



2014 update on atopic dermatitis in children

Christine R. Totri^{a,b}, Lucia Diaz^{a,b}, and Lawrence F. Eichenfield^{a,b}

Purpose of review

The prevalence of pediatric atopic dermatitis (AD) has increased throughout the world, now ranging from 10 to 20% in developed countries. Pediatric patients with AD make up a substantial proportion of patients seen by general pediatricians, allergists, dermatologists, and other specialists. As such, there is a need to optimize understanding and management of AD.

Recent findings

The traditional atopic comorbidities of AD have now expanded to include associations with nonatopic conditions such as attention deficit hyperactivity disorder. Furthermore, with insights from basic, translational, and clinical research, experts have a more comprehensive knowledge of the genetic, immunological, and environmental factors influencing the development of AD. With this new perception, innovative approaches to the management of AD have developed with an emphasis on preventive rather than reactive care. The role of biological agents in the treatment of this common, yet chronic, disease of the skin has not been clearly elucidated.

Summary

There have been several recent breakthroughs in the diagnosis, pathophysiology, and management of AD. Despite these advances, much work is still needed in order to ensure optimal care for AD sufferers.

Keywords

atopic dermatitis, atopic march, filaggrin mutations, topical calcineurin inhibitors, topical corticosteroids

INTRODUCTION

All pediatricians are familiar with the rash that causes 'itchy, scaly, and red skin.' Atopic dermatitis (AD) is the most common chronic inflammatory skin condition in children, responsible for 7.4 million health-care visits between 1997 and 2004 and costing an estimated \$364 million to \$3.8 billion per year [1]. From the 2003 National Survey of Children's Health, the United States prevalence of AD was estimated to be 10.7% in children [2], indicating that AD has become an important public health concern domestically. Pediatricians and primary care physicians treat approximately 30% and 20% of patients with AD, respectively [3]; therefore, they need to be well informed about this chronic, relapsing disease of the skin. This review article aims to update the reader on the new developments in AD, including guidelines for its diagnosis and management, advancements in the understanding of the pathophysiology and comorbidities associated with AD, and, finally, new approaches in its treatment.

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ATOPIC DERMATITIS

The diagnosis of AD is a clinical one, usually based upon criteria set forth by Hanifin and Rajka in 1980.

A diagnosis of AD requires three of four major criteria and three of 23 minor criteria [4]. In a clinical setting, the Hanifin and Rajka criteria may be difficult to utilize, and several of the secondary criteria have poor sensitivity and specificity [5]. With a desire for easier guidelines for clinical use, an American Academy of Dermatology Consensus Group recommended diagnostic criteria in 2003, categorizing these into essential features, important features, and associated features (Table 1) [6]. Although validation studies are still needed, these diagnostic guidelines were established with a pragmatic approach, allowing for their use by nondermatologists and in clinical settings.

As part of updated American Academy of Dermatology Guidelines for the care and management of AD, new recommendations for the diagnosis and assessment of AD along with the strength of the recommendations have been published. The

^aUniversity of California, San Diego, La Jolla and ^bRady Children's Hospital, San Diego, California, USA

Correspondence to Lawrence F. Eichenfield, 8010 Frost St #602, San Diego, California 92123, USA. Tel: +1 858 966 6795; e-mail: leichenfield@rchsd.org

Curr Opin Pediatr 2014, 26:466–471

DOI:10.1097/MOP.000000000000109

KEY POINTS

- The increased prevalence of atopic dermatitis (AD) has translated into more healthcare dollars being spent for the care and treatment of patients suffering from the disease.
- New links between AD and both allergic and nonallergic comorbidities are being elucidated, spurring the need for healthcare providers to optimize disease management.
- The identification of mutations in the *FLG* gene has placed an emphasis on barrier dysfunction in the development of AD.
- Both topical corticosteroids and topical calcineurin inhibitors remain at the core of AD treatment, with bleach baths serving as adjuvant treatment for patients with moderate-to-severe disease.
- Proactive, rather than reactive, management of AD is an important strategy to prevent flares.

following C-level recommendations are based on consensus, usual practice, opinion, disease-oriented evidence, or case series [7]:

- (1) Diagnosis made using criteria in Table 1
- (2) Available disease severity scales not for routine clinical use

- (3) Available quality of life severity scales not for routine clinical use
- (4) Should query patients about itch, sleep, impact on daily activity, and disease persistence
- (5) Awareness and discussion of common associations (see 'Comorbidities' below)
- (6) Integrated, multidisciplinary approach to care

The guidelines highlight that, to date, there are no specific, or clinically specific, biomarkers for AD assessment. In particular, the use of immunoglobulin E levels to monitor disease severity is not recommended [8*].

