TRIGGERS IN ATOPIC DERMATITIS/ECZEMA: SEPARATING FACT FROM FICTION

Kannenberg SM, MBChB, MMed (Derm), Jordaan HF, MBChB, MMed (Derm), M Akad SA

Correspondence:
Division of Dermatology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Academic Hospital
Email: surethak@sun.ac.za

ABSTRACT
Atopic dermatitis/eczema (ADE) is a common condition affecting up to 20% of children in some countries. Atopic dermatitis/eczema impairs quality of life, not only of the patient, but also of family members. Due to the increasing prevalence noticed in westernised populations since the 1940s, particular attention should be paid to triggers, which may be contributing to this rise. Identifying a trigger is fraught with difficulty due to the fluctuating natural course of ADE. Triggers of ADE include irritants (such as soap and detergents), allergens (including standard patch test defined allergens, aeroallergens and food allergens), skin infections (such as Staphylococcus aureus, group A streptococci, herpes simplex virus, malassezia and tinea infections) and others, including cigarette smoke exposure and psychological stress. Many commonly believed triggers, such as extreme temperatures and exposure to sand, have meagre supporting evidence. Nevertheless, they may aggravate the disease. The literature dealing with triggers is sparse. In this article an overview will be given regarding the relevant literature dealing with this difficult topic.

TRIGGER - AN EVENT THAT PRECIPITATES OTHER EVENTS.
This is the definition of a trigger according to thefreeonlinedictionary.com.

Atopic dermatitis/eczema (ADE) is a common condition affecting up to 20% of children in some countries. Atopic dermatitis/eczema impairs quality of life not only physically, but also financially and emotionally, of the patient and their families. Due to the increasing prevalence noticed in westernised populations since the 1940s, particular attention should be paid to triggers, which may be contributing to this rise.

Atopic dermatitis/eczema is a chronic inflammatory disease caused by a complex interplay of genes, impaired barrier function, immune dysfunction and environmental factors, namely allergens and irritants. Skin lesions can be classified as acute, sub-acute or chronic according to the clinical morphology and microscopic findings. Incessant pruritus is the only symptom of ADE and sufferers often scratch themselves uncontrollably. Although pruritus may be present in the first few weeks of life, parents become more aware of the itch as the itch-scratch cycle matures, when the patient is aged approximately 3 months. Pruritus elicits rubbing and scratching leading to eczematisation with eventual lichenification. Existing skin lesions of ADE may also lichenify by a similar mechanism. The question is often asked: is it the itch that rashes or the rash that itches? More likely both statements are correct. Thus, any factor that leads to pruritus in apparently normal skin or any factor leading to worsening of existing eczema could be regarded as a trigger. With this said one should keep in mind that ADE intrinsically has an intermittent course with alternating flares and remissions, often for unexplained reasons.

Various factors have been proposed as triggers for ADE, mostly following epidemiological studies in which exposure to these factors were associated with increased incidence of ADE and/or exacerbation of established ADE. However, studies related to this topic are of poor quality, and even though clinical experience may dictate otherwise, good scientific evidence for most triggers are lacking. The ideal means by which the role of a ‘flare factor’ in causing a flare of disease is established, is to demonstrate a temporal relationship between exposure and worsening of the disease, a dose-response effect and, ideally, remission of the flare following withdrawal of the relevant factor.
TRIGGERS IN ATOPIC DERMATITIS/ECZEMA:

A. CHEMICAL IRRITANTS SUCH AS SOAPS, DETERGENTS AND CHLORINE

Soaps, bubble baths, detergents and surfactants (e.g. sodium lauryl sulphate) emulsify surface and intercellular lipids, which can then be washed off with water. They also increase the pH of the skin, leading to increased protease activity with premature desquamation of the stratum corneum and therefore an impaired barrier function. Increased transepidermal water loss and dry skin are the result, leading to pruritis and sensitivity to irritants.\(^5,\(^8\)\)

