

A REVIEW OF THE RISK FACTORS AND CLINICAL PRESENTATION OF CHILDHOOD ATOPIC ECZEMA AT THE PRIMARY HEALTHCARE LEVEL

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ABSTRACT

Atopic eczema (AE) is a chronic and often debilitating skin disorder with a high prevalence in young children. This article briefly describes predisposing factors that are currently known to contribute to the development of AE, as well as the clinical presentation of AE.

This article has been peer reviewed.

INTRODUCTION

AE is one of the most common chronic inflammatory skin diseases in children,¹ affecting about 17% of children in the United States and between 5–20% of children in Western communities in South Africa this is estimated to be around 17% and in Kenya up to 20%, with trends in AD increasing.^{1,2} The condition most often begins in infancy or early childhood, with more than 90% of cases appearing in the first five years of life. One-third of these children can also be affected in adolescence.²

A spontaneous remission of atopy occurs in 75% of affected individuals in late childhood and adolescence, and the remainder continue to have AE. This may affect the choice of career for these individuals and cause psychological distress.³

RISK FACTORS

AE originates due to various risk factors, which include: genetic pre-dispositioning, skin barrier dysfunction, allergen exposure (food, pollen, dust, etc), cutaneous hyper-reactivity, immunological dysfunction and superficial bacterial infections of the skin, of which *Staphylococcus aureus* is most prevalent.^{4,5,6,7,8} Figure 1 demonstrates the interplay between these risk factors in the disease development.

GENETIC FACTORS

Allergies tend to be familial.^{7,9} If one parent has an atopic condition, the chances that the child will also suffer one or other form of atopy is 60%, and 80% – if both parents have suffered from some form of atopy.¹⁰ It has been established that chromosomal regions related to allergic pathology are

inherited from the affected parents.⁴ The disease involves an interplay between the genetic predisposition and the environmental factors that cause characteristic epidermal defects and immunological abnormalities.¹¹

To this effect, twin studies reveal that monozygotic twins have a much larger correlation (77%) between them in terms of their allergies, as compared to dizygotic twins (17%).^{4,7}

Polymorphisms in genes responsible for the recognition of micro-bacteria, can lead to an altered balance between Type 1 T helper (Th1) and Type 2 helper (Th2) cells. Genetic predisposition in individuals with inadequate exposure to bacteria and bacterial materials during childhood can lead up to atopic tendencies, due to inadequate Th1-mediated immune responses. This increases the likelihood of the development of a Th2-biased response.^{9,12}

Genetic mutations in the *filaggrin* (FLG) gene, which codes for a protein (profilargin) responsible for epidermal structure, has been identified as an important risk factor in AE as this mutation causes deteriorating skin barrier function.¹³ This reduction in profilargin with a subsequent reduction in fillargin has been found in up to 50% of AE sufferers.⁸ Fillargin is not only a key role-player in retaining fluid in the epithelial layer and maintaining skin barrier function, but also binds to water in the stratum corneum and maintains the skin's pH.¹³ Much of the xerosis can be attributed to a decreased production of fillargin.¹⁴

The epidermal barrier is furthermore stabilised by a balance between proteases and protease inhibitors that

may be disrupted by exogenous proteases released, for example from house dust mites, causing digestion of corneo-desmosomes. This process is inhibited by serine proteases and this is an important step in the regulation of the dermis. The proteinase inhibitor (lymphoepithelial Kazal type 5) is encoded by *SPINK 5* gene. In individuals suffering from AE, genetic polymorphism has been identified in the *SPINK 5* gene in some studies, however, not consistently in subsequent research.¹¹

To date, genome-wide studies and candidate gene studies have revealed up to seven susceptible loci, with various polymorphisms which are thought to be responsible for the genetic inheritability of AE. However, many more gene loci, involved in AE, are yet to be discovered.¹³

ACQUIRED SENSITISATION

Bowel flora

The microflora hypothesis postulates a correlation between immune function and exposure to intestinal microbiota, stating that changes in the microbiological composition within the gastrointestinal tract (GIT) may lead to a disruption in immune tolerance.^{8,17,18} There are more than 500 different species of bacteria from seven to ten phyla that colonise the intestinal tract and can reach to 100 trillion of these microbes within the protection and nutrient-rich environment of the GIT.¹⁷

