



# Role of immunoglobulin E sensitization in eczema, previously referred to as atopic dermatitis

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This review aims to clarify existing knowledge on the relationship between eczema and immunoglobulin (Ig)E sensitization. Over the years this debate has been complicated by unclear definitions of what constitutes an atopic individual. The new, uniform allergy nomenclature introduced by the European Academy of Allergy and Clinical Immunology and the World Allergy Organization uses the term eczema to denote what was previously known as 'atopic dermatitis' or 'atopic eczema'. Despite detailed knowledge of localized IgE-allergen interactions at the level of the skin, the exact role of IgE and IgE antibody sensitization in the disease process remains widely debated. The association between IgE sensitization and eczema has been clearly demonstrated in population-based studies. There is, however, variation in the strength of the association between IgE sensitization and eczema in hospital versus community studies. While IgE sensitization is not a useful disease discriminator, once other factors have been taken into account, knowledge of atopic status appears to have prognostic value in children with eczema, since IgE sensitization is associated with an increased risk of developing allergic respiratory disease later in life. These children may also experience a more persistent and severe disease.

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The first case of allergy was reported by John Bostock to the Royal Medical and Chirurgical Society of London in 1819 when he described his own 'periodical affection of the eyes and chest' [1]. The symptoms associated with the nose and eyes occurred during June and July and could be linked to grass pollen exposure; that is, a case of seasonal, allergic rhinitis also referred to as hay fever. Since then, symptoms from the respiratory and gastrointestinal tract and skin that are due to allergy have increased to dramatic levels. Today, approximately 30–40% of people in industrialized countries suffer from an allergic disease [2].

Similarly to asthma and allergic rhinitis, the prevalence of eczema has increased [3]. 'Atopic dermatitis' is the term that has traditionally been used, regardless of mechanisms, to describe this pruritic, chronic inflammatory skin condition that typically affects the skin

creases of the arms and legs (FIGURE 1). It begins in infancy in approximately 70% of cases and often persists into adulthood [4,5]. Eczema persists in many cases and is often severe and debilitating in those with early onset. Severe eczema in early life, early onset, concomitant asthma, hay fever and a family history of eczema may predict a more persistent course [4]. To date, the cumulated incidence of children in industrialized countries suffering from this affliction is approximately 15–20% [6]. This has led to a significant reduction in quality of life and a burden on healthcare resources. The disease is associated with higher socioeconomic status and is inclined to be more common in cities than in rural areas [7,8].

Although the association between elevated serum immunoglobulin (Ig)E levels and 'atopic dermatitis' is well known, the exact link between the disease and allergen-specific IgE

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sensitization remains uncertain and hotly debated. Over the years this debate has been complicated by unclear definitions of what constitutes an atopic individual, and the context in which the association between IgE and 'atopic dermatitis' is being considered. This review aims to clarify existing knowledge on the relationship between eczema and IgE sensitization.

### Nomenclature

The term atopy was introduced in the early 1920s to describe certain hypersensitivity disorders characterized by hay fever and asthma, a hereditary trait and positive wheal-and-flare skin test reactions [9,10]. However, since the underlying mechanism was unknown, terms such as allergy, atopy and hypersensitivity were understood differently by clinicians of different specialties, patients, press and politicians. The discovery of IgE allowed studies of and explanations for the mechanisms of the most common, immediate type of allergic reactions [11]. In their position statement in 2001, the European Academy of Allergology and Clinical Immunology (EAACI) nomenclature task force proposed to restrict the use of the term atopy to describe the genetic constitution of high IgE antibody responders [12]. Atopy usually occurs in childhood or adolescence. It is a personal and/or familial tendency to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, these people can develop typical symptoms of asthma, rhinoconjunctivitis or eczema. Although this is a clinical definition, it cannot be reached without ascertainment of IgE sensitization, either by positive skin prick tests (SPTs) or the presence of IgE antibodies in the blood.

The EAACI nomenclature task force introduced a transitional term, atopic eczema/dermatitis syndrome (AEDS), to supplant 'atopic dermatitis'. Most recently, the entire nomenclature of

allergic skin diseases has been further updated by the World Allergy Organization nomenclature review committee [13]. In this new nomenclature, eczema is used instead of AEDS. The term 'atopic dermatitis' is no longer used. The term atopic eczema is reserved exclusively for patients who demonstrate the classic clinical signs of the disease and who are also atopic, as shown by SPT or the demonstration of IgE antibodies in the blood (FIGURE 2).

