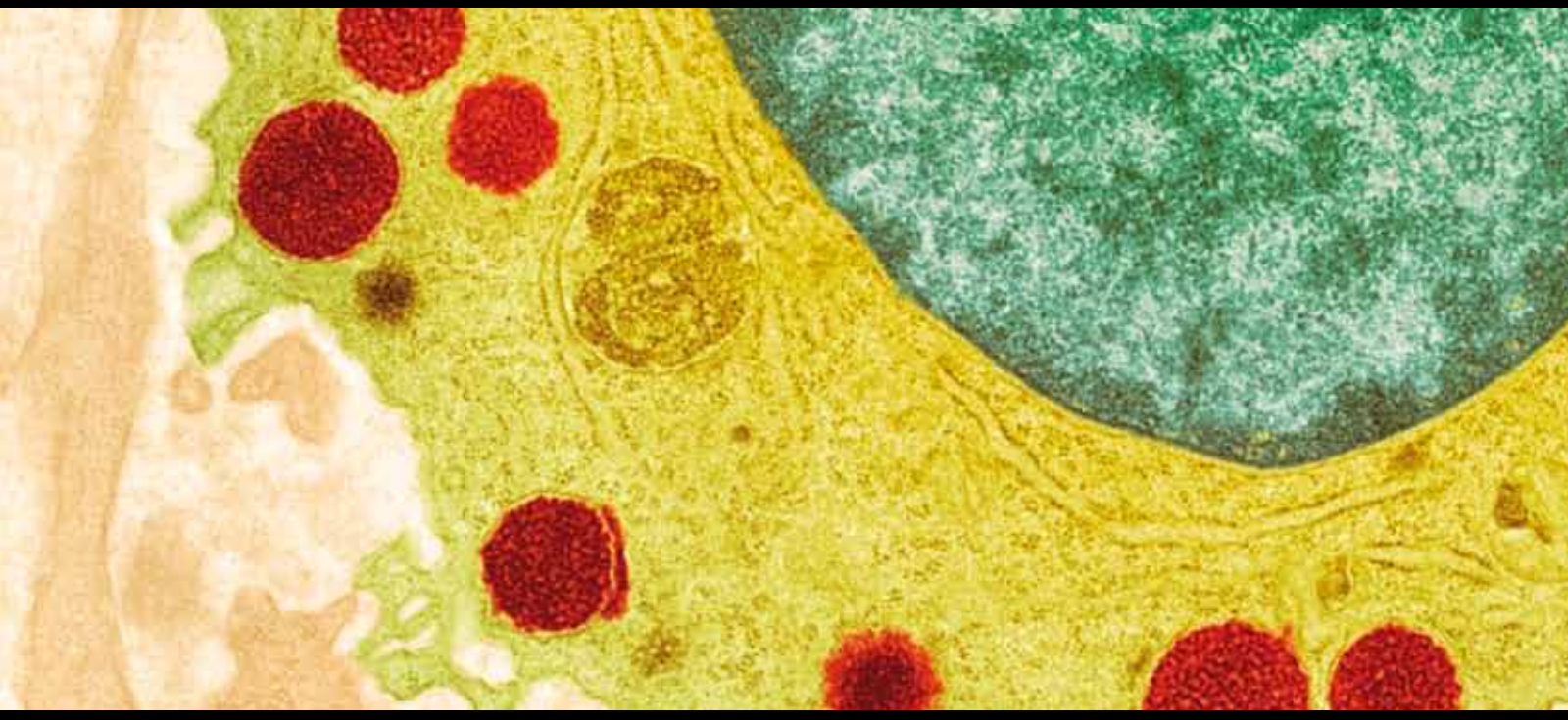
Journal of Allergy

Pediatric Allergy

Guest Editors: Mary Beth Hogan, Jacqueline A. Pongracic, and John Bastian



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Editorial Board

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Editorial
Pediatric Allergy

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Allergist/immunologists who treat children are often left to apply clinical solutions that were developed in adult populations. Pediatric allergists intuitively know that differences in disease between adults and children have widely divergent contributory factors. The inception of allergic sensitization followed by the development of diseases such as atopic dermatitis and asthma suggests a different treatment paradigm than adult diseases in which inflammation is typically long standing and may possibly be irreversible. In fact, pediatric clinicians are focused on (1) treatments specifically designed for children, (2) treatments which may prevent allergic sensitization, and (3) the prevention of disease progression. Research that is focused upon these objectives is uniquely positioned to advance the understanding and treatment of pediatric allergic diseases.

There are other factors which have adversely affected progress in this area. New investigators who are trained in pediatrics are difficult to find. This is a significant problem in the particularly small field of pediatric allergy/immunology. The discipline is in the process of establishing a significant presence in general pediatric training programs. This special issue is designed to showcase pediatric allergy/immunology investigators. The research articles are focused on identifying elements surrounding the onset of atopy or therapies designed for children. The review articles are aimed at new and provocative thinking regarding the development of atopy. This issue unites pediatric allergists worldwide in establishing a forum of discussion around the issues of atopic sensitization in children and the treatment of these diseases.

New clinically relevant research in pediatric allergy is vital to our field. M. Ben-Shoshan et al. report on demographic factors as predictors of development of food allergy. This work could identify which populations should be targeted for prevention, education, and therapeutic strategies in the future. A. Gangemi et al. present a provocative preliminary study outlining a possible role of L-carnitine in the treatment of pediatric asthma. Their findings could lead to investigation of alternative treatments for asthma in children. Other investigators have focused on the therapy of Hymenoptera venom anaphylaxis with an ultrarush protocol. Venom allergy, like asthma, is clearly different in children than adults. The establishment of the safety of this protocol advances the care of children with this potentially life-threatening disease. In addition, the effect of regional pollen exposure upon the development of aeroallergen sensitization is a practical reminder to pediatric allergists of the origins of allergic rhinitis and asthma. This study illustrates the importance of understanding the changing aeroallergen environment in which children live and in which pediatric allergists practice.

Immune responsiveness and allergy are integrally related and multiple organ systems can be affected, even in childhood. A review article regarding the potential of a linkage between allergy and immune deficiency takes us back to fundamental elements in immunology. Another factor in the development of atopy is discussed in an article reviewing the role of skin barrier function in the atopic march. Failures of barrier function can increase exposure of the immune system to allergen, thereby potentiating the onset of allergic sensitization. R. J. Hopp reviews pediatric eosinophilic esophagitis and illustrates the complex and progressive nature of this increasingly common allergic disease. As in the case of venom allergy and asthma, eosinophilic esophagitis is different in children versus adults. Clinical studies are lacking

in pediatric eosinophilic esophagitis. This article is a siren call to address the initiating factors for this disease and of the need for pediatric-based therapies tailored for the chronicity and complexity of eosinophilic esophagitis. A broad view of the environmental factors that affect exhaled nitric oxide levels in asthmatic children reveals that indoor and outdoor pollutants can affect the inflammatory factors involved in the pulmonary tree. In addition, these triggers may affect the interpretation of obtained levels.

Psychosocial issues in pediatric anaphylaxis are frequently debilitating and hinder effective management. This review article outlines these common problems. Psychosocial influences in pediatric allergic diseases are taken one step further in a provocative review by C. L. Duncan et al. This article suggests that not only do psychosocial factors influence the development and treatment of atopic diseases, but those psychosocial factors might influence the development of atopy via a novel epigenetic route.

This issue revolves around original research in pediatric allergy/immunology and thoughtful review articles in this field. This mixture was designed to discuss hot issues in our understanding of the initiation of pediatric allergic diseases and the treatment of those diseases once established. We hope that clinicians who treat children with allergic diseases will enjoy this blend of exciting new research and reevaluation of the customary way of thinking of these problems. Pediatric allergists interested in food allergy, atopic dermatitis, asthma, and anaphylaxis should continue to question and investigate the many avenues of "Why do children develop allergies?" The fruit of their labors will not only benefit children but also adults. What a wonderful reversal of the usual trend would this be !

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Review Article

Skin Barrier Function and Its Importance at the Start of the Atopic March

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Atopic dermatitis can be due to a variety of causes from nonatopic triggers to food allergy. Control of egress of water and protection from ingress of irritants and allergens are key components of cutaneous barrier function. Current research suggests that a degraded barrier function of the skin allows the immune system inappropriate access to environmental allergens. Epidermal aeroallergen exposure may allow sensitization to allergen possibly initiating the atopic march. Further research into connections between epidermal barrier function and possible allergen sensitization will be important to undertake. Future clinical trials focused on skin barrier protection may be of value as a possible intervention in prevention of the initiation of the atopic march.

1. Introduction

The atopic march refers to the natural progression of atopic diseases from atopic dermatitis in infancy to atopic asthma in school age children. Recent research has uncovered exciting data concerning the initiation of the atopic march. A previously little valued component of the epidermis, the strateum corneum, has become an area of scientific attention in the study of the allergic diathesis. This focus on epidermal barrier function potentially provides a heightened understanding of both atopic dermatitis and the initiation of the atopic march. Improving barrier function with reduced water loss and minimized ingress of allergens might become an important tool to controlling the onset of the atopic march.