Exposure to microbial flora early in life allows for a change in the T helper 1 Th1/Th2 cytokine balance, favouring a Th1-cell response.^{5,8} The presence of all of these microbes within the intestinal tract helps to regulate immune

responses. When there is a shift in the balance between these different microbes the immune system reacts to this change. Mice born to germ-free environments with high doses of antibiotics exhibited an underdeveloped immune system, with an elevated Th2 cellular response.¹⁹ This elevation in Th2 responsiveness has given rise to an increased IgE production. Therefore, there is a strong likelihood that exposure to high dosages of antibiotics in early neonates may alter the composition of their intestinal flora and have an effect on the normal immune responses, leading to an elevated Th2 immune responsiveness and a decrease in Th1-cell mediated immunity.¹⁷

Infections and endotoxin exposure

Within the atopic diseases a hypothesis exists which predicts that the prevalence of atopic diseases is decreased when a child is exposed to microorganisms during childhood. This is called the 'hygiene hypothesis' and it attempts to explain why children who are exposed to animals, viruses, bacteria and various endotoxins are less likely to develop atopic diseases. It was first defined as the decreased risk of developing hayfever in larger households where there was an increased exposure to various microbes.²⁰ This has led to a 'revised' hygiene hypothesis that explains why the youngest of all siblings has the lowest risk of developing AE, and microbial exposure plays a significant role in decreasing the incidence of AE in children within the first year of life.⁸ Allergic tendencies were less pronounced in those children who attended day care and who were exposed to a dog within the first year of life.^{8,21} This, most likely, has to do with the fact that bacterial-, viral- and endotoxin-exposure triggers an immune response of Th1