In this review, the authors will therefore use the term eczema to denote what was previously known as 'atopic dermatitis' or 'atopic eczema' [13], unless the authors specifically refer to the atopic phenotype of the disease. When discussing other studies where the terms used are not clear they will be given in quotation marks.

### Aims

The aim of this review is to specifically discuss the following:

- What role do IgE ('total IgE') and IgE antibodies play in the pathophysiology of eczema?
- How strong is the association between atopy and the clinical diagnosis of eczema?
- Is knowledge of IgE sensitization helpful in making a diagnosis of eczema?
- Does knowledge of IgE sensitization assist in the management of eczema, especially with regard to disease prognosis and responsiveness to treatment?

The review is based on relevant papers identified through systematic searches of Medline from 1966 to February 2005. Clear and explicit criteria for electronic searches were derived and have been described elsewhere [14]. The online search was supplemented by an extensive hand search of the literature, through references identified from retrieved articles and by contact with various experts in the field.

### Role of IgE in the pathophysiology of eczema

Environmental and genetic factors must amalgamate to produce the classic phenotype of eczema, mediated by inflammatory immunologic mechanisms. In atopic eczema, there is evidence to suggest that this is partly due to an imbalance between Type 1 and 2 T-helper (Th) cells, possibly as a result of deprivation from obligatory stimulation of the immune system through certain microbial antigens. However, the inflammatory processes that ultimately lead to atopic eczema are more complex than this. One of the current hypotheses is that so-called regulatory T-cells play a crucial role in the transition from atopic to nonatopic phenotypes, potentially induced by non-pathogenic microbial stimulation of dendritic cells at the level of the gastrointestinal mucosa or other lymphoid tissues [15]. Whereas a Th2-cell-dominated cytokine milieu (interleukin [IL]-4, -5 and -13) is instrumental in the initiation of eczematous skin lesions, Th1 cells act as mediators in chronic phases of the disease. This illustrates the need to study the dynamic nature of the disease mechanism over time. The mechanism mediating nonatopic eczema is less well known.



Figure 1. The association between immunoglobulin E sensitization and eczema varies with location and disease severity.

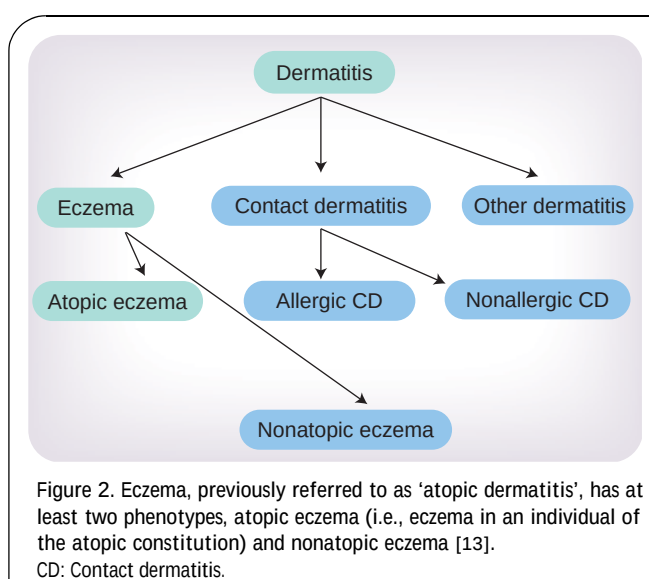
Another finding in eczema is the reduced capacity of peripheral blood mononuclear cells to produce interferon- $\gamma$  [16]. This in turn may be due to an IL-18 deficiency, also found in eczema. This may be one explanation as to why patients with eczema commonly synthesize high levels of 'total IgE'.

Eczematous skin of atopic individuals is rich in IgE-bearing antigen-presenting dendritic cells, which are considered to be instrumental in the capture of environmental allergens [17]. This is supported by the observation that sensitization to food allergens can stimulate eczematous skin lesions in animals with existing 'atopic dermatitis', and similar observations have been made secondary to inhalation of house dust mite allergens in predisposed patients. In addition, it is known that IgE receptors are required for the clinical expression of atopic eczema as a result of skin application of aeroallergens under experimental conditions using the atopy patch test [18]. This approach has, in recent years, been promoted as an experimental allergen provocation method to identify potential environmental triggers of eczematous skin lesions [19]. However, the place of atopy patch testing in routine work up of eczema patients remains uncertain. This is primarily due to difficulties in method standardization and clinical interpretation of test results, especially where atopy-patch-test-positive patients have no history suggestive of a specific allergic trigger or other signs of IgE sensitization.

