytokines increase *Staphylococcus aureus* alpha toxin-induced keratinocyte death through the signal transducer and activator of transcription 6 (STAT6). *J Invest Dermatol.* 2014;134:2114–2121.
  65. Nakamura Y, Oscherwitz J, Cease KB, et al. *Staphylococcus*  $\delta$ -toxin induces allergic skin disease by activating mast cells. *Nature.* 2013;503:397–401.
  66. Novak N, Allam JP, Bieber T. Allergic hyperreactivity to microbial components: A trigger factor of “intrinsic” atopic dermatitis? *J Allergy Clin Immunol.* 2003;112:215–216.
  67. Hirasawa Y, Takai T, Nakamura T, et al. *Staphylococcus aureus* extracellular protease causes epidermal barrier dysfunction. *J Invest Dermatol.* 2010;130:614–617.
  68. Kita K, Sueyoshi N, Okino N, et al. Activation of bacterial ceramidase by anionic glycerophospholipids: possible involvement in ceramide hydrolysis on atopic skin by *Pseudomonas* ceramidase. *Biochem J.* 2002;362:619–626.
  69. Miedzobrodzki J, Kaszycki P, Bialecka A, et al. Proteolytic activity of *Staphylococcus aureus* strains isolated from the colonized skin of patients with acute-phase atopic dermatitis. *Eur J Clin Microbiol Infect Dis.* 2002;21:269–276.
  70. Arden-Jones MR, Black AP, Bateman EA, et al. Bacterial superantigen facilitates epithelial presentation of allergen to T helper 2 cells. *Proc Natl Acad Sci USA.* 2007;104:5557–5562.
  71. Nemoto-Hasebe I, Akiyama M, Nomura T, et al. Clinical severity correlates with impaired barrier in filaggrin-related eczema. *J Invest Dermatol.* 2009;129:682–689.
  72. Nickoloff BJ, Naidu Y. Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J Am Acad Dermatol.* 1994;30:535–546.
  73. Wood LC, Elias PM, Calhoun C, et al. Barrier disruption stimulates interleukin-1 alpha expression and release from a pre-formed pool in murine epidermis. *J Invest Dermatol.* 1996;106:397–403.
  74. Fort MM, Cheung J, Yen D, et al. IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. *Immunity.* 2001;15:985–995.
  75. Salimi M, Barlow JL, Saunders SP, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med.* 2013;210:2939–2950.
  76. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol.* 2002;3:673–680.
  77. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity.* 2005;23:479–490.
  78. Halim TY, Hwang YY, Scanlon ST, et al. Group 2 innate lymphoid cells license dendritic cells to potentiate memory TH2 cell responses. *Nat Immunol.* 2016;17:57–64.
  79. Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest.* 1994;94:870–876.
  80. Hamid Q, Naseer T, Minshall EM, et al. In vivo expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol.* 1996;98:225–231.
  81. Bilsborough J, Leung DY, Maurer M, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2006;117:418–425.
  82. Ungar B, Garcet S, Gonzalez J, et al. An integrated model of atopic dermatitis biomarkers highlights the systemic nature of the disease. *J Invest Dermatol.* 2017;137:603–613.
  83. Suárez-Fariñas M, Tintle SJ, Shemer A, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *J Allergy Clin Immunol.* 2011;127:954–964.
  84. Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. *J Invest Dermatol.* 2001;117:977–983.



85. Daines MO, Chen W, Tabata Y, et al. Allergen-dependent solubilization of IL-13 receptor  $\alpha 2$  reveals a novel mechanism to regulate allergy. *J Allergy Clin Immunol*. 2007;119:375–383.
86. Herberth G, Heinrich J, Röder S, et al. Reduced IFN-gamma- and enhanced IL-4-producing CD4<sup>+</sup> cord blood T cells are associated with a higher risk for atopic dermatitis during the first 2 yr of life. *Pediatr Allergy Immunol*. 2010;21:5–13.
87. Zheng T, Oh MH, Oh SY, et al. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. *J Invest Dermatol*. 2009;129:742–751.
