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Optimizing outcomes for paediatric atopic dermatitis

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Summary

Atopic dermatitis (AD) is considered the most prevalent chronic inflammatory condition in very young children, with a prevalence approaching 20% in some industrialized countries. Recent advances in the understanding of the aetiology and pathogenesis of AD – particularly in relation to genetically

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determined skin barrier dysfunction and the role of microbial infections in AD flares – have helped to galvanize thinking on approaches to treatment in young patients. Topical anti-inflammatory medicines (corticosteroids and calcineurin inhibitors) in addition to emollients are the mainstay of therapy in children, but parents need help to understand how and when to apply them and reassurance to allay their fears about the long-term effects of these treatments. At the same time, more work is required in order to identify which clinical signs, symptoms, long-term control of flares, and quality of life measures are the best outcome domains for AD clinical trials in order to continue to improve control of AD in children.

Atopic dermatitis (AD) is considered to be the most prevalent chronic inflammatory condition in children. In the U.S.A. and other industrialized countries, the estimated prevalence of AD is between 10% and almost 20% in the first few years of life, with persistence into adulthood in 1–3% of individuals.¹ In the past few years, new advances in research have helped strengthen our understanding of the epidemiology and pathogenesis of AD, the effects of microbial colonization and infection, the comorbidities associated with AD, and treatment strategies. This article aims to review this new information as it relates to improving outcomes in paediatric AD.

Atopic dermatitis outcomes

When managing patients, clinicians must consider what the end results of disease processes and treatments actually are. Depending on medical therapy, the outcomes can vary dramatically from decreasing symptoms, to minimizing secondary complications of the disease process, to completely curing the patient.

Paediatric patients with AD and their families usually have idealistic outcomes in mind, and naturally desire a cure for their condition. At the very minimum, they would like sustained remission of any associated symptoms and avoidance of any complications associated with AD. In addition, they desire convenient medications that do not have side-effects and require very infrequent administration.

With their background understanding of the disease, physicians tend to have more pragmatic expectations of what is considered to be a good outcome. They have similar desires, such as sustained remissions and minimal disease impact on individuals and families, but they have to balance these against the realities of practical treatment strategies for families and the toxicities associated with currently available treatments.

Desired ‘best outcomes’ for children with AD would be short duration of disease with minimal impact of the disease on the individual, along with minimum development of associated comorbidities. Good outcome measures should be valid, reliable, clinically meaningful, and responsive to interventions. These measures, while designed for clinical studies, should reflect what patients consider important in the signs, symptoms and quality of life impact of AD. An international consortium has been working to define and delineate useful outcome measures for AD research,² a process that has not been completed as of this time. Aspects influencing approaches to managing paediatric AD to achieve these goals are discussed below.

Pathogenesis and barrier dysfunction

Historically, immune dysregulation, infection, allergy and pruritus have all been suggested to be involved in the pathogenesis of AD. More recently, the identification of mutations in the filaggrin gene (*FLG*) in patients with AD has placed an emphasis on barrier dysfunction. *FLG* encodes an important epidermal protein abundantly expressed in the outer layers of the epidermis.³ Research has consistently shown that a significant percentage of patients have intrinsic barrier defects based on a variety of genetic mutations. In the last decade, *FLG* mutations have been shown to have the strongest predictive value for any complex genetic trait in the skin. Patients with both quantitative and qualitative mutations in *FLG* manifest clinically with drier skin. Functionally, patients with filaggrin deficiency manifest with decreased natural moisturizing factor and increased epidermal permeability, causing loss of the natural acidic pH in the skin. These changes ultimately result in disrupted cell cohesion and increased skin permeability.⁴ *FLG* defects have also been associated with increased rates of asthma, allergic rhinitis, immunoglobulin E (IgE) sensitization, and more severe AD that persists into late childhood and adulthood.

Studies have shown that there are many variations in *FLG* mutation rates among different populations. Studies in the Irish population showed that there are five very common recurrent *FLG* mutations, all of which are associated with ichthyosis vulgaris and AD. Other populations have different sets of *FLG* mutations. In addition, instead of having a few highly prevalent mutations as in the Irish, the Singaporean Chinese population have larger numbers of *FLG* mutations, each at a lower frequency.⁵ These types of variation throughout the world have been termed 'ethno-specific profiles'.