PATHOPHYSIOLOGY

Although understanding of the pathophysiology of AD remains incomplete, experts agree that a complex relationship between a hyperactive immune system and skin barrier dysfunction, along with environmental factors, may drive the development of AD. Immune dysfunction, including impaired innate immunity, allergic sensitization, and upregulation of a TH2 inflammation pattern, is thought to play a core role in the development of AD [9]. Many patients with AD have high serum total immunoglobulin E (IgE) levels representative of immune hyper-reactivity. Yet IgE antibody levels are neither specific nor sensitive to the diagnosis of AD.

Table 1. American Academy of Dermatology Consensus Group recommended diagnostic criteria for atopic dermatitis

Essential features (must be present)	Important features (seen in most cases, adding support to the diagnosis)	Associated features (These clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used for defining or detecting AD for research and epidemiological studies.)	Exclusionary conditions (It should be noted that a diagnosis of AD depends on excluding conditions.)
Pruritis	Early age of onset	Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)	Scabies
Eczema (acute, subacute, chronic)	Atopy	Keratosis pilaris/pityriasis alba/hyper-linear palms/ichthyosis	Seborrheic dermatitis
1. Typical morphology and age-specific patterns ^a	1. Personal and/or family history	Ocular/periorbital changes	Contact dermatitis (irritant or allergic)
2. Chronic or relapsing history	2. Immunoglobulin E reactivity	Other regional findings (e.g., perioral changes/periauricular lesions)	Ichthyoses
	Xerosis	Perifollicular accentuation/lichenification/prurigo lesions	Cutaneous T-cell lymphoma
			Psoriasis
			Photosensitivity dermatoses
			Immune deficiency diseases
			Erythroderma of other causes

Adapted from [6].

^aPatterns include: facial, neck, and extensor involvement in infants and children; current or previous flexural lesions in any age group; sparing of the groin and axillary regions. AD, atopic dermatitis.

The importance of the skin barrier in atopic patients has recently been elucidated with mutations in filaggrin, a key structural protein in the outermost layer of the skin, impacting stratum corneum function. The intact stratum corneum is a physical barrier that prevents the loss of moisture through the epidermis, and prevents microbial colonization and secondary infection [10]. A loss-of-function mutation of *filaggrin* (*FLG*) encoding for filaggrin protein is considered the most significant genetic risk factor leading to the development of AD [11]. Filaggrin's association with AD was first identified in a study assessing an Irish population in 2006, and has since been consistently replicated in over 30 different, independent studies [12].

Despite filaggrin's importance, the genetic factors playing a role in the development of AD are still being uncovered. Recently, for example, Margolis *et al.* reported an association of thymic stromal lymphopoietin (TSLP) variant with disease remission in children with AD, especially in those with *FLG* mutations. TSLP promotes dendritic cell-mediated T-helper type 2 inflammatory responses, which are thought to be pathogenic for AD [13²²]. These new findings suggest that TSLP could be another important consideration, with the potential to influence the effects of *FLG* mutations in patients with AD [14].

Like most genetic conditions, environmental factors also affect the course of AD. Climatic influences on the prevalence of AD were highlighted in a merged analysis of the 2007 National Survey of Children's Health and the 2006–2007 National Climate Data Center and Weather Service [15²]. The study found a significantly lower prevalence of pediatric eczema in areas of the country with lower precipitation and less indoor heating, higher mean temperatures, higher ultraviolet (UV) index, and higher relative humidity. The most dominant combinations of climate variables in the United States were also analyzed. The combination of high temperature and UV exposure was found to be protective against AD. Interestingly, although higher humidity was shown to have an overall protective effect against AD as an isolated variable, most likely by improving skin barrier function, areas with high humidity combined with high precipitation and low UV index were associated with increased eczema prevalence [15²]. This discrepancy is likely because areas of the country with rainy climate have decreased UV exposure from clouds, with residents spending more time indoors exposed to low indoor humidity from heating.