Whereas high concentrations of chlorine, as is found in swimming pools, may have similar irritating effects on ADE sufferers’ skin, the sterilising effect of dilute chlorine baths is sometimes harnessed to decrease the bacterial load on the skin of ADE patients. Soaps and detergents are the most common causes of irritant contact dermatitis of the hands and can trigger flares of ADE.\(^9\) Avoidance of irritants are central in the management of ADE. When exposure is unavoidable protective rubber gloves with a cotton lining should be worn and application of appropriate emollients and barrier creams should promptly follow the exposure. When using shampoos, care should be taken to choose the correct products, i.e. those approved for use in ADE, and extended exposure, such as when washing the hair in the bath, should be avoided. Patients with ADE may sometimes also develop allergic contact dermatitis to surfactants. In a recent article it was shown that atopic individuals were significantly more likely to develop allergic contact dermatitis to the surfactant cocamidopropyl betaine (CAPB).\(^10\) The authors suggested that cleansers containing the surfactant sodium
laureth sulfate (SLES) would be a safer alternative for the atopic patient than products containing CAPB, as SLES is a rare irritant and not a sensitiser.11

B. PHYSICAL IRRITANTS SUCH AS WOOL OR NYLON
Textile fibres have been reported to cause acute and cumulative irritant and allergic contact dermatitis, exacerbation of ADE and contact urticaria (e.g. nylon causing allergic contact dermatitis and contact urticaria, and wool causing acute and cumulative irritant dermatitis).12 The ‘spiky’ texture of wool fibers is the main problematic factor. Cotton is generally advised as an alternative, as it is comfortable and can be layered in the winter to avoid overheating and sweating. Unfortunately some studies suggest that cotton may also present a roughness that irritates the skin of children affected by ADE.13 Silk garments have shown promising results as it has a very smooth non-irritating texture, protects the covered areas against aeroallergens and friction from clothing, and decreases the possibility of scratching the skin with fingernails.14 Wool products should therefore be avoided, cotton clothing be used with caution and silk clothing be worn where possible. Contrary to popular belief, laundry detergents are rare causes of exacerbation of ADE.15 Clothes should be washed in a mild detergent followed by the addition of a fabric softener.16 To ensure no residual product in the clothing, an extra rinse with clean water should be performed.

C. ALLERGIC CONTACT DERMATITIS TO TOILETRIES AND PERFUMES
Patients with ADE are more likely than non-atopic individuals to develop hypersensitivity to allergens on the standard patch test panel and, in particular, to metal allergens including nickel, cobalt chloride and potassium dichromate.17 They are also significantly more likely to develop allergic contact dermatitis to formaldehyde releasers, such as quaternium-15, imidazolidinyl urea, 1,3-Dimethylol-5,5-dimethylhydantoin (also known as DMDM hydantoin), and 2-bromo-2-nitropropane-1,3-diol. Formaldehyde releasers are used as preservatives in toiletries, including perfumes and make-up. They are less likely to develop reactions to parabens, formaldehyde, or diazolidinyl urea.18 The preservative methylisothiazolinone (MI) has the dubious honor of being selected the American Contact Dermatitis Society Contact Allergen of the Year for 2013 – that after recent reports that this allergen has shown an alarming increase in prevalence in different European countries.19 MI is used as a preservative in wet wipes and baby products (including lotions and powders); cosmetics such as eyeliners and eye make-up remover; bath, shaving and skin care products; hair care and hair-colouring products; nail care products, deodorants, suntan products, and sunscreens, among others. Occupational sources of MI include paints, inks, glues, lacquers, varnishes, and cutting oils. Household products containing MI include dishwashing liquid soaps (even in some “green” household cleaning products), laundry detergents, laundry stain removers, fabric softeners, all-purpose cleansers, glass cleaners, and wood cleansers.20 Understandably avoiding all these products is very difficult - even impossible. Sensitivities to these products often lead to exacerbation of ADE and care should be taken when choosing the correct products.

D. FOOD ALLERGENS
The role of food in ADE has always been and remains controversial. Cases where an early onset and increased severity of AD, and where gastrointestinal tract symptoms are prominent, a food allergen should be considered.21 This topic will be discussed in more detail elsewhere in this journal.