In the U.S.A., Margolis *et al.*⁶ evaluated DNA from 857 children and found that, overall, 16.3% of them showed *FLG* mutations, while only 5.8% of African-American children had detectable *FLG* mutations. Importantly, those children with identified mutations were more likely to have symptomatic skin. Patients with *FLG* mutations were 50% less likely to have skin free of AD symptomatology. Also, children with the *FLG* R501X mutation had a greater need for medications over time.⁶

From a clinical standpoint, advising patients with AD about general skin care (i.e. bathing practices and use of moisturizers) has long been known to improve barrier function and thus to have a huge impact on the disease. This standard has been reinforced by the recent literature on *FLG* mutations. However, not all experts agree in their recommendations for optimal bathing and moisturizing practices. As an example, some major centres (such as the Mayo Clinic) recommend infrequent bathing with the use of moisturizers as a standard intervention for AD.⁷ In contrast, the National Jewish Hospital (Denver, CO, U.S.A.) – among others – recommends once- or even twice-daily bathing for severe AD.⁸

A study conducted at the Rady Children's Hospital (San Diego, CA, U.S.A.) evaluated the impact of bathing and moisturizing sequences in skin hydration in both atopic and nonatopic individuals. Individuals participated in bathing and moisturizing regimens in a research setting. The regimens required soaking in water only (without emollient application), soaking followed by immediate emollient application, soaking and application of emollients 30 min later, and emollient application alone (without soaking). The study showed that bathing without subsequent application of emollient left the skin drier than prior to bathing, while emollient application either immediately following bathing or with a delay increased the hydration content of the skin. Importantly, emollient application without bathing had the highest hydration rate at the conclusion of the 2-h observation period.⁹ While

bathing frequency recommendations vary, from a practical standpoint, use of moisturizers after bathing and at least daily is a core component of therapy for AD.

Microbial colonization and infection in atopic dermatitis

The advent of new genome-based research techniques has brought enormous insight into how microbes colonize the skin of patients with AD. Traditionally, basic bacterial culture techniques were utilized for this purpose, but these permitted only a selected group of microbes to be grown and studied. For example, bacterial culture provided good evidence that *Staphylococcus aureus* is an important organism in AD. *S. aureus* is associated with high rates of colonization and infection, and is responsible for impetiginized dermatitis and pustules. Currently, however, individual 'genetic signatures' for a broad set of skin-dwelling microbes are being used to evaluate the entire skin microbiome.

Studies by Grice *et al.*¹⁰ have shown that there is a tremendous diversity of micro-organisms on normal skin. These organisms vary according to body site and local environment. For instance, different sets of organisms inhabit sebaceous and moist sites and dry sites on the body.¹⁰ Studies have also looked at changes in a patient's microbial fauna during a flare compared with during quiescent periods. In the absence of active flares, there is a great diversity of organisms present. During active flaring, however, there is a decrease in microbial variety and an increase in *S. aureus* as it becomes the most prevalent organism on the affected skin. The question of whether the loss in microbial diversity is due to *S. aureus* replacing the other resident flora, or whether there is simply overgrowth of *S. aureus* with persistence of the resident skin flora remains to be answered. Furthermore, it is unclear whether it is the presence of *S. aureus* that is driving the flares, or whether the dermatitis itself is changing the colonization.¹¹ From a clinical standpoint, it is generally recommended that infected dermatitis be treated with systemic, or occasionally, topical antimicrobial medication. In noninfected AD, broad use of antibiotics is not indicated. In fact, appropriate bacterial stewardship is reasonable to help prevent bacterial resistance.