2. Epidemiology and Definition of Atopic Dermatitis

Atopic dermatitis is one of the most significant and common skin diseases of childhood. Studies from Japan suggest that the prevalence for atopic dermatitis in childhood may be as high as 11–25% [1, 2]. There is a 15.8% prevalence of atopic dermatitis in 3–5-year-old children in New Zealand [3]. A US-population-based study revealed that the prevalence of atopic dermatitis amongst 5–9-year olds was 17.2% [4, 5].

Atopic dermatitis is an inflammatory cutaneous disease characterized by erythema, pruritus, altered barrier function, and immune dysfunction resulting in IgE sensitization. Dysfunction of antimicrobial peptides such as defensins, psoriasins, and cathelicidins is associated with the development of atopic dermatitis [6–8]. Functional alteration of these peptides has been associated with eczema herpeticum. A perturbation in the function of these peptides can result in cutaneous infection with *Staphylococcus aureus*. Infectious sequelae frequently result in atopic dermatitis exacerbations. These and other developments in atopic dermatitis are exciting. However, the emphasis of this paper will be confined to defining the importance of altered strateum corneum function and its possible link to the atopic march.

3. Components of the Strateum Corneum Establishing Skin Barrier Function

Epidermal layers of the skin include, the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum,

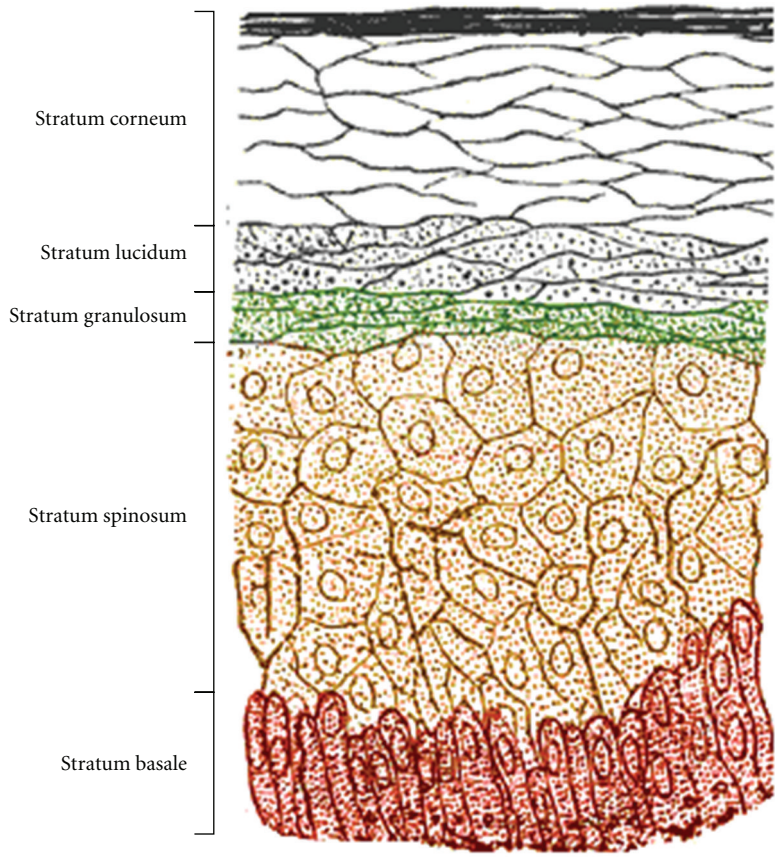

Figure 1: Layers forming the protective epidermal barrier.

and stratum basale. The structure of these layers is demonstrated in Figure 1 [9]. Until recently, the outermost layer of the dermis was relatively ignored as a factor in the development of atopic dermatitis. In the epidermis there are multiple components important to barrier function. These components include claudin, desmoglein, filaggrin, ceramide, and proper control of proteases (Table 1). When properly functioning, this layer prevents water loss and provides a barrier to epidermal invasion of allergens and bacteria.

Each corneocyte in the stratum corneum is held together by tight junctions and scaffolding proteins. Claudins are a family of proteins that are important components of the tight junctions between corneocytes that help to maintain the skin barrier. Claudin-deficient patients have aberrant formation of tight junctions that cause disruption of the bioelectric barrier [10]. Claudins are an essential component controlling the paracellular barrier flow of molecules in the intercellular space between the cells of an epithelium. These tight junctions help prevent moisture loss through this layer of the skin as well as block access through the skin of external environmental allergens. Claudin expression in atopic dermatitis patients has been inversely correlated to increased T_H2 biomarker expression [10]. This suggests that claudin may help inhibit immune exposure to allergic stimuli.

Similar tight junction dysfunction has been found in desmoglein transgenic mice. Desmogleins play a role in the formation of desmosomes that promotes cell-to-cell tight junction adhesion in the stratum corneum. Mice without desmoglein were ultimately found to die from dehydration presumably due to increased transepidermal water loss mediated by lack of corneocyte adhesion [11].

A different genetic knock-out mouse model of atopic dermatitis examined the relationship between scaffolding proteins and skin barrier function. Scaffolding proteins are required to overlaying tight junction linked corneocytes with cross-linked proteins and lipids to form an effective epidermal barrier. Loss of epidermal scaffolding proteins such as involucrin, envoplakin, and periplakin is associated with alterations in epidermal barrier function such as filaggrin and desmoglein-1 processing with formation of an abnormal cornified epidermal envelope [12]. Immune regulatory dysfunction after disruption of scaffolding proteins was associated with increased CD4+ T cell infiltration and lack of gamma delta+ T cells. This association suggests that an abnormal epidermal layer may contribute to the allergic inflammatory process associated with atopic dermatitis.

Another factor allowing proper function of the epidermis is the control of the on or off activity of skin proteases. SPINK is a protein that inhibits serine protease action in the skin. The SPINK gene is absent in Netherton's syndrome. This syndrome is characterized by severe atopic dermatitis, scaling, and an elevated serum IgE [13]. In this potentially

Table 1: Functions of epidermal barrier components and possible protective role in prevention of atopic march.

Barrier component	Type	Function	Possible role in preventing atopic march
Claudin	Tight junction protein	Prevention of water loss	Prevention of T_H2 activation
Desmoglein	Desmosome formation	Prevention of water loss	Blocking allergen penetration
Involucrin/envoplakin/periplakin	Scaffolding protein	Structural components to create epidermal barrier	Allowing appropriate immunoregulatory T-cell environment
Urocanic acid	Chromophore	Hygroscopic acid-base regulator/photoprotection	Maintaining skin barrier function
Filaggrin	Protein	Decreased permeability of water soluble molecules/epidermal differentiation	Blocking allergen penetration
Ceramide	Lipid	Contribution to skin permeability barrier and epidermal differentiation	Blocking mast cell infiltration/expression of TNF Blocking Mast production of allergic cytokines. Blocking allergen penetration
Skin protease inhibitors (SPINK)	Protein	Prevention of protease alteration in filaggrin and ceramide production	Maintaining skin barrier function

lethal disease, lack of SPINK results in uncontrolled serine protease elastase-2 activity. Increased protease activity negatively alters filaggrin and lipid (ceramide) processing thereby decreasing skin barrier function. It has been suggested that barrier function in populations with SNP alterations of SPINK5 may lead to increased susceptibility to asthma [14].

Increased protease functioning also occurs in atopic dermatitis patients. Allergens such as dust mite, cockroach and mold can activate serine proteases, adversely affecting the epidermal barrier [15]. In fact, dust mite and cockroach allergens themselves can be proteolytically active and stimulate the serine protease pathway thereby decreasing skin barrier function [16, 17].

Filaggrin is an important protein found in lamellar bodies of stratum granulosum corneocytes. When these granules are released they become a vital component of the extracellular matrix of the stratum corneum. Mutations of the filaggrin gene have been associated with ichthyosis vulgaris and persistent atopic dermatitis [18, 19]. Filaggrin gene defects may exist in as many as 50% of atopic dermatitis patients [20, 21]. Meta-analysis of filaggrin polymorphism data has identified a genetic alteration in filaggrin as a significant risk for development of atopic dermatitis [22]. The results of filaggrin gene mutations are striking as several studies have demonstrated that the severity of atopic dermatitis correlates with the number of filaggrin gene defects [23–26].

4. Permeability Layer Disruption Is Bidirectional Allowing Both Epidermal Water Loss and Allergen Penetration.

The lipid lamellar matrix is an integral component in controlling the barrier function of the skin. Decreased protein-bound omega-hydroxyceramides are found in the lesional skin of atopic dermatitis patients as compared to control patients [27]. In this study, deficiency of barrier lipid free ceramides was determined to be a major contributing factor in damaging the permeability barrier of the skin.