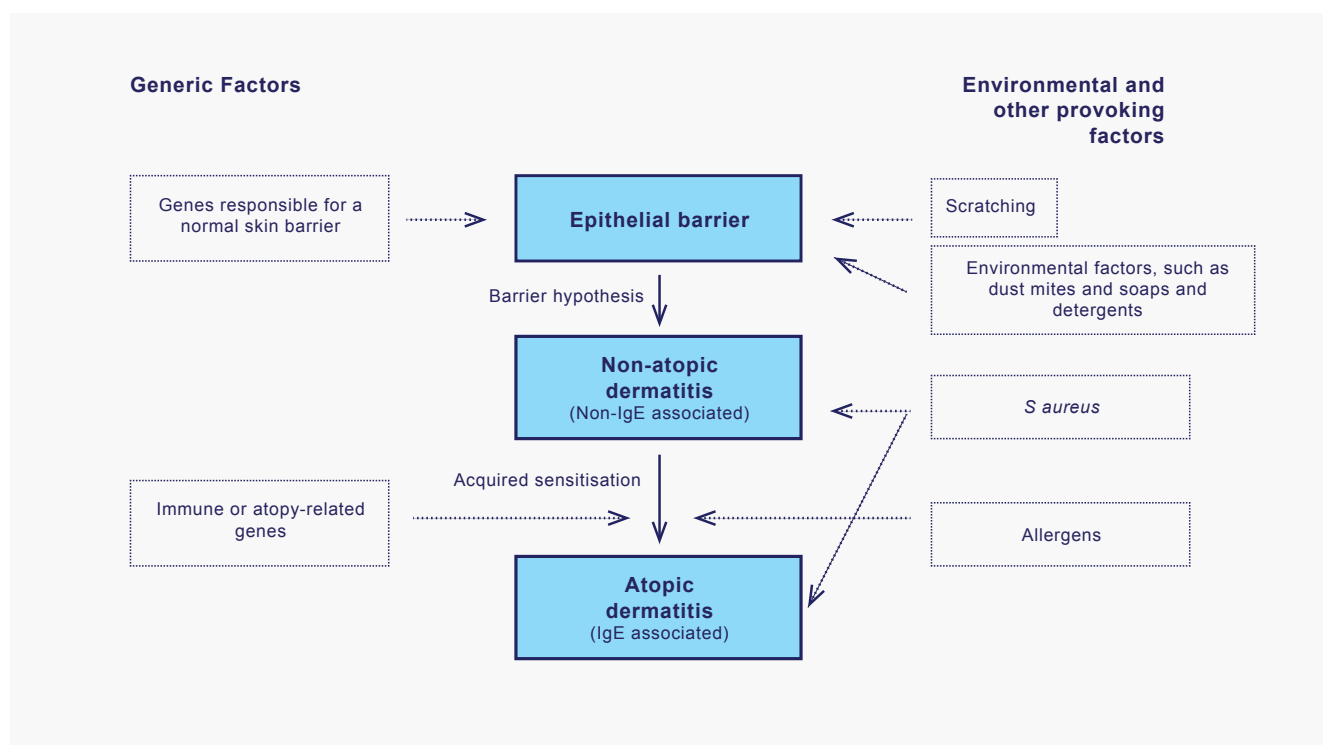


Figure 1: Risk factors involved in developing AE⁷

TABLE I: GENETIC POLYMORPHISMS IDENTIFIED AT DIFFERENT SITES^{11,12,13,14,15,16}

MUTATION SITE	SYSTEM AFFECTED	RESULTING ABNORMALITY
Chromosome 5q31–33	Adaptive immune system	Increased Th2 cytokines, ie, IL-3, IL-4, IL-5, IL-13 and GM-CSF
T-allele of 590C/T polymorphism	Adaptive immune system	Increased IL-4 production
Chromosome 16q12, IL-4 α -subunit polymorphism	Adaptive immune system	Increased IL-4 receptor sensitivity
Chromosome 11q13	Innate immune system	β -chain polymorphism of the high affinity receptor for IgE (Fc ϵ RI β).
Chromosome 3q21	Adaptive immune system	Molecules CD80 and CD86 are encoded within this chromosome and may contribute to abnormal T-cell responses.
Glu420Lys polymorphism within the SPINK5 gene	Skin barrier	Serine protease inhibitor, lymphoepithelial Kazal type 5 serine inhibitor, leads to reduced activity of serine protease.
Chromosome 1q21	Skin barrier	Decreased production of profillargin, with subsequent decrease in fillargin.
G2722C	Innate immunity	Genes responsible for protein 15, an intracellular receptor for lipopolysaccharides implicated in NF- κ B activation.

lymphocytes, preventing a Th2-biased response.^{8,21}

Interactions between helminths, bacteria, viruses and the immune system have been decreased post-industrialisation. The decreased appearance of these interactions with the immune system is thought to be one of the many elements contributing to the development of atopy.²²

Allergen exposure

In order to develop a hypersensitivity reaction towards an allergen, one needs to be exposed to that allergen. After the initial exposure to an allergen, the risk of the development of atopic diseases increases.⁶ Food allergies identified early in children may be predictive of severe AE. The main food allergies identified include cow's milk, hen's eggs and peanuts. Other allergens identified include house-dust mites, pollens and pets.⁸ The amount of allergen exposure does not correlate to an increased or decreased risk of sensitisation to that allergen. This also strengthens the belief that the existence of an atopic disease is hereditary, with patient exposure to an allergen simply increasing the likelihood of the development of an allergy.⁹ The 'inside-out hypothesis' refers to the allergen being considered as co-associated with or an exacerbating factor of AE, rather than as a causative factor. Food allergies present as 'late events' with clinical manifestations on the skin and the

gastrointestinal and respiratory systems.⁸

Conversely, low levels of allergen exposure are not sufficiently adequate to produce a response, while high levels of allergen exposure will induce tolerance to that allergen (partial desensitisation). This confirms that, although the disease exists within an individual's genetic makeup, environmental factors play a determining role in one's chance of developing an atopic condition.⁹

ENVIRONMENTAL RISK FACTORS

Differences between the incidences of AE in different countries have prompted the belief that environmental factors play a large role in its development. Environmental factors may either be protective in its associated effect or they may increase the risk of developing AE.⁸ Figure 2 depicts some environmental and microbiological exposures and the resultant effects on AE.⁸

AE PATHOGENESIS AND PATHOPHYSIOLOGY

AE pathophysiology represents a vicious cycle of cellular events. Defects in the skin barrier function and the biased Th2 cellular response lead to increased susceptibility of the skin to allergens.