In the next 5–10 years it is expected that more data on the changing skin microbiome (specifically in the neonatal and early childhood years) will become available. Oh *et al.*¹² have examined the skin in the context of changes seen with sexual maturation according to Tanner stages. In their study, the microbial communities at body sites that are often involved in inflammatory and infectious skin diseases were significantly different in children and adults. Interestingly, the incidence of *S. aureus* in the nares of younger individuals (Tanner groups 1–3) was higher than that seen in older individuals. Ultimately, these so-called maturation-dependent shifts in the skin microbiome may be playing a significant role in the development and course of AD, and this may have implications for future treatments.¹²

There is also interest in gut colonization and how it might impact cutaneous colonization and inflammation in AD. The potential link between gut colonization and AD may impact on the consideration of probiotics and prebiotics for AD. There is some evidence that, in certain populations, some probiotics and prebiotics may have a preventive effect,¹³ but further studies are required to

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confirm this. On the other hand, to date, there is insufficient evidence to support the use of probiotics and prebiotics in patients with established AD.

Comorbidities in atopic dermatitis

Within the last few years, research has highlighted an expanded set of comorbidities that extend beyond the traditional atopic comorbidities associated with AD and include behavioural and psychological conditions. Studies have shown that there are higher rates of depression, anxiety and conduct disorder among patients with AD. Furthermore, there are some data that associate autism with AD.¹⁴

Attention-deficit/hyperactivity disorder (ADHD) was first reported in children with AD by Schmitt *et al.* in 2009.¹⁵ A recent epidemiological study by Yaghmaie *et al.*,¹⁴ drawing from a database of 90 000 children, found similar higher rates of ADHD in patients with paediatric AD. Interestingly, they found a 'dose-dependent' relationship. Patients with more severe AD had higher rates of ADHD compared with those with less severe AD or without AD.¹⁴ This emerging evidence should reinforce physicians' conviction to aggressively treat AD, and it is hoped that further research may guide strategies in eczema care that will minimize these secondary comorbidities.

Recently, Deckert *et al.*¹⁶ published an overview of systematic reviews on nonallergic comorbidities of AD. Utilizing only systematic reviews in their inclusion criteria, they found a consistent positive association between AD and ADHD. Of the nine systematic reviews examined, six found an association between cancer and AD: a decreased risk of acute lymphoblastic leukaemia, glioma and meningioma was found in patients with current or previous AD. Based on cross-sectional and case-control studies, there was no significant association between AD and multiple sclerosis or type 1 diabetes mellitus.¹⁶

Principles of therapy

Bleach baths

In recent years, there has been data to show that bleach baths may be useful as adjuvant therapy in AD. The use of bleach baths is not new; in fact, their use goes back to the First World War. British chemist Henry Dakin and French surgeon Alexis Carrel developed the Carrel-Dakin method of irrigating wounds with Dakin's solution, a combination of 0.4–0.5% sodium hypochlorite and 4% boric acid. The concept of the therapeutic use of bleach baths for AD developed over many years amid anecdotal reports from physicians that their patients improved when swimming in chlorinated pools. In 2009, Jennifer Huang and coworkers¹⁷ were able to show that patients with AD who took bleach baths twice weekly along with concurrent intranasal mupirocin had a significant reduction in Eczema Area and Severity Index (EASI) scores, from baseline to month 1 and month 3 compared with the placebo group. Patients in both arms had received oral cephalexin for 14 days prior to the intervention.¹⁷ Some recommendations for dilutions of bleach products for tub soaks are listed in Table 1.

There are several commercially available bleach-based preparations which include sodium hypochlorite body wash (CLn Body Wash® by TopMD®), sodium hypochlorite and hypochlorous acid

(Aurstat® by Onset Dermatologics) and microcyn-based antipruritic hydrogel and sprays (Atapro® by Quinnova Innovative Sciences, Inc.) that may also be effective antimicrobials.

Anti-inflammatory therapy

Inflammation is a significant component of AD, and topical anti-inflammatory medications – such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs) – serve as a cornerstone of therapy. They control inflammation, minimize skin eruption and reduce pruritus. There is a long history of use of these medications for acute disease and for the management and prevention of flares. It is reasonable to assume that, over time, adequate disease control can diminish the impact of the disease on the individual. Studies are still needed to investigate whether early therapeutic intervention that yields excellent and timely control of the disease can impact the overall disease course. Similarly, more research is needed to assess if therapies such as phototherapy and systemic therapy, reserved for more severe and refractory disease, have any disease-modifying effects beyond their short-term benefits.