A murine model of atopic dermatitis illustrates the importance of ceramide in preventing allergen-induced atopic dermatitis. In this model, a synthetic ceramide was applied to the skin of mice noted for the ability to develop atopic dermatitis [28]. In this model of dust-mite-induced atopic dermatitis, ceramide application reduced skin thickness and actually blocked components of allergic inflammation. Inflammatory factors prevented were the cutaneous infiltration by mast cells and expression of tumor necrosis factor. An *in vitro* study has demonstrated that ceramide inhibits mast cell production of IL-5, IL-10, and IL-13 [29]. These models suggest that an intact lipid matrix in the strateum corneum may actually prevent epidermal penetration of allergen and allergic atopic dermatitis.

Filaggrin is another key protein in protecting against water loss through the strateum corneum and is present in

the epidermis as early as 3 months of age [30]. Filaggrin-deficient atopic dermatitis patients have decreased filaggrin-derived natural moisturization factors [31, 32]. The function of filaggrin in the development of the epidermal barrier has been confirmed in murine models of atopic dermatitis. Scharschmidt et al. describe altered lamellar body secretion in an atopic dermatitis flaky tailed mouse model. In this model, a decrease in stratum corneum extracellular matrix component correlated with increased permeability of water soluble molecules [33].

Degradation products of filaggrin have been found to contribute to the formation of the epidermal barrier by providing acidity. This critical function of acidification and hydration of the skin has been linked to filaggrin gene defects in atopic dermatitis [34]. *In vitro* models of skin demonstrate that urocanic acid is a key filaggrin-derived amino acid linked to skin acidity [35]. In this study, skin pH became more basic with decreased filaggrin, which was associated with an increase in dye penetration. The skin performs a vital function in providing barrier function, and if this is interrupted by filaggrin deficiency, then inflammatory irritants, haptens, and infections have greater access to the deeper layers of the skin.

5. Barrier Proteins May Be One Line of Defense against Allergic Diseases

In studies of filaggrin-deficient children, increased transepidermal water loss along with development of specific IgE antibody to dust mite and cat was found with asthma [36, 37]. A recent meta-analysis confirmed that the risk of developing asthma was increased in those with eczema but not in those without atopic dermatitis. Filaggrin gene mutations were linked directly to atopic dermatitis, allergic rhinitis, and the development of asthma in children [38, 39]. These studies together suggest that the lack of barrier function itself may contribute to the development of allergy and asthma.

This reduction in barrier function may allow for the development of inflammation due to increased penetration of allergen through the skin allowing IgE sensitization. In a filaggrin-deficient murine model, allergen exposure over lesional skin was linked to the development of allergen-specific IgE and Th17 expression [40]. Facilitation of allergen sensitization in individuals with filaggrin deficiency is believed to be due to reduced barrier function. This hypothesis of increased skin penetrability correlating with diminished barrier function has been tested with both water and lipid soluble dyes *in vivo*. Dye penetration was deepest with severity of atopic dermatitis and correlated to increasing serum IgE as compared to control patients [34, 35].

6. The Atopic March

Children with atopic dermatitis have a significant risk of going on to develop other atopic diseases such as allergic sensitization and asthma. Whether eczema precedes or postdates the development of allergic sensitization is not clear for all children [41]. Thirty to fifty percent of the children who develop atopic dermatitis go on to develop asthma and two-thirds go on to have allergic rhinitis [36, 42]. In one study of 169 infants with eczema, 35% developed subspecialist-diagnosed asthma and these children had inhalant-induced allergy [36].

The allergic march has a pattern of allergic sensitization that changes as children age. In a study with 262 children with atopic dermatitis, IgE sensitization to food was common under 2 years of age. Between 2 and 5 years of age the children had food allergy but also started to develop inhalant allergy. After 5 years of age the children had mostly inhalant allergy as a significant allergic factor associated with their atopic dermatitis [43].

Dust mite and cockroach are allergens associated with atopic dermatitis [44]. *Alternaria* allergy eventually develops in 56% of atopic dermatitis children by 12 years of age [45]. When 30 children with atopic dermatitis were compared with 30 patients with respiratory symptoms without atopic dermatitis, aeroallergen allergy was significant in a selected population of atopic dermatitis patients. Of these children with atopic dermatitis, 70% were skin test positive for mite, 70% were positive for cockroach, 63% were skin test positive to house dust, 50% had evidence of IgE sensitization to mold, and 43% had IgE reactivity to grass. However, only 10 percent of the kids with respiratory symptoms (and no atopic dermatitis) were allergic to any aeroallergen in this study [46]. This suggests an important link between atopic dermatitis and development of inhalant allergy rather than inhalation of allergen resulting in allergic sensitization and asthma.

Studies suggest that a significant number of these children develop atopic dermatitis first and subsequently become sensitized to aeroallergens. Allergic rhinitis and asthma then follow. Suggested risk factors for this chain of events include atopic parents, possibly cat ownership [47], and presence of eczema prior to 4 years of age [48]. The progression to asthma is as high as 29.5% in children with eczema [49]. Cumulative smoke exposure may be an additional risk factor influencing the development of asthma in FLG-null patients [50]. A recent genome-wide study found that FLG mutation was associated with a chromosomal (11q13.5) variant. These individuals had increased risk of developing atopic dermatitis associated with asthma [51]. This risk of atopic dermatitis patients then developing asthma is significant enough that the Asthma Predictive Index utilizes the presence of atopic dermatitis in a wheezing infant as one of two major criteria for predicting eventual asthma [52].

7. Therapeutic Options Involving Barrier Function and Atopic Dermatitis

Identification of ceramide as a critical element in barrier function has led to the development of ceramide-based emollients. In a study of mild-moderate atopic dermatitis patients, application of ceramide emollient resulted in 69% of patients having no symptoms of eczema and skin

hydrations scores improving significantly [53]. Ceramide-dominant lipid-based emollient was used in 24 children with stubborn atopic dermatitis. In this study, skin cohesion and transepidermal water loss levels improved with atopic dermatitis scores as a result of the reestablishment of extracellular lamellar membranes in the stratum corneum [54]. As in murine studies, ceramide-based emollients in humans have been shown to decrease inflammatory cytokine interleukin-4 expression and decrease transepidermal water loss in atopic dermatitis patients [55].

Strategies for possible prevention of atopic dermatitis include encouraging the natural acidification of the skin. Treating mice with lactobionic acid was associated with normal barrier function in addition to normalization of atopic inflammatory markers such as serum IgE [56]. These atopic dermatitis mice achieved normal lamellar body secretion and lipid bilayer formation after lactobionic acid treatment only. In human patients, early studies suggest that neutral pH soaps may be an effective therapeutic component when treating atopic dermatitis [57]. Whether neutral "baby washes" or water washing alone after birth protects the epidermal barrier and prevents the onset of atopic dermatitis remains to be studied.

Immediate barrier repair can even be implemented on a delipidized stratum corneum with petrolatum without application of ceramide [58]. A preliminary study investigated whether petrolatum can be used immediately after birth to prevent atopic dermatitis. High-risk neonates with first-degree relatives having atopic dermatitis or asthma were enrolled at birth in a feasibility of prevention study [59]. The study utilized an emollient cream and rescue petrolatum at birth as a prevention of atopic dermatitis. This population historically has a 30–50% risk of developing atopic dermatitis by 2 years of age. Only 15% of these treated infants developed eczema and barrier function measurements reflective of normal skin, which suggests a protective effect.

8. Questions for the Future

Murine models suggest that allergen penetration through the skin barrier is important to the development of atopic dermatitis. Human studies show a link between barrier protein dysfunction and development of atopic dermatitis and possibly asthma. Clinical trials have not yet directly looked at allergen penetration through a disordered skin barrier and subsequent development of asthma. Controlled trials with a significant number of patients would be important in determining whether prevention strategies for decreasing allergic sensitization and atopic dermatitis are effective. Longer-term follow-up studies determining whether the onset of allergic rhinitis and asthma is decreased by decreasing the incidence of eczema would also be exciting.

It is apparent that not all patients with filaggrin deficiency go on to develop atopic dermatitis [60]. In fact, if they do develop eczema, remission is possible. It has not been studied whether these patients also are the same atopic dermatitis patients who do not have disease progression to asthma. Factors determining nonexpression of allergic rhinitis and asthma have not been elucidated. Which populations are destined to have a milder disease course? Patients may "naturally" modify disease expression such as self-treatment with hydration and if they do can it be applied as prevention in high-risk infants? Which genetic modifiers associated with filaggrin deficiency lead to or prevent the atopic march?

Research in the alteration and prevention of loss of stratum corneum barrier function may provide answers to questions raised regarding the development of atopic dermatitis and asthma. Early identification of at-risk individuals and developing treatment strategies allowing retention of good skin barrier function may assist in the prevention of allergic sensitization in some individuals. The atopic march may not be inevitable for certain genetically predisposed individuals. Research into maintenance of barrier function in patients at risk for atopy may elucidate the ability to control skin barrier function and prevent onset of atopic dermatitis, and, hopefully, asthma.

Conflict of Interests

None of the authors have any conflict of interests.