COMORBIDITIES

It is well established that AD is associated with certain allergic comorbidities such as asthma,

allergic rhinitis/rhinoconjunctivitis, and food allergies [16]. The 'atopic march' is the notion that AD often precedes the development of the other allergic conditions. Estimates reveal that, among children with AD, one-third of children go on to develop asthma and two-thirds eventually develop allergic rhinitis [11,17]. In certain mouse models, TSLP has been implicated as a crucial contributor to the atopic march [18–20]; however, this has yet to be studied in humans. Although AD often precedes the other atopic conditions, it is still unclear how eczema might influence their development [21²]. For healthcare practitioners managing patients with AD, however, the importance of the atopic march lies in educating patients and their families about the possibility of developing these allergic comorbidities in the future.

More recently, studies have pointed to an association between AD and nonallergic conditions. A review of systematic reviews revealed that individuals with current or previous AD had reduced risks of acute lymphoblastic leukemia, meningioma, and gliomas. Furthermore, no association was found between AD and diabetes mellitus type I or multiple sclerosis [22].

Among the nonatopic comorbidities, strong data have emerged highlighting an association between AD and the neurobehavioral disorder of attention deficit hyperactivity disorder (ADHD), the most frequent psychiatric disorder in children, with an estimated prevalence of approximately 5.0% [23]. In 2009, the possible connection between the two conditions was first reported by Schmitt *et al.* [24] in a correlational study utilizing a healthcare database of 600 000 individuals from Germany. Since then, the independent association between AD and ADHD has been confirmed by several studies [25,26], most recently, in a systematic review of 20 studies addressing the association [27].

A dose-dependent relationship between AD and certain comorbidities has been suggested. Analyzing approximately 90 000 children between the ages of 0 and 17 years, Yaghamaie *et al.* showed that more severe eczema is correlated with poorer overall health, impaired sleep, and increased healthcare utilization as compared with children with mild or moderate AD. Moderate and severe AD was associated with higher rates of ADHD proportionate to the severity [28²²]. In addition to ADHD, the study also pointed to a link between eczema and other mental health disorders, including depression, anxiety, and autism [28²²].

To date, the majority of studies that have examined and assessed the relationship between AD and nonallergic comorbidities have been cross-sectional or case–control studies. Prospective studies

are still needed to better define and understand the relationship of AD with these other conditions. Yet, the possible link should serve as an impetus for all healthcare practitioners to better manage children with AD.

TOPICAL ANTI-INFLAMMATORY MEDICATIONS

Topical corticosteroids (TCS) remain the cornerstone of treatment for AD. Despite their history and proven efficacy, issues with adherence and undertreatment remain a major obstacle for healthcare professionals managing patients with the condition. Steroid phobia, or the fear of the use of corticosteroids, is a well-documented phenomenon among patients and caregivers. In a survey-based study, close to 75% of patients were worried about using TCS on their own or their child's skin, and 24% admitted to being noncompliant because of these fears [29]. Despite a side-effect profile that includes skin atrophy, telangiectasia, striae, and Cushing's syndrome, appropriate use among patients can greatly minimize occurrence. Furthermore, several studies have been conducted to illustrate the safety profile of TCS, all of which have concluded that hypothalamic-pituitary-adrenal axis suppression is very rare in children when utilizing mild or moderately potent TCS [30–32]. Directly addressing patients' misconceptions about TCS use is essential to get their AD under control.

Since their approval in 2000–2001, topical calcineurin inhibitors (TCIs) have become important medications in the treatment of AD, especially for the use of sensitive areas of the body (e.g., face, groin, and armpit region) and for long-term use in maintenance therapy, in which the risk of side-effects from TCS becomes more pronounced. Two TCIs are available, topical tacrolimus ointment (0.03% and 0.1% strengths) and pimecrolimus cream (1% strength). Tacrolimus is approved for moderate-to-severe disease, whereas pimecrolimus is indicated for mild-to-moderate AD. The most common side-effects seen are local reactions including burning and stinging. These two symptoms are more frequent in TCIs than in TCS, but tend to lessen in severity after multiple applications or when first preceded by a short period of TCS use [33].

A meta-analysis of 25 randomized controlled trials (RCTs) found tacrolimus 0.1% to be as effective as the mid-potency TCS hydrocortisone butyrate 0.1%, whereas tacrolimus 0.03% is less effective than hydrocortisone butyrate 0.1% but more effective than the low-potency TCS hydrocortisone acetate 1% [34]. Pimecrolimus cream has not been directly compared with low-potency TCS, but is less

effective than mid-potency and high-potency TCS [34,35].