88. Mori A, Kaminuma O, Suko M, et al. Cellular and molecular mechanisms of IL-5 synthesis in atopic diseases: a study with allergen-specific human helper T cells. *J Allergy Clin Immunol*. 1997;100:S56–S64.
89. Grimstad O, Sawanobori Y, Vestergaard C, et al. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol*. 2009;18:35–43.
90. Savinko T, Matikainen S, Saarialho-Kere U, et al. IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. *J Invest Dermatol*. 2012;132:1392–1400.
91. Wood N, Whitters MJ, Jacobson BA, et al. Enhanced interleukin (IL)-13 responses in mice lacking IL-13 receptor alpha 2. *J Exp Med*. 2003;197:703–709.
92. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med*. 2002;347:1151–1160.
93. 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;119:870–875.
94. Demehri S, Morimoto M, Holtzman MJ, et al. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. *PLoS Biol*. 2009;7:e1000067.
95. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372:803–813.
96. Flohr C, Johansson SG, Wahlgren CF, et al. How atopic is atopic dermatitis? *J Allergy Clin Immunol*. 2004;114:150–158.
97. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113:832–836.
98. Anderson YMF, Egeberg A, Gislason GH, et al. Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2013;138:310–312.e3.
99. Silverberg JL. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. *Allergy*. 2015;70:1300–1308.
100. Arana A, Wentworth CE, Fernández-Vidaurre C, et al. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the UK. *Br J Dermatol*. 2010;163:1036–1043.
101. Andersen YMF, Egeberg A, Skov L, et al. Comorbidities of atopic dermatitis: beyond rhinitis and asthma. *Curr Derm Rep*. 2017;6:35–41.
102. NHS. Providing care for patients with skin conditions: guidance and resources for commissioners. London: Department of Health; 2008. Available from: <http://www.pcds.org.uk/images/stories/nhs-pcpcsc.pdf>.
103. NICE. Atopic eczema in under 12s: diagnosis and management. Clinical guideline [CG57]. London: NICE; 2007. Available from: <https://www.nice.org.uk/guidance/cg57>.
104. NICE. Treating eczema in people over 12. London: NICE; 2019. Available from: <http://pathways.nice.org.uk/pathways/eczema>
105. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol*. 2006;118:152–169.
106. Leung DY, Nicklas RA, Li JT, et al. Disease management of atopic dermatitis: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2004;93(3 Suppl. 2):S1–S21.
107. Lucky AW, Leach AD, Laskarzewski P, et al. Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatr Dermatol*. 1997;14:321–324.
108. Giordano-Labadie F, Cambazard F, Guillet G, et al. Evaluation of a new moisturizer (Exomega milk) in children with atopic dermatitis. *J Dermatolog Treat*. 2006;17:78–81.
109. Holden C, English J, Hoare C, et al. Advised best practice for the use of emollients in eczema and other dry skin conditions. *J Dermatolog Treat*. 2002;13:103–106.
110. Danby SG, Brown K, Higgs-Bayliss T, et al. The effect of an emollient containing urea, ceramide NP, and lactate on skin barrier structure and function in older people with dry skin. *Skin Pharmacol Physiol*. 2016;29:135–147.
111. Grether-Beck S, Felsner I, Brenden H, et al. Urea uptake enhances barrier function and antimicrobial defense in humans by regulating epidermal gene expression. *J Invest Dermatol*. 2012;132:1561–1572.
112. Cork MJ, Timmins J, Holden C, et al. An audit of adverse drug reactions to aqueous cream in children with atopic eczema. *Pharm J*. 2003;271:746–747.
113. Tsang M, Guy RH. Effect of aqueous cream BP on human stratum corneum in vivo. *Br J Dermatol*. 2010;163:954–958.
114. Danby SG, Al-Enezi T, Sultan A, et al. The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *Br J Dermatol*. 2011;165:329–334.
115. Lammintausta K, Maibach HI, Wilson D. Human cutaneous irritation: induced hyporeactivity. *Contact Dermatitis*. 1987;17:193–198.
116. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134:818–823.
117. Åkerström U, Reitamo S, Langeland T, et al. Comparison of moisturizing creams for the prevention of atopic dermatitis relapse: a randomized double-blind controlled multicentre clinical trial. *Acta Derm Venereol*. 2015;95:587–592.
118. Batchelor JM, Ridd MJ, Clarke T, et al. The Eczema Priority Setting Partnership: a collaboration between patients, carers, clinicians and researchers to identify and prioritize important research questions for the treatment of eczema. *Br J Dermatol*. 2013;168:577–582.

119. Ellison JA, Patel L, Ray DW, et al. Hypothalamic-pituitary-adrenal function and glucocorticoid sensitivity in atopic dermatitis. *Pediatrics*. 2000;105:794–799.
120. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol*. 2000;142:931–936.
121. Kojima R, Fujiwara T, Matsuda A, et al. Factors associated with steroid phobia in caregivers of children with atopic dermatitis. *Pediatr Dermatol*. 2013;30:29–35.
122. Hon KL, Kam WY, Leung TF, et al. Steroid fears in children with eczema. *Acta Paediatr*. 2006;95:1451–1455.
123. Moret L, Anthoine E, Aubert-Wastiaux H, et al. TOPICOP®: a new scale evaluating topical corticosteroid phobia among atopic dermatitis outpatients and their parents. *PLoS One*. 2013; 8:e76493.
124. Ellis C, Luger T, Abeck D, et al. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. *Br J Dermatol*. 2003;148(Suppl. 63):3–10.
125. du Vivier A. Tachyphylaxis to topically applied steroids. *Arch Dermatol*. 1976;112:1245–1248.
126. Danby SG, Chittock J, Brown K, et al. The effect of tacrolimus compared with betamethasone valerate on the skin barrier in volunteers with quiescent atopic dermatitis. *Br J Dermatol*. 2014;170:914–921.
127. Ibbotson SH, Bilsland D, Cox NH, et al. An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. *Br J Dermatol*. 2004;151:283–297.
128. Stern RS, Nichols KT, Väkevä LH. Malignant melanoma in patients treated with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med*. 1997;336:1041–1045.
129. Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. *Int J Dermatol*. 2005;44:355–360.
130. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Derm Venereol*. 2012;26:22–31.
131. Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol*. 2017; 77:623–633.
132. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71:327–349.
133. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet*. 2006;367:839–846.
134. Sowden JM, Berth-Jones J, Ross JS, et al. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet*. 1991;338: 137–140.
135. Schram ME, Roekevisch E, Leeflang MM, et al. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol*. 2011;128:353–359.
136. Fuggle NR, Bragoli W, Mahto A, et al. The adverse effect profile of oral azathioprine in pediatric atopic dermatitis, and recommendations for monitoring. *J Am Acad Dermatol*. 2015;72:108–114.
137. Baron ED, Barzilai D, Johnston G, et al. Atopic dermatitis management: comparing the treatment patterns of dermatologists in Japan, USA and UK. *Br J Dermatol*. 2002;147: 710–715.
138. Proudfoot LE, Powell AM, Ayis S, et al. The European TREatment of severe Atopic eczema in children Taskforce (TREAT) survey. *Br J Dermatol*. 2013;169:901–909.
139. Dupixent® (dupilumab) injection: Highlights of prescribing information. Tarrytown, NY/Bridgewater, NJ: Regeneron Pharmaceuticals, Inc./Sanofi-Aventis US LLC; 2019 [cited 2019 Sept]. Available from: [https://www.regeneron.com/sites/default/files/Dupixent\\_FPI.pdf](https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf)
140. Dupixent® (dupilumab) summary of product characteristics. Brussels: European Commission; 2019. Available from: [https://ec.europa.eu/health/documents/community-register/2019/20190801145601/anx\\_145601\\_en.pdf](https://ec.europa.eu/health/documents/community-register/2019/20190801145601/anx_145601_en.pdf).