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References

[1] J. Kay, D. J. Gawkrodger, M. J. Mortimer, and A. G. Jaron, "The prevalence of childhood atopic eczema in a general population," *Journal of the American Academy of Dermatology*, vol. 30, no. 1, pp. 35–39, 1994.

[2] M. H. Shamssain and N. Shamsian, "Prevalence and severity of asthma, rhinitis, and atopic eczema: the north east study," *Archives of Disease in Childhood*, vol. 81, no. 4, pp. 313–317, 1999.

[3] D. J. Purvis, J. M. D. Thompson, P. M. Clark et al., "Risk factors for atopic dermatitis in New Zealand children at 3.5 year of age," *British Journal of Dermatology*, vol. 152, no. 4, pp. 742–749, 2005.

[4] D. Laughter, J. A. Istvan, S. J. Tofte, and J. M. Hanifin, "The prevalence of atopic dermatitis in Oregon schoolchildren," *Journal of the American Academy of Dermatology*, vol. 43, no. 4, pp. 649–655, 2000.

[5] J. M. Spergel, "Epidemiology of atopic dermatitis and atopic March in children," *Immunology and Allergy Clinics of North America*, vol. 30, no. 3, pp. 269–280, 2010.

[6] T. R. Hata, P. Kotol, M. Boguniewicz et al., "History of eczema herpeticum is associated with the inability to induce human β-defensin (HBD)-2, HBD-3 and cathelicidin in the skin of patients with atopic dermatitis," *British Journal of Dermatology*, vol. 163, no. 3, pp. 659–661, 2010.

[7] R. Gläser, U. Meyer-Hoffert, J. Harder et al., "The antimicrobial protein psoriasin (S100A7) is upregulated in atopic dermatitis and after experimental skin barrier disruption," *Journal of Investigative Dermatology*, vol. 129, no. 3, pp. 641–649, 2009.

[8] P. Y. Ong, T. Ohtake, C. Brandt, I. Strickland et al., "Endogenous antimicrobial peptides and skin infections in atopic

dermatitis," *The New England Journal of Medicine*, vol. 347, no. 15, pp. 1151–1160, 2002.

[9] J. G. Marks Jr. and J. J. Miller, *Lookingbill and Marks' Principles of Dermatology*, Elsevier Health Sciences, Philadelphia, Pa, USA, 4th edition, 2006.

[10] A. De Benedetto, N. M. Rafaels, L. Y. McGirt et al., "Tight junction defects in patients with atopic dermatitis," *Journal of Allergy and Clinical Immunology*, vol. 127, no. 3, pp. 773–786, 2011.

[11] P. M. Elias, N. Matsuyoshi, H. Wu et al., "Desmoglein isoform distribution affects stratum corneum structure and function," *Journal of Cell Biology*, vol. 153, no. 2, pp. 243–249, 2001.

[12] L. M. Sevilla, R. Nachat, K. R. Groot et al., "Mice deficient in involucrin, envoplakin, and periplakin have a defective epidermal barrier," *Journal of Cell Biology*, vol. 179, no. 7, pp. 1599–1612, 2007.

[13] C. Bonnart, C. Deraison, M. Lacroix et al., "Elastase 2 is expressed in human and mouse epidermis and impairs skin barrier function in Netherton syndrome through filaggrin and lipid misprocessing," *Journal of Clinical Investigation*, vol. 120, no. 3, pp. 871–882, 2010.

[14] Q. Liu, Y. Xia, W. Zhang et al., "A functional polymorphism in the SPINK5 gene is associated with asthma in a Chinese Han Population," *BMC Medical Genetics*, vol. 10, article 59, 2009.

[15] S. K. Jeong, H. J. Kim, J. K. Youm et al., "Mite and cockroach allergens activate protease-activated receptor 2 and delay epidermal permeability barrier recovery," *Journal of Investigative Dermatology*, vol. 128, no. 8, pp. 1930–1939, 2008.

[16] T. Roelandt, C. Heughebaert, and J. P. Hachem, "Proteolytically active allergens cause barrier breakdown," *Journal of Investigative Dermatology*, vol. 128, no. 8, pp. 1878–1880, 2008.

[17] F. Mascia, V. Mariani, A. Giannetti, G. Girolomoni, and S. Pastore, "House dust mite allergen exerts no direct proinflammatory effects on human keratinocytes," *Journal of Allergy and Clinical Immunology*, vol. 109, no. 3, pp. 532–538, 2002.

[18] A. Sandilands, G. M. O'Regan, H. Liao et al., "Prevalent and rare mutations in the gene encoding filaggrin cause ichthyosis vulgaris and predispose individuals to atopic dermatitis," *Journal of Investigative Dermatology*, vol. 126, no. 8, pp. 1770–1775, 2006.

[19] J. N. Barker, C. N. Palmer, Y. Zhao et al., "Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood," *Journal of Investigative Dermatology*, vol. 127, no. 3, pp. 564–567, 2007.

[20] G. M. O'Regan and A. D. Irvine, "The role of filaggrin in the atopic diathesis," *Clinical and Experimental Allergy*, vol. 40, no. 7, pp. 965–972, 2010.

[21] J. M. Jungersted, H. Scheer, M. Mempel et al., "Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema," *Allergy*, vol. 65, no. 7, pp. 911–918, 2010.

[22] H. Baurecht, A. D. Irvine, N. Novak et al., "Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data," *Journal of Allergy and Clinical Immunology*, vol. 120, no. 6, pp. 1406–1412, 2007.

[23] C. N. Palmer, A. D. Irvine, A. Terron-Kwiatkowski et al., "Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis," *Nature Genetics*, vol. 38, no. 4, pp. 441–446, 2006.

[24] T. Nomura, A. Sandilands, M. Akiyama et al., "Unique mutations in the filaggrin gene in Japanese patients with ichthyosis vulgaris and atopic dermatitis," *Journal of Allergy and Clinical Immunology*, vol. 119, no. 2, pp. 434–440, 2007.

[25] A. Ruether, M. Stoll, T. T. Schwarz, S. Schreiber, and R. Folster-Holst, "Filaggrin loss-of-function variant contributes to atopic dermatitis risk in the population of Northern Germany," *British Journal of Dermatology*, vol. 155, no. 5, pp. 1093–1094, 2006.

[26] S. J. Brown, C. L. Relton, and H. Liao, "Filaggrin haploinsufficiency is highly penetrant and is associated with increased severity of eczema: further delineation of the skin phenotype in a prospective epidemiological study of 792 school children," *British Journal of Dermatology*, vol. 161, no. 4, pp. 884–889, 2009.

[27] O. Macheleidt, H. W. Kaiser, and K. Sandhoff, "Deficiency of epidermal protein-bound ω-hydroxyceramides in atopic dermatitis," *Journal of Investigative Dermatology*, vol. 119, no. 1, pp. 166–173, 2002.

[28] J. S. Kang, W. K. Yoon, J. K. Youm et al., "Inhibition of atopic dermatitis-like skin lesions by topical application of a novel ceramide derivative, K6PC-9p, in NC/Nga mice," *Experimental Dermatology*, vol. 17, no. 11, pp. 958–964, 2008.

[29] N. Chiba, A. Masuda, Y. Yoshikai, and T. Matsuguchi, "Ceramide inhibits LPS-induced production of IL-5, IL-10, and IL-13 from mast cells," *Journal of Cellular Physiology*, vol. 213, no. 1, pp. 126–136, 2007.

[30] C. Flohr, K. England, S. Radulovic et al., "Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age," *British Journal of Dermatology*, vol. 163, no. 6, pp. 1333–1336, 2010.

[31] S. Kezic, G. M. O'Regan, and N. Yau, "Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity," *Allergy*, vol. 66, no. 7, pp. 934–940, 2011.

[32] I. Nemoto-Hasebe, M. Akiyama, T. Nomura, A. Sandilands, W. H. McLean, and H. Shimizu, "Clinical severity correlates with impaired barrier in filaggrin-related eczema," *Journal of Investigative Dermatology*, vol. 129, no. 3, pp. 682–689, 2009.

[33] T. C. Scharschmidt, M. Q. Man, Y. Hatano et al., "Filaggrin deficiency confers a paracellular barrier abnormality that reduces inflammatory thresholds to irritants and haptens," *Journal of Allergy and Clinical Immunology*, vol. 124, no. 3, pp. 496–506, 2009.

[34] T. Knor, A. Meholji-Fetahovic, and A. Mehmedagic, "Stratum corneum hydration and skin surface pH in patients with Atopic dermatitis," *Acta Dermatovenerologica Croatica*, vol. 19, no. 4, pp. 242–247, 2011.

[35] M. Mildner, J. Jin, and L. Eckhart, "Knockdown of filaggrin impairs diffusion barrier function and increases UV sensitivity in a human skin model," *Journal of Investigative Dermatology*, vol. 130, no. 9, pp. 2286–2294, 2010.

[36] J. M. Spergel and A. S. Paller, "Atopic dermatitis and the atopic march," *Journal of Allergy and Clinical Immunology*, vol. 112, no. 6, pp. S118–S127, 2003.