In 2006, a boxed warning was placed on both TCIs (tacrolimus and pimecrolimus) secondary to a theoretical risk of malignancy such as lymphoma and skin malignancies. Several professional societies, including the American Academy of Dermatology and American Academy of Allergy, Asthma, and Immunology, have criticized the warnings. The academies contending that: the label was based on animal studies not translatable to humans; the incidence of lymphoma in TCI-treated patients was no greater than that in the general population; and the risk–benefit ratio had not been appropriately assessed [36]. In fact, since the boxed warning, the number of lymphomas and malignancies observed in postmarketing surveillance and reported to the Food and Drug Administration is considerably lower among patients exposed to TCI as compared with the expected number for the general population [37]. As such, there is currently no evidence for a causal relationship between TCI use and malignancy, which may be highlighted when counseling patients about the risk-to-benefit ratio of TCI use.

BLEACH BATHS

The most common secondary complication of poorly controlled AD is superinfection of atopic skin by *Staphylococcus aureus*. Traditionally, management of infected atopic skin has relied solely on treatment with topical and/or oral antibiotics. With the development of resistant strains such as methicillin-resistant *S. aureus* and concerns of antibiotic overuse by healthcare providers, adjuvant therapies for the treatment of infected skin have been explored [38]. Clinically, diluted bleach (sodium hypochlorite) baths have been shown to reduce the need for systemic antibiotics in patients with AD, especially in those who are heavily colonized or who have superinfected skin [39].

In a randomized, placebo-controlled study of 42 subjects, 18 individuals bathed in dilute bleach for 10 min, twice a week for 2 months. This treatment arm had significantly reduced Eczema Area and Severity Index scores, a validated method of assessment in clinical studies of AD. Moreover, there was a 41.9% reduction in *S. aureus* density from baseline at 1 month [40]. Bleach baths may therefore be helpful in cases of moderate-to-severe disease. Furthermore, in contrast to topical and oral antibiotics, the use of bleach baths is unlikely to lead to the development of bacterial resistance.

Interestingly, the effectiveness of bleach baths may rely on a mechanism of action other than

sodium hypochlorite's antimicrobial qualities. Leung *et al.* recently showed that, in primary human keratinocytes, hypochlorite inhibited two important genes of nuclear factor- κ B, which regulates inflammatory responses in the skin. Furthermore, in mice with acute radiation dermatitis, topical hypochlorite not only inhibited the expression of nuclear factor- κ B but also reduced disease severity and prevented skin ulceration [41].

Commercially available alternatives to bleach are available and include sodium hypochlorite body wash (CLN Body Wash by TopMD Skin Care Inc., Dallas, Texas, USA), hypochlorous acid (Aurstat by Onset Dermatologics, Cumberland, Rhode Island, USA), and microcyn-based antipruritic hydrogel and sprays (Atapro by Quinova Innovative Sciences, Inc., Jamison, Pennsylvania, USA).

PROACTIVE TREATMENT STRATEGIES

The traditional 'reactive' approach for managing patients with AD entails the use of TCS and/or TCIs during clinically evident flares marked by erythematous and eczematous plaques with intense pruritis, excoriations, and lichenification. Although this 'as needed' method works to control the flares, ultimately the patient relapses, as there is no preventive focus. With new insights from both basic science and clinical research, a proactive approach has been adopted by many for the treatment of AD. The reason for this change stems from the new understanding that the previously described periods of quiescence of the disease may actually be characterized by subclinical inflammation not seen by the naked eye. In nonlesional AD skin, histopathological differences still remain, including reduced long-chain fatty acids in the lipid bilayer of the stratum corneum [42], increased density of IgE receptors on the surface of the epidermal Langerhans cells [43], and activation of the venules as well as low-grade lymphocytic infiltration [44]. Therefore, proactive therapy (e.g., the application of TCS or TCIs for 2 days a week to normal-appearing skin that might otherwise flare) is a useful strategy to prevent flares in patients with moderate to severe eczema whose disease is initially controlled [45]. In a systematic review assessing proactive therapy by Schmitt *et al.*, all eight studies included compared TCS with vehicle or TCIs with vehicle. The meta-analysis performed by the authors showed that both TCS and TCIs were superior to vehicle in preventing flares [46].