Despite detailed knowledge of localized IgE–allergen interactions at the level of the skin, the exact role of IgE and IgE antibody sensitization in the disease process remains widely debated, not least because there is a significant proportion of eczema patients (i.e., the nonatopic eczema subgroup) who are not IgE sensitized, even in severe disease [20]. At the same time, IgE antibodies in serum to allergens normally present on the skin such as *Malassezia*, previously referred to as *Pityrosporum* [21], and *Staphylococcus aureus* [22], appear to be related to the severity of atopic eczema. It has been proposed that allergens penetrate inflamed skin more easily due to a loss of protective properties. In addition, an IgE-mediated autoimmune mechanism has been proposed [23].

#### Association between atopy & eczema

In eczema patients, IgE sensitization to common allergens tends to be higher in hospital- (47–75%) than in population-based surveys (7–75%). Although this may be partly explained by differences in the quality and design of the studies, the most rigidly conducted hospital study found the lowest prevalence of IgE sensitization (47%). This was in contrast to the population-based samples, where large studies that applied rigid diagnostic criteria tended to find a stronger association between atopy and eczema. The age span of the study group is also important. Young children often develop eczema prior to an IgE sensitization that will identify them as atopic. For example, approximately two-thirds of 2-year-olds with eczema in the BAMSE cohort study were nonatopic [24].



One factor that may explain part of this trend is geography. Whereas participants with eczema in European countries are more likely to be sensitized to environmental allergens, no statistically significant association was found for people living in Hong Kong, China, Malaysia, Ethiopia and Costa Rica [14].

Yet another explanation for the variation in the degree of the association between IgE sensitization and eczema in hospital versus community studies are differences in disease severity, with the most severe cases being observed in hospital settings [25]. For example, Schäfer and colleagues found a significant association between IgE sensitization and eczema severity, such as serum IgE levels and disease prevalence, in a recent cross-sectional, population-based study among over 2000 school children aged 5–14 years [26]. These findings have been echoed by Wolkerstorfer and colleagues in a large birth cohort study, especially for sensitization to hen's egg and cow's milk [27].

#### Role of IgE & IgE antibodies in the diagnosis of eczema

When Hanifin and Lobitz developed the first clinical diagnostic criteria for what they referred to as 'atopic dermatitis', they suggested that measurements of IgE should be included [28]. Their criteria was formalized into major and minor criteria in 1980. One of the major criteria was a personal or family history of clinical allergic disease. In addition, 'elevated total serum IgE' was included as a minor feature [29]. At the time, this was based on expert opinion rather than objective clinical validation. A more systematic evaluation of Hanifin and Rajka's diagnostic criteria, including IgE sensitization, has since suggested that although detectable IgE antibodies are associated with eczema, exclusion of IgE antibody measurements from the diagnostic criteria do not change the criteria's sensitivity and specificity in logistic regression [30]. In other words, although there is statistical evidence of an association between eczema and IgE sensitization, the latter is not a useful disease discriminator once other factors have

been taken into account. These findings could be expected in the light of eczema (then referred to as 'atopic dermatitis') being an umbrella term describing a clinical entity with different mechanisms, of which IgE sensitization might be of importance in only a subgroup.

IgE antibodies to local skin allergens such as the yeast *Malassezia* may also imply that specific local therapy (e.g., antifungals) may be beneficial in head and neck eczema [31]. Other studies have suggested that head and neck eczema may respond to systemic antifungal therapy regardless of IgE sensitization, thus the role of IgE sensitization in predicting clinical treatment responses thereby remains unclear [32].