[37] J. Henderson, K. Northstone, S. P. Lee et al., "The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study," *Journal of Allergy and Clinical Immunology*, vol. 121, no. 4, pp. 872–877, 2008.

[38] Y. Ohshima, A. Yamada, M. Hiraoka et al., "Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year follow-up study," *Annals of Allergy, Asthma and Immunology*, vol. 89, no. 3, pp. 265–270, 2002.

[39] R. van den Oord and A. Sheikh, "Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis," *BMJ*, vol. 339, Article ID b2433, 2009.

[40] M. K. Oyoshi, G. F. Murphy, and R. S. Geha, "Filaggrin-deficient mice exhibit TH17-dominated skin inflammation and permissiveness to epicutaneous sensitization with protein antigen," *Journal of Allergy and Clinical Immunology*, vol. 124, no. 3, pp. 485–493, 2009.

[41] R. Osawa, M. Akiyama, and H. Shimizu, "Filaggrin gene defects and the risk of developing allergic disorders," *Allergology International*, vol. 60, no. 1, pp. 1–9, 2011.

[42] J. M. Spergel, "Epidemiology of atopic dermatitis and atopic March in children," *Immunology and Allergy Clinics of North America*, vol. 30, no. 3, pp. 269–280, 2010.

[43] I. J. Wang, Y. T. Lin, Y. H. Yang et al., "Correlation between age and allergens in pediatric atopic dermatitis," *Annals of Allergy, Asthma and Immunology*, vol. 93, no. 4, pp. 334–338, 2004.

[44] S. Michel, N. Yawalkar, B. Schnyder, B. Fischer, and A. Helbling, "Eczematous skin reaction to atopy patch testing with cockroach in patients with atopic dermatitis," *Journal of Investigational Allergology and Clinical Immunology*, vol. 19, no. 3, pp. 173–179, 2009.

[45] M. T. Hedayati, A. Arabzadehmoghadam, and Z. Hajheydari, "Specific IgE against Alternaria alternata in atopic dermatitis and asthma patients," *European Review for Medical and Pharmacological Sciences*, vol. 13, no. 3, pp. 187–191, 2009.

[46] S. Wananukul, P. Huiprasert, and P. Pongprasit, "Eczematous skin reaction from patch testing with aeroallergens in atopic children with and without atopic dermatitis," *Pediatric Dermatology*, vol. 10, no. 3, pp. 209–213, 1993.

[47] A. J. Lowe, M. J. Abramson, C. S. Hosking et al., "The temporal sequence of allergic sensitization and onset of infantile eczema," *Clinical and Experimental Allergy*, vol. 37, no. 4, pp. 536–542, 2007.

[48] T. G. Epstein, D. I. Bernstein, L. Levin et al., "Opposing effects of cat and dog ownership and allergic sensitization on eczema in an atopic birth cohort," *Journal of Pediatrics*, vol. 158, no. 2, pp. 265–271, 2010.

[49] A. E. van der Hulst, H. Klip, and P. L. Brand, "Risk of developing asthma in young children with atopic eczema: a systematic review," *Journal of Allergy and Clinical Immunology*, vol. 120, no. 3, pp. 565–569, 2007.

[50] N. D. Berg, L. L. Husemoen, B. H. Thuesen et al., "Interaction between filaggrin null mutations and tobacco smoking in relation to asthma," *Journal of Allergy and Clinical Immunology*, vol. 129, no. 2, pp. 374–380, 2012.

[51] I. Marenholz, A. Bauerfeind, J Esparza-Gordillo et al., "The eczema risk variant on chromosome 11q13 (rs7927894) in the population-based ALSPAC cohort: a novel susceptibility factor for asthma and hay fever," *Human Molecular Genetics*, vol. 20, no. 12, pp. 2443–2449, 2011.

[52] J. A. Castro-Rodriguez, C. J. Holberg, A. L. Wright, and F. D. Martinez, "A clinical index to define risk of asthma in young children with recurrent wheezing," *American Journal of Respiratory and Critical Care Medicine*, vol. 162, no. 4 I, pp. 1403–1406, 2000.

[53] J. I. Na, J. S. Hwang, H. J. Park et al., "A new moisturizer containing physiologic lipid granules alleviates atopic dermatitis," *Journal of Dermatological Treatment*, vol. 21, no. 1, pp. 23–27, 2010.

[54] S. L. Chamlin, J. Kao, I. J. Frieden et al., "Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity," *Journal of the American Academy of Dermatology*, vol. 47, no. 2, pp. 198–208, 2002.

[55] K. Y. Park, D. H. Kim, M. S. Jeong, K. Li, and S. J. Seo, "Changes of antimicrobial peptides and transepidermal water loss after topical application of tacrolimus and ceramide-dominant emollient in patients with atopic dermatitis," *Journal of Korean Medical Science*, vol. 25, no. 5, pp. 766–771, 2010.

[56] J. Bikowski, "The use of cleansers as therapeutic concomitants in various dermatologic disorders," *Cutis*, vol. 68, no. 5, supplement, pp. 12–19, 2001.

[57] E. L. Simpson, T. M. Berry, P. A. Brown, and J. M. Hanifin, "A pilot study of emollient therapy for the primary prevention of atopic dermatitis," *Journal of the American Academy of Dermatology*, vol. 63, no. 4, pp. 587–593, 2010.

[58] M. Lodén, "Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders," *American Journal of Clinical Dermatology*, vol. 4, no. 11, pp. 771–788, 2003.

[59] Y. Hatano, M. Q. Man, Y. Uchida et al., "Maintenance of an acidic stratum corneum prevents emergence of murine atopic dermatitis," *Journal of Investigative Dermatology*, vol. 129, no. 7, pp. 1824–1835, 2009.

[60] J. Thyssen, B. Carlsen, and H. Bisgaard, "Individuals who are homozygous for the 2282del4 and R501X filaggrin null mutations do not always develop dermatitis and complete long-term remission is possible," *Journal of the European Academy of Dermatology and Venereology*, vol. 26, no. 3, pp. 386–389, 2012.

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Research Article

Early Pollen Sensitization in Children Is Dependent upon Regional Aeroallergen Exposure

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Introduction. Aeroallergen sensitization occurs at an earlier age than previously noted. The purpose of this paper was to identify which pollens cause early sensitization in young children presenting with rhinitis symptoms. *Methods*. This paper was a retrospective analysis of skin test results from 2- to 8-year-old patients presenting with a history consistent with allergic rhinitis. Patients were tested to aeroallergens common to the Great Basin along with a histamine and saline control. Pollen counts were obtained from a Reno, NV-certified counting station. *Results*. 123 children less than 8 years of age were identified. Over 50% of these children were sensitized to at least one aeroallergen. Chemopodaciae, timothy, alfalfa, black walnut, olive, mountain cedar and willow were predominating sensitizing aeroallergens of the Great Basin Region. Pollen counts were notable for a early spring peak for the tree season, grass season in May and weed season in August. Pollen levels continued to November at low levels. *Discussion*. Aeroallergens causing early sensitization differed from those which had predominately been reported in other regions of the United States. Pediatric allergists should consider performing a local review of sensitizing aeroallergens in their region to assist with identification and management of allergic rhinitis in their youngest patients. Please make style changes as appropriate.

1. Introduction

The prevalence of allergic diseases in childhood has increased considerably in developed countries over the last several decades [1]. Research has been published recently suggesting that children do in fact become sensitized to outdoor allergens at an early age and, thus, should be referred for skin testing earlier. One study found that outdoor allergens are as common sensitizing agents as indoor allergens by three years of age [2]. Another study found that the prevalence and incidence of seasonal allergic rhinitis increases after age two [3]. Furthermore, it has been found that sensitization to inhalant allergens occurring in the first few years of life is a major risk factor for developing persistent wheeze in childhood [4]. This study found children with allergic rhinitis before the age of five were significantly more likely to have developed wheezing between age 5 and 13. They were nearly four times more likely to have childhood-onset wheezing. Children with early allergic rhinitis accounted for 41% of all cases of childhood wheezing.

The current research regarding outdoor allergen sensitization is limited to research conducted in eastern North America and other countries. There is little data concerning sensitization to allergens common to the western part of North America specifically the Great Basin of Nevada. This geographically unique region extends south along the entire Sierra Nevada Mountain Range from the Snake River Plain in southern Oregon to southern California and eastward to the Wasatch Mountain Range encompassing most of Nevada and a large portion of Utah with major cities of Las Vegas and Reno, Nevada, and Salt Lake City, Utah. Elevation ranges from near sea level to 13,000 feet. This is a closed drainage basin with rain and snow eventually leaving the basin by either evaporation, flowing into lakes (mostly saline), or sinking underground. This region is amongst the most arid regions in Continental North America.

The aim of this study was to identify in children the most frequent sensitizing pollen aeroallergens found in the Great Basin desert region. The identification of common sensitizers is relevant for both the identification and management of

allergic disease, specifically allergic rhinitis and asthma in young children.