Adherence in atopic dermatitis

With aggressive use of TCS playing such a critical role in the treatment of AD, adherence is essential for successful outcomes. In general, nonadherence to medications is very common in medicine. Clinicians most often rely on subjective reports from the patient and/or their carers to determine if medication is being used as prescribed. In the absence of reliable tools, Steven Feldman *et al.*¹⁸ have sought to dependably assess patient adherence to topical medications in AD. They conducted a study in which paediatric subjects were prescribed topical triamcinolone 0.1% ointment to be applied twice daily. The medication was provided in a bottle fitted with a Medication Event Monitoring System (MEMS) cap. The MEMS cap is a powerful tool because it contains a microprocessor that is able to record the exact number of times that the bottle is opened. Twenty-six children completed the 8-week study and the technology showed that mean adherence throughout this period was 32%. As a trend, adherence was highest on or near clinic visits with rapid drops in adherence thereafter.¹⁹ The tendency for medication adherence to be maximal around the time of clinic visits is a phenomenon known as ‘white coat compliance’.¹⁸

Nonadherence has been clearly shown to be a setback in AD treatment. Naturally, then, understanding the rationale for patient nonadherence is important in order to minimize recurrence in the future. While reasons vary from patient to patient, some common explanations include the complexity of drug regimens, simple forgetfulness by the patient and the carers, and general fear of the medication side-effect profile. In AD, with the common use of TCS, steroid phobia is a major reason for nonadherence among patients. As an illustrative example, Charman *et al.*²⁰ showed that 72.5% of patients or parents of children with AD were worried about using topical steroids and 24% admitted to nonadherence.

Among patients and even some healthcare practitioners, there are many misconceptions that contribute to the prevalent fear of TCS. This confusion partly stems from the numerous factors that affect the absorption of the TCS and, consequently, the variable risk of systemic side-effects. These include the actual drug molecule, the vehicle, the application site and the duration of use. In the paediatric population, the patient’s body surface area is an important consideration as a higher ratio of

skin surface area to body mass puts infants and children at greater risk of TCS side-effects than their adult counterparts.²¹

Topical corticosteroids in children: safety studies

The local side-effects of TCS are well known and include skin atrophy, striae, rosacea, perioral dermatitis, acneiform eruptions and purpura. The true incidence of these toxicities with routine use is less well known.²⁰ Hong *et al.*²² sought to study the atrophogenic potential of TCS with varying potency in children requiring long-term use. Only children with good disease control (as measured by a maximum EASI score of 1.0) were included. There was no significant atrophy in any of the 70 children exposed to TCS or in 22 TCS-naïve children in the study, illustrating that when used appropriately, even in the long term, TCS skin atrophy is very rare in children.²²

Although less common than local side-effects, the systemic consequences of TCS are often more concerning to patients, their families and the treating clinicians. The literature is full of paediatric studies showing rare effects on the hypothalamic–pituitary–adrenal (HPA) axis following the use of various low to moderately potent steroids in 3–4 week courses (Table 2^{21–37}). With high-potency corticosteroids, HPA axis suppression can occur with greater frequency in children,³⁸ an important consideration all clinicians should be aware of. The results from observational studies examining growth retardation with the use of TCS are mixed, with some reporting effects on growth while others showing no significant effects.²⁰ Growth retardation is usually clinically insignificant, and children experience catch-up growth after the discontinuation of the TCS.³⁹

Therapeutic patient education

The obstacles of steroid phobia and the chronicity of AD create a great demand for approaches that can minimize patient and family concerns and improve adherence. The therapeutic patient education (TPE) movement for AD has been developing over the past decade. TPE, which has been utilized in other chronic medical conditions such as asthma, is based on the notion that for many such diseases, education limited to handouts and brief explanations of the disease may not be an adequate strategy.⁴⁰ According to the World Health Organization (WHO), individuals with chronic conditions need to acquire and maintain skills in order to manage their life in the best possible way.⁴¹ TPE is especially applicable for those with severe disease, diminished quality of life, and lack of therapeutic adherence.