When allergens come into contact with the skin, the inflammatory cascade, favouring the Th2-cell subset, is activated.²³

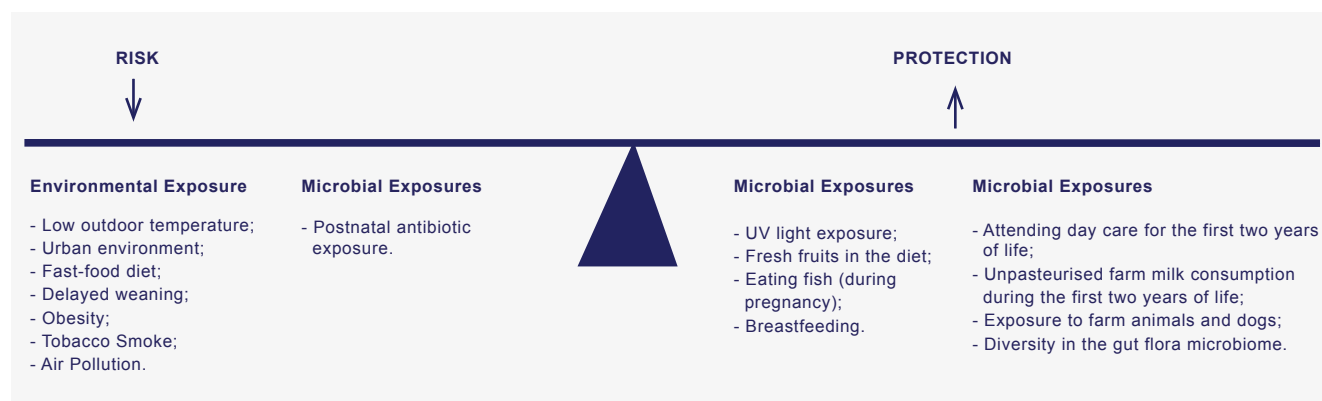


Figure 2: Environmental and microbiological exposure and the effects on AE⁸



Figure 3: AE lesions with a secondary bacterial infection. *Staphylococcus aureus* infections on AE lesions typically present with golden crusts

This inflammatory cascade is fuelled by the imbalance between Th2 cells and Th1 cells, favouring the Th2 cellular responses. This imbalance leads to a Th2-mediated release of interleukins, IL-4, IL-5, IL-10 and IL-13, as well as an increased IgE production.²⁴ A decrease in Th1 subset production results in decreased levels of interferon gamma (IFN- γ), interleukin (IL)-2, tumour necrosis factor-beta (TNF- β) and IgG.^{4,25} IgG antibodies have the ability to suppress the production of allergy-promoting cytokines: Interleukins (IL) 4, 5, 9 and 13 (Th1 indirectly suppresses Th2 activity).²⁵

The Th2-biased response predisposes patients to various microorganisms. Th1 cellular responses to these organisms are diminished as a result of a lack of Th1 cells.²³ The lack of Th1 cellular responses coupled with extensive tissue remodelling of the skin²⁶ promotes the colonisation of the skin by various pathogens, *Staphylococcus aureus* (SA) being the most prevalent organism.^{8,26}

In animal models, studies found that SA colonisation of the skin was significantly higher in animals with a Th2-mediated skin inflammation compared to those who had a Th1-mediated skin inflammation¹² (refer to Figure 1).

Patients with AE who have been colonised by SA, *Herpes simplex* and other microorganisms frequently suffer from exacerbated AE lesions when the bacteria or viruses have overgrown.^{8,26} The colonisation of SA may lead to IgE sensitisation, causing transitioning from the non-atopic state of AE to the atopic state of AE (refer to Figure 1).^{8,26} SA secretes toxins, called 'super-antigens'. Patients suffering AE will produce IgE antibodies directed at these antigens. These IgE antibodies, directed at the super-antigen toxins

secreted by positively, correlate with AE severity.¹² Patients with an overgrowth of SA may present with impetigo, which will necessitate topical antibiotics, or preferably oral antibiotics.²⁷ Figure 3 and illustrates an atopic eczema lesion with a secondary bacterial infection of SA.