2. Methods

Pollen counts were recorded by the NAB as pollen grains/cumbic meter with trees at 1–14 low, 15–89 moderate, 90–1499 high and >1500 as very high. Grass pollen levels were recorded as 1–4 low, 5–19 moderate, 20–199 high. Weeds were noted to be 1–9 low, 10–49 moderate and 50–499 as high. This study were a retrospective analysis of skin testing completed on 2- to 18-year-old patients who presented with a history consistent with allergic rhinitis conducted over 18 months from January 2009 ending June 2010. Patients were tested using commercially available extracts to common Great Basin outdoor allergens including weeds, grasses, and trees. The panel of common allergens was determined by consultation with the University of Nevada Agricultural Extension regarding frequency of allergenic plants native to the region and those upwind allergenic plants within 200 miles of the Great Basin to determine common pollens transferred to this region. In addition, local nurseries were called to determine which nonnative species were commonly sold.

Skin testing was performed using the prick-puncture method with a Greer DermaPik (Greer Laboratories, Lenoir, NC, USA) [5]. Saline and histamine controls were used in all patients. Test allergens producing a wheal of 3 mm or greater and at least half the size of the histamine wheal control were regarded as a positive reaction. False positive dermatographic saline controls were subtracted from all skin test results including the histamine before determining if the positive histamine size and positive skin test size were reached. The skin test results of 268 patients who met inclusion criteria were entered into an Excel spreadsheet for analysis. No unique identifiers were associated with the data collection, and the study met requirements for an IRB waiver.

Pollens relevant to the region included a possible panel of 10 weeds, 6 grasses, and 20 trees (Table 1). Pollen counts for the Great Basin Region correlating to the first continuous year of collected patient data were obtained from a Reno, NV-certified pollen counting station on the National Allergy Bureau (NAB) website. Pollen counts were recorded by the NAB as pollen grains/cubic meter with trees at 1–14 low, 15–89 moderate, 90–1499 high, >1500 very high, with grasses at 1–4 low, 5–19 and moderate, 20–199 high and weeds 1–9 low, 10–49, moderate and 50–499 at high. The 2009 description of air-borne pollen levels in Reno, NV, USA are reported if changes in pollen counts are recorded at least two weeks in a row without change in level. Most common sensitizing plants were also noted if reported at least in two consecutive weeks. This is to avoid possible discrepancies induced by changing wind patterns.

Table 1: Great Basin aeroallergens available in skin test panel.

Weeds	Grasses	Trees	
Dock	Timothy	Privet	Birch
Pigweed	Brome	Mountain Cedar	Olive
Russian thistle	Bermuda	Sycamore	Ash
Saltbush	Saltgrass	Pine	Aspen
Sagebrush	Johnson	Elm	Willow
Western ragweed	Alfalfa	Ailanthus	Cottonwood
Tall and short ragweed		Locust	Pecan
Rabbitbush		Maple	Walnut
Marsh elder		Sweet gum	Alder
Plantain		Mulberry	Oak

3. Results

A total of 268 patients, ages 2–18 were included in this study. While all pediatric patients were initially included, it was noted that the sensitization rate for all trees, grasses, and weeds plateaued at age eight; 91% of children had a positive test to at least one weed, 82% were positive to at least one grass, and 83% were positive to at least one tree (Figure 1). In addition, the most common sensitizing tree, grasses, and weeds after age 7 were unchanged from the 6-7-year-old age group.

A total of 46% of the patients were under the age of eight years old, and this group was further defined due to observed differences in sensitization rates from children 8 years of age and older. Specifically, sixteen children in the age group 2-3 years, fifty-one children in the age group 4-5 years, and fifty-six children in the age group 6-7 years were evaluated.

In the age group 2-3 years, 63% of children tested positive to at least one weed, 57% of children tested positive to at least one grass, and 53% tested positive to at least one tree. As age increased, the percentage testing positive to at least one weed, one grass, or one tree also increased. The percentage of positive skin tests to outdoor allergens is seen in Figure 1 for each age group.

Pollen counting began in the Great Basin region at the start of the 2009 tree season in mid-January. Counts started at the low range mid-January and were observed in the high range by mid-February. Very high counts for trees became noted briefly in April and returning to the high range from May to end of June. Moderate levels of trees are noted in the Great Basin mid-July and fell to low counts noted mid-August. The tree season ended completely mid-November.

Grass season started with low counts in mid-April, moderate counts at the start of May and achieved briefly high counts at the end of May. Moderate counts in the 2009 season persisted to mid-July, when counts entered the low range consistently. Grass season ended at the end of September 2009.

Weed season started in the low range mid-May of 2009. Moderate counts were noted at the end of July. Weed pollen measurements dropped to the low range mid-Octorber and persisted in this range until the end of counting season in mid-November.

This 2009 season is notable in that all pollens were not generally noted to be in the very high range. However, the pollen season in the Great Basin is continuous from the

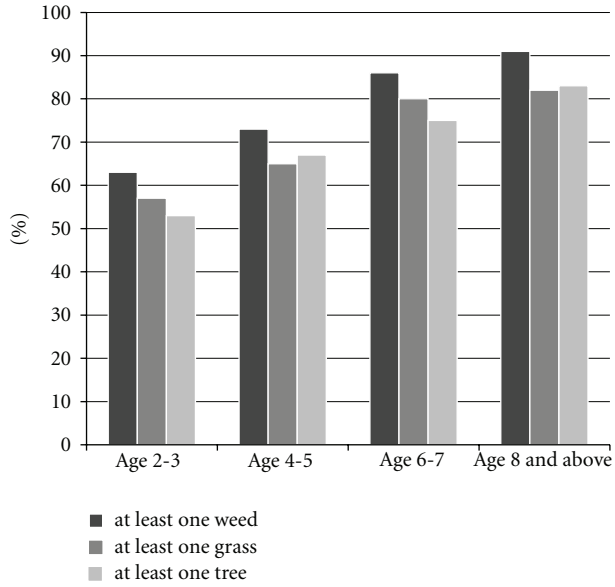

Figure 1: IgE reactivity to weed, grass, and trees of young children presenting with allergic rhinitis symptoms.

beginning of consistent notation of low levels of tree pollen counted in January to the end of weed season. Tree season is extensive in length from mid-January to mid-November. Grass season is prolonged from mid-May to the middle of September. Weed season also is prolonged from mid-May to mid-November.

Not all pollens appear to sensitize young children. However, in the Great Basin Region, the Chenopodiaceae family, Timothy, and Alfalfa were frequently found. In addition, several trees such as walnut, olive, sweet gum, willow, and mulberry were frequently found. Thses sensitization patterns are outlined in (Table 2) by age groups of 2-3 years, 4-5 years, and 6-7 years of age. The most common sensitizing allergenic plants were unchanged after 6 years of age. Sensitization to birch, cedar, mulberry, and maple was present in young children. Pine is not frequently thought to be a sensitizing tree but is found for prolonged lengths of time in the Great Basin region and is found to be early sensitizing tree pollen in our young children.

Sagebrush and pigweed were the most commonly noted weeds (Table 2). These weeds and their family members were reported consistently through the 2009 weed season. The ragweed family was not amongst the 3 most common weeds in this region even though this weed is the most commonly reported weed in the eastern half of the United States (east of the Rocky Mountain Range). Correlation of skin test sensitization frequency with the most prolific weeds in the Great Basin was seen in our young children and was notable for sagebrush and pigweed as the most frequently found sensitizing weeds. Skin test frequency for ragweed family was lower in these children than sagebrush and pigweed possibly a reflection of the lower ragweed pollen levels in the Great Basin.

Table 2: Most common aeroallergens by age group.

2-3-year-old children	Pollen	Positive percent of 16 children
Most common weeds	Russian thistle	60%
	Pigweed	58%
Most common grasses	Timothy	45%
	Alfalfa	56%
	Brome	40%
	Johnson	40%
Most common trees	Walnut	75%
	Olive	55%
	Mountain cedar	50%
	Willow	50%
	Sweet gum	33%
	Mulberry	43%
	Pine	25%
4-5-year-old children	Pollen	Positive percent of 51 children
Most common weeds	Russian thistle	54%
	Pigweed	46%
	Sagebrush	43%
Most common grasses	Timothy	42%
	Johnson	44%
	Alfalfa	37%
Most common trees	Olive	42%
	Maple	39%
	Willow	31%
	Sweet gum	23%
	Mulberry	29%
	Pine	19%
6-7-year-old children	Pollen	Positive percent of 56 children
Most common weeds	Russian thistle	68%
	Pigweed	61%
	Sagebrush	49%
Most common grasses	Saltgrass	58%
	Timothy	48%
	Bermuda	45%
	Johnson	45%
Most common trees	Willow	39%
	Sweet gum	32%
	Mulberry	36%

4. Discussion

There is much debate as to whether children under the age of five are sensitized to outdoor allergens, and if so, which allergens are the culprits. In our study, we found that a large percentage of children were sensitized to at least one outdoor aeroallergen by the age of three. Reasons for this early sensitization in Westernized countries are unclear. Novel data in this study demonstrate that unlike other studies

conducted in eastern North America, young children in the desert region of the Great Basin are sensitized to a different set of allergens. In fact, we found that young children living in the Reno area of the Great Basin are capable of being sensitized to allergens that were not previously appreciated to cause significant sensitization in this region at all.