CONCLUSION

We have made great progress in our understanding of the diagnosis, pathogenesis, comorbidities,

and treatment options available for AD. As we continue to better elucidate the pathophysiology of AD, therapeutic strategies that directly target these factors can be developed via basic, translational, and clinical research. Recently, increased *FLG* expression in human and murine keratinocytes attenuated the development of AD-like skin inflammation in mice, suggesting that regulation of *FLG* expression can be a therapeutic target for AD [47[■]]. The potential for biological agents that target pathogenic molecules in AD indicates a promising future for both AD sufferers and the healthcare practitioners who manage them.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest for C. Totri and L. Diaz. Dr. Eichenfield has served as an investigator and consultant to Astellas Pharma, Valeant Pharmaceuticals, and TopMD Skin Care, Inc.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Horii KA, Simon SD, Liu DY, Sharma V. Atopic dermatitis in children in the United States, 1997-2004: visit trends, patient and provider characteristics, and prescribing patterns. *Pediatrics* 2007; 120:e527–e534.
2. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011; 131:67–73.
3. Valeant Pharmaceuticals North America. Data on file, 2012.
4. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; 92:44–47.
5. Rudzki E, Samochocki Z, Rebandel P, *et al.* Frequency and significance of the major and minor features of Hanifin and Rajka among patients with atopic dermatitis. *Dermatology* 1994; 189:41–46.
6. Eichenfield LF, Hanifin JM, Luger TA, *et al.* Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 2003; 49:1088–1095.
7. Ebell MH, Siwek J, Weiss BD, *et al.* Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004; 69:548–556.
8. Eichenfield LF, Tom WL, Chamlin SL, *et al.* Guidelines of care for the management of atopic dermatitis: Section 1 Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol* 2014; 70:338–351.

A work group of recognized AD experts identified the most important questions in the diagnosis and assessment of AD. A systematic search of several databases was utilized in order to provide an evidence-based model for the most up-to-date guidelines for AD.

9. Levin J, Friedlander SF, Del Rosso JQ. Atopic dermatitis and the stratum corneum: part 1: the role of filaggrin in the stratum corneum barrier and atopic skin. *J Clin Aesthet Dermatol* 2013; 6:16–22.
10. Cork MJ, Danby SG, Vasilopoulos Y, *et al.* Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol* 2009; 129:1892–1908.
11. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med* 2011; 365:1315–1327.
12. Brown SJ, McLean WH. One remarkable molecule: filaggrin. *J Invest Dermatol* 2012; 132:751–762.
13. Margolis DJ, Kim B, Apter AJ, *et al.* Thymic stromal lymphopoietin variation. ■ Filaggrin loss of function, and the persistence of atopic dermatitis. *JAMA Dermatol* 2014; 150:254–9.

A prospective cohort study utilizing approximately 800 children found that certain TSLP variations were associated with less-persistent disease, suggesting TSLP may be a therapeutic target for AD. Further studies that provide functional investigations and fine-mapping of TSLP protein are still needed.