In practical terms, TPE can be used in several different ways to improve adherence and, ultimately, outcomes. For example, it is crucial to have a discussion about steroid strengths and safety with paediatric patients and their families. In our own paediatric dermatology practice, we have found it useful to emphasize the specific quantity of TCS that we expect patients to use over a period of time (i.e. ‘We would like you to use the whole 80 g tube of triamcinolone 0.1% ointment over the next 2 weeks.’) In this context, it is emphasized that used in this particular way, TCS are safe.

Recently, the use of a ‘reactive and proactive’ approach to AD therapy has been highlighted in the literature. The traditional approach to therapy has been the application of anti-inflammatory medications at the first signs of an acute flare, with tapering and complete discontinuation once the

eczematous lesions are no longer visible to the naked eye. This so-called 'reactive approach' has been augmented with the notion that flare prevention is important in eczema therapy, especially in moderate-to-severe persistent and/or frequently flaring AD. As illustrated above, both subclinical inflammation and barrier dysfunction in AD skin persists even after skin flares. During quiescent periods, 'proactive therapy', in the form of long-term emollient treatment along with intermittent application of low-dose anti-inflammatory medications (either TCS or TCIs) to previously affected skin is recommended.⁴²

The utility of proactive therapy in AD has been evaluated in several studies. Thaçi *et al.*⁴³ conducted a multicentre, randomized study to determine the efficacy of twice-daily proactive application of 0.03% tacrolimus ointment. Children in remission (disease-control period), as assessed by an investigator global assessment score of ≤ 2 , were randomized to receive the tacrolimus or vehicle ointment twice weekly for 1 year. It was found that application of 0.03% tacrolimus ointment twice weekly was effective in preventing, delaying and decreasing the occurrence of AD flares.⁴³ A study of three-times weekly tacrolimus 0.03% ointment in children and adolescents showed similar findings with increased disease-free days and longer times to relapse vs. vehicle ointment.⁴⁴

A systematic review and meta-analysis conducted in 2010 (and published in 2011) by Schmitt *et al.*⁴⁵ reviewed the literature on proactive treatment. Eight vehicle-controlled trials, each of which utilized proactive therapy with topical tacrolimus, fluticasone propionate or methylprednisolone aceponate, were included. All three agents were found to be efficacious for proactive therapy; it was suggested that topical fluticasone propionate might be more efficacious than topical tacrolimus, although further studies are needed to confirm this.⁴⁵

Educating children with AD and their families about the usefulness of proactive therapy can prove to be greatly beneficial. From a patient perspective, this dual approach means that the disease no longer controls the patient's actions, but that the patient is actively controlling the disease.⁴⁶ Use of educational instructional materials – such as written action plans, websites, video training modules, texts, emails and software applications – are useful and creative ways to reinforce education and incorporate TPE in clinical practice.

Conclusion and future directions

As the understanding of AD continues to evolve, advances in outcome measures are also required to ensure that clinicians can be confident that they are basing their practice on the best evidence in paediatric dermatology. There is a global initiative to improve outcome measures in AD, which has generated a significant amount of medical literature on the need to have the best methodologies to show outcomes. The Harmonization of Outcomes Measures in Eczema (HOME) is a group with more than 180 members worldwide, which includes patients, clinicians, methodologists and pharmaceutical companies. The goal of the group is to define what the most appropriate core measures of AD in clinical studies should be. The measures must be valid, reliable and feasible in clinical trials.⁴⁷ At the same time, instruments need to measure outcomes that are important to patients, families and clinicians alike. Ongoing work to identify what clinical signs, symptoms, long-term control of flares, and quality of life measures are the best outcome domains for AD clinical trials must continue.

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With reliable disease measures, new therapies, and improved understanding of the pathogenesis of AD, it is hoped that treatment and clinical outcomes in paediatric AD can improve.

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Table 1. Commonly used bleach bath preparations^a

Sodium hypochlorite (%)	Volume required (mL)	Volume required (cups)	Volume of bathwater (bathtub = 51–227 L; 40–60 gallons)
0.009 (90 ppm)	~ 60	¼	¼ tub
0.019 (190 ppm)	~120	½	¼ tub
0.005 (50 ppm)	~60	¼	½ tub
0.009 (90 ppm)	~120	½	½ tub
0.005 (50 ppm)	~60	½	Full tub

^aBased on standard commercial 6% bleach preparations.