Although allergic inflammation is initiated by IgE antibodies reacting with their allergen, and not by IgE molecules in general, an increased concentration of 'total IgE' is sometimes regarded as a marker for allergy. However, studies have found increased levels of 'total IgE' in nonallergic/nonimmunologic disorders such as those related to cigarette smoke exposure [33,34] and alcohol consumption [35]. Elevated levels of IgE have also been found in infections caused by certain viruses [36], bacteria such as *S. aureus* [22], helminth infestations [37], over-the-counter cough syrups [38], and even in very special, immunologic situations such as the graft-versus-host reaction after bone marrow transplantation [39]. Plasma cells can be stimulated to increase IgE production in many different ways. Since IgE molecules, which are not allergen-specific antibodies, do not have any known biologic function, such as the complement activation of IgG, it is not clear if IgE can be taken as a surrogate marker for any clinical event. Another situation could be an eczema colonized with *S. aureus* or an agent with a similar superantigen potency. A dose/response relationship has been found between airway reactivity and serum IgE concentration [40] and also between alcohol consumption during pregnancy and early onset of eczema in the offspring of atopic parents [41]. Further studies are required to understand the clinical implications of these findings.

#### **Prognostic value of IgE antibody measurement in eczema**

To date, only three cohort studies have investigated whether IgE sensitization can predict eczema development in later life. Two of these studies found no significant association between IgE antibody levels to egg at 12 months and eczema at 2 and 7 years of age, respectively. The third study suggested that sensitization to egg at 1 year of age can predict eczema by the age of 7 years. In addition, IgE sensitization may not yet have developed at these ages.

A number of earlier descriptive studies have claimed that children with eczema and a positive family history of allergic disease may eventually develop allergic asthma and rhinitis [42–44]. However, these studies did not differentiate between atopic and nonatopic phenotypes [45].

Two small prospective studies recently demonstrated that the risk of developing allergic respiratory disease appeared to be increased in IgE-associated versus non-IgE-associated

eczema [46,47]. Only very few population-based surveys have systematically investigated the clinical predictive value of eczema with and without coexisting IgE sensitization [48,49]. A recent study of 1314 German children followed from birth to 7 years of age found that early wheeze and IgE sensitization pattern were significant predictors of wheezing at school age, irrespective of early eczema [50]. Early eczema without early wheeze or IgE sensitization constituted no increased risk of subsequent wheeze or bronchial reactivity. The same study found that children with eczema and wheeze had a marked loss in lung function, suggesting a distinct phenotype, rather than a simple progression from eczema to asthma as part of so-called allergic march.

Finally, the authors found two studies that investigated whether IgE sensitization influenced overall eczema prognosis. In particular, sensitization to egg and cow's milk appeared to be associated with disease persistence and severity in a recent study by Wolkerstorfer and colleagues [27]. Patients were 1–2 years old, had established eczema, a family history of allergic disease and were followed up for 18 months. However, Novembre and colleagues found no association between atopic state and eczema persistence in a smaller hospital study [51]. The authors did not identify any studies on treatment responsiveness in IgE-associated versus non-IgE-associated eczema [52].

#### **Expert commentary**

Eczema, previously referred to as 'atopic dermatitis' or 'atopic eczema', is a chronic, pruritic inflammatory disorder of the skin with typical morphology and an age-related distribution; for example, on the face and flexural areas in young people and the hands of adults. While the association between IgE sensitization and eczema has been clearly demonstrated in population-based studies, partly depending on geographic location and disease severity, the determination of IgE sensitization does not help to make a diagnosis of eczema. However, knowledge of atopic status appears to have prognostic value in children with eczema, since IgE sensitization is associated with an increased risk of developing allergic respiratory disease later in life. These children may also have more persistent and severe disease.

#### **Five-year view**

- The precise role of IgE sensitization in eczema deserves further study, preferably through cohort studies of well-defined populations followed up for several years
- Identification of atopy, which must be performed by skin tests or IgE antibody assays, should be included in epidemiologic studies, where possible, as an important and possibly independent explanatory variable for disease outcome
- Application of a uniform, recognized nomenclature is a prerequisite for communicating study findings among scientists, healthcare providers, patients and society

## Key issues

- The association between immunoglobulin (Ig)E sensitization and eczema has been clearly demonstrated in population-based studies.
- However, the determination of IgE sensitization is of some value in diagnosis, but fails to become useful when other systematic and examined signs are taken into account.
- Knowledge of atopic status appears to have prognostic value in children with eczema.
- Previously, the definition of what constitutes an atopic individual has been unclear. New nomenclature proposed by the European Academy of Allergology and Clinical Immunology and the World Allergy Organization will facilitate continued research and communication of results in this area.

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