In Washington DC, tree pollen accounted for 91.2% of the local total annual pollen production, while weeds and grasses accounted for only 3.8% and 3.2% of the pollen production respectively [6]. As such, in the eastern continental region of North America trees tend to be the common sensitizers of children with up to 56% of 10–12-year-old children becoming sensitized [7]. In a Boston area study, 17% of children fewer than 4 years of age were sensitized to trees. While lower than the sensitization rates achieved in the Great Basin, sensitization rates in Boston are still considerable. The Boston region likely has less aeroallergen sensitization than the Great Basin as it has the advantage of a much higer rate of rainfall. Available rain fall will likely shorten the allergy season by washing pollen away.

As our pollen data demonstrates, in the Great Basin Region of North America, unique geographic features are associated with prolonged detection of pollen in a more classic perennial fashion, rather than pollens solely acting as transient seasonal exposures. Features distinctive of the Great Basin include a lack of rainfall to remove pollen from the area and extremely windy conditions within a geographic bowl which cause pollens to become reairborne after settling on the desert floor. Due to these geographic factors, detection of some tree and grass pollen during the fall pollination season has been reported on a yearly basis albeit at low pollen levels. However, these low pollen levels were still potent causes of asthma exacerbations with increased asthma symptoms and rescue inhaler use [8]. Therefore, it is not surprising that in our area, trees and grasses were the pollens causing significant sensitization in very young children (53% and 57%, respectively).

Unlike the east coast in which ragweed tends to be the most common sensitizing weed, Russian thistle, pigweed, and sagebrush were the significant pollens causing early sensitization in the Great Basin. This is likely reflective of the fact that these weeds comprise a large portion of the plant population in our area This is compared to ragweed being a more significant pollinating plant in the eastern and central plains of North America [9, 10].

While the weeds play a significant role in allergies in children living in the Great Basin, the grasses play almost an equal role. The prevalence of sensitization to at least one grass was lower than that of the weeds, but still was significantly high at 57% in children age 2-3 years old. The early grass sensitizers, Timothy and Alfalfa, are both grasses that are common to the Great Basin. Timothy grass is native to the region, and Alfalfa is planted for hay by cattle ranchers. Thus, it is not surprising that both were significant sensitizers in children. In our study, Brome was also a significant sensitizer which may reflect some cross-reactivity with Timothy. Similarly, the Great Basin native grass, Johnson grass, was a common sensitizer in the 2-3 years old. In our study, the Bermuda/Saltgrass family was a more common sensitizer in older children in the 4–7 age range.

Due to the inclusion of plants occupying western California which have the capability of spreading downwind, there were multiple nonnative plants included in our skin test panel. The best example of this is the pollen of the black walnut. Walnut was the most significant sensitizing tree allergen for children ages 2-3 years old which is surprising since walnut is not native to the Great Basin. Walnut is found in abundance in California, but this aeroallergen is capable of traveling great distances suggesting that it would be likely for California walnut pollen to be wind-borne to the Great Basin [11].

While walnut is a key sensitizer; olive also plays a large role in sensitization of children. Olive is a non-native plant included on our panel just as walnut is. However, members of this family, ash and privet are frequently transplanted and then irrigated by homeowners. In fact, privet has previously been implicated in olive-free regions [12]. It is not surprising that olive is a significant sensitizer in young children. In studies that have been done in the Mediterranean where olive is very common, they have found that olive is the most potent allergen eliciting a Type I reaction [13]. Olive was the second most common allergen causing a reaction in young children in this study. This further substantiates the thought that olive is a powerful sensitizer even in young children.

Previous research has suggested that pines are rarely allergen sensitizers due to their pollen size [14]. Recent studies, however, found that pine pollen is a potential allergen, especially in areas where pine is found abundantly [15, 16]. Pine is commonly found in the Great Basin and in our study was found to cause sensitization in children 16–25% of the time. While sensitization to pine is not as high as some of the other tree allergens, pine should not be overlooked as a potential allergen in young children living in regions with high prevalence of this tree.

Finally, willow, sweet gum, and mulberry are not native species to the area, yet they still cause sensitization in young children. A reason for this sensitization to nonnative species may be due to the transplantation of these trees to this area. In addition, one study suggests that willows are not important aeroallergens since they are pollinated via insects as opposed to the wind [14]. However, willow is also pollinated by wind-borne means and frequently found as a transplanted tree in Reno area. Another study found strong cross-reactivity among members of the family, *Salicales* with which willow, poplar, and cottonwood belong to [11]. In our study willow was a significant early sensitizer with a large prevalence in children ages 2-3 years, and this occurred in the absence of poplar and cottonwood suggesting that cross-reactivity was not the reason for IgE responses to willow. This suggests that willow's large presence in the Great Basin may account for its ability to provoke IgE sensitization response.

Our data suggests that many children with allergic rhinitis living in the Great Basin were sensitized to an outdoor allergen by as early as 2 years of age. This further supports previous publications demonstrating that children less than 5 years of age develop allergic rhinitis and deserve evaluation. Specifically, there are several weeds, grasses, and

trees that are native to the Great Basin region including native, wind-borne, and transplanted species that cause significant sensitization leading to allergic rhinitis in these young children. Allergic rhinitis first appears in the preschool years and was found to be a predictor of the onset of wheezing later in childhood [17]. For preschool children with allergic rhinitis, assessment of allergic sensitization might help in identifying a group at high risk of wheezing and therefore may be candidate for allergy immunotherapy as a disease modifier. For these reasons, we believe that even young children patients with allergic rhinitis who live in the Great Basin should have allergy testing to the most likely pollens to each of the weeds, grasses, and trees that cause sensitization at an early age. More importantly, we encourage other pediatric allergists to determine which aeroallergens are early sensitizers in their region to help specifically plan targeted aeroallergen skin testing in these small but symptomatic allergic rhinitis and asthmatic children.

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References

[1] A. Høst, S. Andrae, S. Charkin et al., "Allergy testing in children: why, who, when and how?" *Allergy*, vol. 58, no. 7, pp. 559–569, 2003.

[2] P. R. Ogershok, D. J. Warner, M. B. Hogan, and N. W. Wilson, "Prevalence of pollen sensitization in younger children who have asthma," *Allergy and Asthma Proceedings*, vol. 28, no. 6, pp. 654–658, 2007.

[3] M. Kulig, U. Klettke, V. Wahn, J. Forster, C. P. Bauer, and U. Wahn, "Development of seasonal allergic rhinitis during the first 7 years of life," *Journal of Allergy and Clinical Immunology*, vol. 106, no. 5, pp. 832–839, 2000.

[4] P. G. Holt, J. Rowe, M. Kusel et al., "Toward improved prediction of risk for atopy and asthma among preschoolers: a prospective cohort study," *Journal of Allergy and Clinical Immunology*, vol. 125, no. 3, pp. 653–e7, 2010.

[5] W. T. Corder, M. B. Hogan, and N. W. Wilson, "Comparison of two disposable plastic skin test devices with the bifurcated needle for epicutaneous allergy testing," *Annals of Allergy, Asthma and Immunology*, vol. 77, no. 3, pp. 222–226, 1996.

[6] S. E. Kosisky, M. S. Marks, and M. R. Nelson, "Pollen aeroallergens in the Washington, DC, metropolitan area: a 10-year volumetric survey (1998–2007)," *Annals of Allergy, Asthma and Immunology*, vol. 104, no. 3, pp. 223–235, 2010.

[7] W. J. Sheehan, P. A. Rangsithienchai, S. N. Baxi et al., "Age-specific prevalence of outdoor and indoor aeroallergen sensitization in boston," *Clinical Pediatrics*, vol. 49, no. 6, pp. 579–585, 2010.

[8] C. T. Dellavalle, E. W. Triche, B. P. Leaderer, and M. L. Bell, "Effect of ambient pollen concentrations on frequency and severity of asthma symptoms among asthmatic children," *Epidemiol*, vol. 23, no. 1, pp. 55–63, 2012.

[9] J. F. White and D. I. Bemstein, "Key pollen allergens in North America," *Annals of Allergy, Asthma and Immunology*, vol. 91, no. 5, pp. 425–435, 2003.

[10] G. Gadermaier, A. Dedic, G. Obermeyer, S. Frank, M. Himly, and F. Ferreira, "Biology of weed pollen allergens," *Current Allergy and Asthma Reports*, vol. 4, no. 5, pp. 391–400, 2004.