14. Wang WL, Li HY, Zhang MS, *et al.* Thymic stromal lymphopoietin: a promising therapeutic target for allergic diseases. *Int Arch Allergy Immunol* 2013; 160:18–26.
 15. Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol* 2013; 133:1752–1759.
- This cross-sectional study is important because it highlights the complex pathophysiology driving AD with specific climatic factors affecting the US prevalence of AD.
16. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003; 112 (6 Suppl):S118–S127.
 17. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol* 2007; 120:565–569.
 18. Zhang Z, Hener P, Frossard N, *et al.* Thymic stromal lymphopoietin overproduced by keratinocytes in mouse skin aggravates experimental asthma. *Proc Natl Acad Sci U S A* 2009; 106:1536–1541.
 19. Demehri S, Morimoto M, Holtzman MJ, Kopan R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. *PLoS Biol* 2009; 7:e1000067.
 20. Han H, Xu W, Headley MB, *et al.* Thymic stromal lymphopoietin (TSLP)-mediated dermal inflammation aggravates experimental asthma. *Mucosal Immunol* 2012; 5:342–351.
 21. Dharmage SC, Lowe AJ, Matheson MC, *et al.* Atopic dermatitis and the atopic march revisited. *Allergy* 2014; 69:17–27.
- This study provides further confirmation of the notion of the atopic march, (i.e., the association of AD with other allergic comorbidities) with evidence from both human and animal studies supporting a biological mechanism. Yet, more research is necessary to identify effective approaches to decrease the burden of allergic conditions on patients.
22. Deckert S, Kopkow C, Schmitt J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. *Allergy* 2014; 69:37–45.
 23. Polanczyk G, Silva de Lima MS, Horta BL, *et al.* The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry* 2007; 164:942–948.
 24. Schmitt J, Romanos M, Schmitt NM, *et al.* Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. *JAMA* 2009; 301:724–726.
 25. Romanos M, Gerlach M, Warnke A, Schmitt J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health* 2010; 64:269–273.
 26. Tsai JD, Chang SN, Mou CH, *et al.* Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study. *Ann Epidemiol* 2013; 23:185–188.
 27. Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. *Allergy* 2010; 65:1506–1524.
 28. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013; 131:428–433.
- The dose-dependent relationship of AD and mental health comorbidities indicates that the potential consequences of uncontrolled AD have now expanded to areas not traditionally associated with AD. Prospective studies are needed to confirm that the severity of AD changes the strength of association, and to investigate potential mechanisms underlying the relationship between AD and mental health conditions.
29. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol* 2000; 142:931–936.
 30. Crespi HG. Topical corticosteroid therapy for children: alclometasone dipropionate cream 0.05%. *Clin Ther* 1986; 8:203–210.
 31. Paller AS, Nimmagadda S, Schachner L, *et al.* Fluocinolone acetonide 0.01% in peanut oil: therapy for childhood atopic dermatitis, even in patients who are peanut sensitive. *J Am Acad Dermatol* 2003; 48:569–577.
 32. Eichenfield LF, Basu S, Calvaresi B, Trancik RJ. Effect of desonide hydrogel 0.05% on the hypothalamic-pituitary-adrenal axis in pediatric subjects with moderate to severe atopic dermatitis. *Pediatr Dermatol* 2007; 24:289–295.
 33. Carr VVW. Topical calcineurin inhibitors for atopic dermatitis: review and treatment recommendations. *Paediatr Drugs* 2013; 15:303–310.
 34. Frankel HC, Qureshi AA. Comparative effectiveness of topical calcineurin inhibitors in adult patients with atopic dermatitis. *Am J Clin Dermatol* 2012; 13:113–123.
 35. Ashcroft DM, Dimmock P, Garside R, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; 330:516.
 36. El-Batawy MM, Bosseila MA, Mashaly HM, Hafez VS. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Sci* 2009; 54:76–87.
 37. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence update with implications for daily practice. *Am J Clin Dermatol* 2013; 14:163–178.
 38. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics* 2008; 122:812–824.
 39. Barnes TM, Greive KA. Use of bleach baths for the treatment of infected atopic eczema. *Australas J Dermatol* 2013; 54:251–258.
 40. Wong SM, Ng TG, Baba R. Efficacy and safety of sodium hypochlorite (bleach) baths in patients with moderate to severe atopic dermatitis in Malaysia. *J Dermatol* 2013; 40:874–80.
 41. Thomas H Leung, Lillian F Zhang, Jing Wang, *et al.* Topical hypochlorite ameliorates NF- κ B-mediated skin diseases in mice. *J Clin Invest* 2013; 123:5361–5370. doi:10.1172/JCI70895.
 42. Macheleidt O, Kaiser HW, Sandhoff K. Deficiency of epidermal protein-bound omega-hydroxyceramides in atopic dermatitis. *J Invest Dermatol* 2002; 119:166–173.
 43. Wollenberg A, R  wer HC, Schaubert J. Innate immunity in atopic dermatitis. *Clin Rev Allergy Immunol* 2011; 41:272–281.
 44. Mihm MC Jr, Soter NA, Dvorak HF, Austen KF. The structure of normal skin and the morphology of atopic eczema. *J Invest Dermatol* 1976; 67:305–312.
 45. Williams HC. Preventing eczema flares with topical corticosteroids or tacrolimus: which is best? *Br J Dermatol* 2011; 164:231–233.
 46. Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol* 2011; 164:415–428.
 47. Otsuka A, Doi H, Egawa G, *et al.* Possible new therapeutic strategy to regulate atopic dermatitis through upregulating filaggrin expression. *J Allergy Clin Immunol* 2014; 133:139–146; e10..
- This basic science study is the first of its kind to report that a compound that promotes increased *FLG* expression improved AD-like skin inflammation in mice. Although these are encouraging results, more studies are needed in order to better define the therapeutic strategy to upregulate filaggrin expression.