AE CLASSIFICATION AND CLINICAL PRESENTATION

The clinical presentation of AE does not differ from other types of eczema, for example contact eczema and so different types of scoring system have to be used, for example SCORAD and EASI.³ Other features of AE display features of the atopic syndrome. This includes a long, pale atopic face, ecchymotic peri-orbital darkening beneath the eyes, a line/secondary crease that is accentuated below the margin of the lower eyelid, also known as the Denny Morgan, other secondary mannerisms that include horizontal rubbing of the nose, known as the 'side swipe' or the 'allergic salute', repetitive sneezing and facial distortions.²⁸ Although clinical manifestations of AE sufferers may be general to other eczemas, they typically present with three different types of lesion: acute, sub-acute and chronic.²⁹

Acute lesions are usually extremely pruritic, presenting with vesicles covering an erythematous background with weeping papules and crusting. The pruritic nature of these lesions easily persuade a child to attempt scratching the lesion for some relief, and as such these lesions often present with excoriations and exudates due to the physical damage inflicted by the child's scratching.

Sub-acute lesions typically form where *acute* exacerbations are frequent, but they present slightly differently, typically with a thicker, paler, dry, scaly, erythematous and excoriated lesion. This *sub-acute* lesion usually is the next step in the disease progression from acute to chronic lesions.³⁰

Chronic lesions have typically undergone extensive tissue remodelling, resulting in lichenified skin due to chronic inflammation (acute eczema exacerbations which are scratched). The lichenified skin presents with thickened plaques, accentuated skin markings and dry, fibrotic papules. Patients may often present with all three types of lesion at any given time.²⁶

Atopic lesions are associated with xerosis, which results in fine scaling of affected skin. Atopic skin that has undergone tissue remodelling due to AE results in the decreased ability of keratinocytes to bind to water, therefore giving patients with AD dry scaly skin.³¹

The clinical presentation of atopic eczema varies during the different stages of early infancy. In *infants* the disease can affect any part of the skin; however, they also experience eczema on the face, scalp and extensor aspects of the arms and legs.³²



Figure 4a: AE lesions on the popliteal fossae of an older child suffering from chronic eczema

As the infant matures into *early childhood*, the lesions become more localised to certain areas. As illustrated in Figures 4a and 4b, most commonly affected areas are usually flexures of the elbows and knees as well as the wrists and ankles. These lesions also become drier and lichenified with excoriations, papules and nodules.³

In older children lesions are localised to the face and neck; a smaller portion develop hand eczema that can influence work activities.^{3,32} Other symptoms include oedema, dryness, crusting, scaling, excoriations and lichenification.^{3,34} It is important to stress that all these symptoms can also be found in other AE sufferers of different ages.

Up to 80% of children with AE can with time develop another atopic manifestation such as allergic rhinitis or asthma.³⁰ This may be due to another endogenous phospholipid mediator of inflammation, which is contained within alveolar macrophages, eosinophils, mast cells, platelets, basophils and neutrophils, namely platelet activating factor (PAF). PAF is released upon allergic and inflammatory reactions.³⁰ The release of PAF is closely associated with an increased vascular permeability, bronchoconstriction, eosinophil chemo-attraction and airway hyper-responsiveness, all of which are involved in the pathophysiology of rhinitis, asthma and anaphylaxis. PAF levels are often elevated in patients with allergic conditions, when compared to healthy controls.³⁰ The existence of other atopic manifestations



Figure 4b: AE on the flexural aspect of the popliteal fossae in a young child

can also aid the clinician in making a diagnosis. The clinician should also educate the parents with regard to further atopic manifestations which may develop during the atopic march. The so-called 'atopic march' refers to the development of different atopic diseases at certain ages during early childhood. It refers to the sequence in which clinical symptoms and atopic diseases manifest themselves as a child grows older. AD is the most common starting point, which then usually develops into conditions of the respiratory tract, such as allergic rhinitis and asthma.^{17,32,33,34,35,36,37,38}

CONCLUSION

AE is a complicated skin disorder that can lead to a significant decrease in a patient's quality of life. AE originates as a result of various risk factors. These include: genetic pre-dispositioning, skin barrier dysfunction, allergen exposure (food, pollen, dust, various triggers, etc), cutaneous hyper-reactivity, immunological dysfunction and superficial bacterial infections of the skin, of which *Staphylococcus aureus* is the most prevalent. Careful assessment in order to determine the risk factors involved as well as the clinical presentation can help the clinician in primary healthcare to make an accurate diagnosis and decide on a treatment plan.

DECLARATION OF CONFLICT OF INTEREST

The authors declare conflict of interest.

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