E. AEROALLERGENS
Sensitisation to aeroallergens does not necessarily translate to clinical relevance.22 A German cohort study demonstrated that sensitisation pattern changes throughout childhood, with the prevalence of sensitisation increased steadily throughout childhood. Sensitisation prevalence hierarchy (grass > birch pollens > HDM > cat > dog) was maintained from age 5 years onwards.23 Performing and interpreting allergy tests (such as skin prick tests and atopy patch tests) require special training, may be expensive and time-consuming. Aeroallergen testing may identify those children with AD at risk for the development of airway disease, so testing should be considered in children with severe ADE and specific IgE to aeroallergens. Additional indications for testing would be in children with AD and typical airway disease symptoms and seasonal variation.24 Unfortunately, desensitisation does not seem to improve the ADE in patients with proven sensitivity to aeroallergens.25

(i) House dust mite (HDM)
The House Dust Mite (HDM) [Dermatophagoides pteronyssinus] is a tiny insect, 0.25-0.3 mm in length, too
small to see with the naked eye and is a cosmopolitan guest in human habitation. The mites mainly live in mattresses and bedrooms as part of the dust. Dust mites feed on organic detritus such as flakes of shed human skin and flourish in the stable environment of dwellings. Some people with eczema are allergic to HDM. HDM affect ADE via two different mechanisms, including a direct proteolytic activity and an immunological action inducing an IgE-mediated response. Two proteins, namely Der p 1 and Der p 2, show direct proteolytic activity causing increased barrier disruption. Of note is that these proteases may also cleave lung epithelium and may thereby lead to respiratory symptoms. In the literature as many studies show improvement with HDM avoidance as those showing no improvement. HDM is ubiquitous in the environment and many of the currently suggested techniques are time-consuming and expensive. Given the conflicting results of the studies, allergen avoidance measures cannot be recommended to relieve symptoms at this time. However, some people with severe recalcitrant eczema may consider trying to clear house dust mite from their home, as much as possible. The management of HDM is beyond the scope of this article.

(ii) Animal dander
Some ADE patients report allergic reactions after contact with animals such as cats, dogs and horses. Dander refers to loose scales formed on the skin and shed from the coat or feathers of various animals. The literature is inconsistent regarding the relationship between ADE and animal dander exposure. A recent meta-analysis reported a favourable effect of exposure to dogs and other pets on the risk of AD in children, whereas no association could be shown with exposure to cats. Tolerance of their own pet is often reported but this tolerance may be lost when the individuals are removed from the home. Some practitioners recommend the removal of the pet in cases of severe allergy, while others suggest limited ‘managed’ exposure, e.g. not sharing a bed with the pet. One has to keep the psychological distress of pet removal in mind, though, as a report was published where children chose their pets as one of their three most favourite items. Removal of the pet may not be justified.

(iii) Pollen
A seasonal variation in the ADE may be a good indication of a pollen-sensitive ADE. In a study published in 2005, it was found that children with a summer-type pattern experienced more symptoms on days with high grass-pollen count. The likelihood of pollen as aeroallergen in patients with symptoms on air-exposed surfaces (such as the face, décolletage, lower arm and hands) is also much higher and especially if the patient shows less or no involvement on skin surfaces covered with clothes. Airborne pollens are the most difficult of aeroallergens to avoid. During windy periods the pollens may be carried long distances from the plant. Some cases may have symptoms limited to a particular time of year and then it is advisable to avoid open-air activities. If possible, spending summers in pollen-free areas such as the seacoast or high-mountains should be considered. As patients carry the pollens on their skin and hair, daily cleansing including hair washing is recommended in the problematic time of year. Hanging the washing in open air to dry should be avoided and regular vacuum cleaning should be performed.

(iv) Mold
A review article published in 2013 could not find any strong evidence implicating molds as a triggering factor for ADE.

(v) Cockroach
Cockroach allergens can induce positive patch test reactions in patients with ADE, however the role of cockroach antigen has not been proven with well-controlled clinical studies.

F. INFECTIONS
Patients with ADE display a significant decrease in the expressions of antimicrobial peptides (AMP) and exhibit innate and adaptive immune defects, which explain their increased susceptibility to skin infections due to bacteria, fungi or viruses.

(i) Bacterial: e.g. *Staphylococcus aureus* (*S. aureus*) and *group A streptococcus*
Patients with ADE are more susceptible to colonisation by *S. aureus* because of dysfunction of the innate and adaptive immune systems. A study published in 2013 found that the *S. aureus* colonisation rate was higher in ADE patients as compared with non-ADE patients, and that the rate was higher in acute lesions of ADE patients versus chronic lesions. The colonisation rate increased with age and the more severe cases demonstrated higher rates of colonisation rates. The severity of ADE decreased when treated for *S. aureus*. *S. aureus* produces superantigens, which affects the immune system by stimulating T cells to produce pro-inflammatory cytokines by a non-MHC, restricted mechanism and suppresses T regulatory cells. By this mechanism *S. aureus* superantigens increase Th2- mediated responses, which in turn suppresses antimicrobial responses in atopic skin. Superantigens also
induce corticosteroid resistance as well as the production of IL-31, a very pruritogenic cytokine that regulates filaggrin expression. In a study by Leung et al, 60% of patients with moderate to severe AD were found to have IgE antibodies to *S. aureus* exotoxins. In this way, *S. aureus* may also trigger an allergic response via allergen-specific activation of Fc3RI-bearing effector cells (e.g. mast cells).