- To be done for 5–10 min, 2–3 times/week
- Infant tub 1–2 tsp/gallon; ~2 ml L⁻¹
- Swimming pool reference: 3 parts per million (available chlorine)

Table 2. Paediatric-specific studies assessing topical corticosteroid and hypothalamic–pituitary–adrenal axis suppression²¹

First author	Drug	Design; dose	Patients: <i>n</i> ; age	Test	Test results
Crespi ²⁵	Aclometasone cream	Open; twice daily × 3 weeks	39; NA	AM cortisol level	All normal
Dohil ²⁶	Fluocinolone acetonide 0.01% in peanut oil	Open; twice daily × 4 weeks	24; 3 months to 2 years	CST	All normal

Eichenfield ²⁷	Lipid-rich, moisturizing formulation of hydrocortisone butyrate 0.1%	MC, open; three times daily $\times$ 4 weeks	20; 5–12 years	CST	All normal
Eichenfield ²⁸	Desonide hydrogel 0.05%	MC, open; twice daily $\times$ 4 weeks	40; 6 months to 6 years	CST	One abnormal, complication in cortisol testing
Ellison ³⁸	Mild, moderate, and potent TCS	Cases of AD requiring TCS since infancy with 14 controls being investigated for short stature	35; 0.7–18.7 years	Plasma cortisol levels	No change for mild or moderate steroids, suppression in all four patients on potent/very potent steroids
Friedlander ²⁹	Fluticasone propionate cream 0.05%	MC, open; twice daily $\times$ 3–4 wks	51; 3 months to 5 years	CST	Two abnormal tests
Hanifin ³⁰	Mometasone cream; hydrocortisone cream	MC, parallel; $\times$ 3 weeks	62; 6 months to 2 years	CST	One abnormal test in mometasone arm
Hebert ³¹	Fluticasone propionate lotion 0.05%	MC, open; twice daily $\times$ 4 weeks	44; 3–71 months	CST	All normal
Hebert ³²	Desonide foam 0.05%	MC, open; twice daily $\times$ 4 weeks	75; 3 months to 17 years	CST	Three abnormal
Lucky ³³	Desonide 0.5%; hydrocortisone 2.5%	Open, parallel; twice daily $\times$ 4 weeks	20; NA	CST	All normal
Moshang ³⁴	Prednicarbate cream 0.1%	Open; twice daily $\times$ 3 weeks	55; 4 months to 12 years	CST	All normal
Paller ³⁵	Fluocinolone 0.01% in oil	MC, open; twice daily $\times$ 4 weeks	32; 2–12 years	CST	All normal

Patel ³⁶	Hydrocortisone 1%, 9 of 14 also used moderate potency TCS	Prepubertal AD cases with controls (prepubertal with constitutional short stature without AD, 3–10 years	14; 3.1–10.7 years	Plasma cortisol levels	Basal and peak normal but peak occurred early
Schlessinger ³⁷	Fluocinonide cream 0.1%	MC, open; once or twice daily × 2 weeks	126; 3 months to 18 years	CST	Three abnormal
Vernon ²³	Mometasone furoate 0.1%; hydrocortisone 1% cream	MC, blinded, randomized, parallel; mometasone once daily, hydrocortisone twice daily	48; 6 months to 12 years	AM cortisol level	One abnormal
Wolkerstorfer ²⁴	Fluticasone cream 0.05%; clobetasone butyrate 0.05%	Blinded, parallel; fluticasone once daily; clobetasol twice daily × when skin lesions were almost cleared (SCORAD < 9) or 4 weeks	22; 3–8 years	24-h urinary cortisol excretion, before and after treatment	All normal

AD, atopic dermatitis; TCS, topical corticosteroids; CST, cosyntropin stimulation test; MC, multicentre study; open, open label study; parallel, parallel study; SCORAD, SCORing of Atopic Dermatitis; NA, not available