The fact that nasal *S. aureus* carriage of caregivers may be a potential source of re-colonisation in children with AD should be kept in mind when treating this problem. Treatment should thereby be extended to include the whole family. Care should be taken when using emollient tubs – a clean spoon should be used to decant the desired amount into another container to avoid introduction of *S. aureus* or other skin organisms into the primary container. A study by Carr et al published in 2008, found that more than half of the containers tested revealed some sort of bacterial growth. *S. aureus* contributed to a quarter of bacterial growth in their study.

A retrospective review from 2011 showed that children with ADE and *group A streptococcal* infections were more prone to invasive disease, including bacteremia and septicemia, than those infected with *S. aureus* alone.

(ii) Fungal

Malassezia yeasts are commensal fungi forming part of the biofilm of the skin. It has always been considered to be unable to cause significant problems, but in recent literature this theory is being questioned. Increased levels of IgE to Malassezia have been found to be associated with refractory cases of head and neck dermatitis. Some of these cases have been found to show improvement on systemic antifungal treatments.

Patients with ADE are more prone to develop acute and chronic dermatophyte and candida infections. These infections lead to pruritus and the activation of the itch-scratch-cycle and should therefore be treated appropriately.

(iii) Viral

Viral infections, including herpes simplex and varicella zoster viruses, in patients with ADE may be very serious. Due to the impaired barrier function and local immunological disturbance, sometimes aggravated by the use of topical corticosteroids, viral infections can spread rapidly over the body. Molluscum contagiosum, in particular, may be a persistent problem disseminating due to autoinoculation (via scratching).

G. CIGARETTE SMOKE

The literature on whether gestational and perinatal exposure to cigarette smoke may be associated with the onset of childhood ADE is inconclusive. A study published in 2011, however, managed to show that adult onset ADE may be influenced by cumulative and current exposure to cigarette smoke, whether via environmental or personal cigarette smoke exposure. An increased risk of hand eczema was found to be associated with smoking more than 10 cigarettes per day.

H. Psychological stress

Psychological stress impairs the barrier function, favours a shift in immunity toward a Th2 response, is associated with an abnormal hypothalamic-pituitary-adrenal axis and produces neuropeptides in the skin leading to neurogenic inflammation. ADE also causes psychological stress in the patient as well as the family. A clear association of psychological stress triggering ADE could not be confirmed by a meta-analysis of the available literature by Williams et al conducted in 2007. However, some people react to stress by habit scratching. This may activate the itch-scratch cycle and make eczema worse. Avoid scratching as much as possible, keep fingernails short, consider wearing cotton gloves at night, and opt rather for rubbing if possible. Psychological and stress-reduction interventions may decrease pruritus, scratching and thereby patient well-being.

I. Dust and sand

HDM resides in dust and in that way exposure to dust may trigger ADE, as HDM is a well-known trigger of ADE. Sand is a commonly believed trigger of ADE, but no clear evidence could be found in the literature to prove this.

J. Extreme temperature and humidity

The role of humidity and extreme temperature in ADE is unclear. These factors should be avoided where possible.

K. Other possible triggers

Sweat may act as an irritant and thereby lead to exacerbation of ADE. Decreased sweating may also trigger ADE as it causes xerosis. Hormonal changes during pregnancy and during the menstrual cycle may affect ADE. Air-conditioning decreases the moisture in the air and may further contribute to the deterioration of ADE, if the filters are not cleaned regularly. ‘Hard water’ does not have scientific evidence of triggering ADE.
CONCLUSION
ADE has a significant impact on the quality of life of the individual suffering with this condition, but also on the rest of the family. Many triggers of ADE have been identified. Some have solid scientific evidence and should be avoided or amended as such. Others have no- or inconclusive evidence and this should be conveyed to ADE patients. Studies on triggers of ADE are ongoing and we should endeavor to continue to separate fact from fiction.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

REFERENCES