[11] R. E. Esch and R. K. Bush, "Aerobiology of outdoor allergens," in *Middleton's Allergy: Principles and Practice*, N. F. Adkinson, J. W. Yunginger, W. W. Busse, B. S. Bochner, S. T. Holgate, and F. E. Simons, Eds., pp. 533–534, Mosby, Philadelphia, Pa, USA, 6th edition, 2003.

[12] R. Asero, "Analysis of hypersensitivity to oleaceae pollen in an olive-free and ash-free area by commercial pollen extracts and recombinant allergens," *European Annals of Allergy and Clinical Immunology*, vol. 43, no. 3, pp. 77–80, 2011.

[13] N. Mothes and R. Valenta, "Biology of tree pollen allergens," *Current Allergy and Asthma Reports*, vol. 4, no. 5, pp. 384–390, 2004.

[14] R. E. Esch, C. J. Hartsell, R. Crenshaw, and R. S. Jacobson, "Common allergenic pollens, fungi, animals, and arthropods," *Clinical Reviews in Allergy and Immunology*, vol. 21, no. 2-3, pp. 261–292, 2001.

[15] G. Gastaminza, M. Lombardero, G. Bernaola et al., "Allergenicity and cross-reactivity of pine pollen," *Clinical and Experimental Allergy*, vol. 39, no. 9, pp. 1438–1446, 2009.

[16] C. Marcos, F. J. Rodriguez, I. Luna, V. Jato, and R. González, "Pinus pollen aerobiology and clinical sensitization in northwest Spain," *Annals of Allergy, Asthma and Immunology*, vol. 87, no. 1, pp. 39–42, 2001.

[17] M. K. Rochat, S. Illi, M. J. Ege et al., "Allergic rhinitis as a predictor for wheezing onset in school-aged children," *Journal of Allergy and Clinical Immunology*, vol. 126, no. 6, pp. 1170–1175, 2010.

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Review Article

A Review of Psychosocial Risk Factors for Pediatric Atopy

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Pediatric atopy is increasing in prevalence and creates a significant financial and quality of life burden for children and families (e.g., frequent clinic visits, academic, and social challenges). Thus, it is important to understand modifiable risk factors related to disease onset or exacerbation in young children. The existing research base suggests that while a genetic link has been identified, specific family psychological factors (e.g., parent stress) also appear to play a significant role in the development of pediatric atopy. The function of psychological stress in the clinical expression and exacerbation of allergic diseases in young children is hypothesized to be due to neuroendocrine and immunologic systems. Specifically, stress-related activation of the sympathetic and adrenomedullary (SAM) system as well as the hypothalamic-pituitary-adrenocortical (HPA) axis from both the intrauterine environment and early childhood experiences may increase risk of childhood atopy above and beyond genetic risk. Consequently, prevention and intervention strategies aimed at reducing children's early exposure to stress and psychological difficulties in parents may prove beneficial in preventing or reducing the likelihood that their children will develop atopy.

1. Introduction

Pediatric atopy is increasingly prevalent and represents a significant financial and quality of life burden for children and families [1]. In addition to significant morbidity, effects of disease and its treatment, such as fatigue and discomfort as well as frequent clinic visits, may result in academic and social challenges for youth with atopy. Thus, it is extremely important to try to understand modifiable risk factors related to disease onset or exacerbation in young children. While a genetic link has been identified, the contributing role of family psychological factors, particularly parent stress, is beginning to be explored in the literature. This relationship is predominantly correlational in nature, and the mechanisms involved are largely unknown but have been hypothesized. The role of parent stress in relation to pediatric allergic sensitization or development of allergic disease in early childhood and a hypothesized underlying psychoneuroimmunological theory are discussed.

2. Parent-Report of Family Stress in Early Childhood

Early psychosocial factors can play a role in disease development later in childhood. In a cohort of youth, family stress early in life (ages 9–24 months) was associated with asthma status at 4 years of age [2]. However, parent stress was highly correlated with asthma symptom severity. Indeed, when both variables were considered, severity of asthma symptoms was a better predictor of asthma status than parent stress. Of note, at baseline participants in this study were already evidencing active wheezing, making it unclear whether parent stress preceded or resulted from asthma symptomatology.

Most research has focused on mothers to the exclusion of paternal factors. As an exception to this methodological approach, both mothers and fathers in a cohort of Puerto Rican twins were interviewed about their psychological functioning during year one of their children's lives using the *Mood and Feelings Questionnaire* and the *World Health Organization Composite International Diagnostic Interview, Version 3.0* [3].

Both maternal and paternal psychological symptoms were associated with negative health outcomes in early childhood. Specifically, paternal symptoms of PTSD, depression, and antisocial behavior were associated with recent asthma symptoms in youth at age one, including daytime and nighttime symptoms, and use of albuterol. For each additional parent endorsing depressive symptoms, there was a one-and-a-half time's increase in odds of a child having recent asthma symptoms. Of note, respiratory symptoms were elicited from parent self-report rather than confirmed diagnoses, and this study did not differentiate between symptoms that may have been present due to other reasons (e.g., respiratory tract infections). Additionally, the use of twins may limit the generalizability of the sample. Again, since parents were interviewed retrospectively, it is unable to be determined whether parental psychological symptoms led to asthma symptoms, or if the presence of these symptoms increased parent stress.

3. Maternal Report of Prenatal Stress

Examining parental stress during pregnancy and its relation to atopy development in early childhood can eliminate some of the confounding factors present when examining stress postnatally. The extant literature provides evidence that maternal stress during pregnancy can impact fetal development, with a variety of maladaptive responses including preterm birth, low birthweight, and increased susceptibility to chronic illness [4]. Utilizing a birth-cohort design, a large sample of infant-mother pairs recruited from hospitals in Taiwan was followed at 3rd trimester gestation as well as at 6 and 24 months of age [5]. Based on maternal self-report on the modified Chinese version of the *Short Form 36 Health Survey*, authors found that greater emotional stress endorsed during pregnancy, including symptoms of depression and anxiety, was associated with atopic dermatitis (AD) in early childhood [5]. A limiting factor of this study is use of parental report of atopic symptoms and purported physician diagnoses, which may have resulted in some youth's AD status being incorrectly classified.

4. Caregiver Stress Measured in Biomarkers

Eliminating a reliance on parental-report of youth atopic symptoms, Wright and colleagues [6] measured physiological markers of immune response in relation to caregiver stress. Their sample included 500 youth with a family history of asthma or allergy who were followed from birth. Caregiver stress was assessed bimonthly for the first two years of life and then yearly using the *Perceived Stress Scale* (PSS); biomarkers of atopy were obtained from blood samples two years later. Higher levels of caregiver stress in early childhood were associated with a corresponding change in atopic-specific biomarkers, including IgE and cytokine production at age 2-3 years.

5. Proposed Psychoneuroimmunological Theory Connecting Family Stress and Development of Pediatric Atopy

Taken together, the literature seems to support the notion that caregiver stress and parental psychological symptoms during pregnancy and early childhood are associated with increased risk of atopy. The role of psychological stress on clinical expression and exacerbation of allergic diseases in young children is hypothesized to be due to neuroendocrine and immunologic systems. Activation of the sympathetic and adrenomedullary (SAM) system as well as the hypothalamic-pituitary-adrenocortical (HPA) axis is documented to be associated with psychological stressors [7].

6. HPA Axis Dysregulation

The HPA axis is influential in regulating homeostasis. These systems may dysregulate in the presence of stressors, and this disturbance in homeostasis and resultant alterations in cortisol levels have been linked to development of disease processes. Effects may be both short- and long-term: the HPA axis is susceptible to early programming, thus prenatal stress may cause physiological dysregulation resulting in development of atopic symptoms, and these youth may be more sensitive to parental stress throughout childhood [8].

Youth cortisol levels also have been shown to be influenced by family stress. Salivary cortisol levels were measured in newborns with and without a genetic predisposition for atopy (e.g., one or more parents with a history of atopy) before and after a heel prick stress procedure [9]. Newborns with a parental history of atopy and elevated IgE (immunoglobulin-E) levels (a biomarker found to be related to atopy) demonstrated a hypercortisol response following the stressor. In contrast, other studies show a decreased cortisol response to stress with school-age youth [10] and adolescents [11] with atopic disorders. Thus, it may be that a genetic risk for atopy (e.g., parental history of atopy), combined with a tendency for HPA dysregulation, may increase risk of developing atopy later in life.

6.1. Epigenetic Influences. Indeed, there has been a line of animal and human research associating the development of atopy with epigenetic changes (i.e., permanent changes in gene function caused by environmental influences). Some research findings support the notion that the influence of prenatal and early life experience of psychosocial and physical stress is related to the development of atopic diseases in children [12]. Specifically, there has been growing evidence to support the theory that transitory family stress (e.g., maternal depression, paternal psychological dysfunction) can have permanent effects on gene regulation and expression in children via epigenetic mechanisms [12, 13]. For example, histone modifications have been linked to bronchial hyperresponsiveness and corticosteroid resistance in asthma [12]. Thus, it has been argued that the HPA axis is changed epigenetically by stress [14]. Taken together, it could be expected that these gene-environment changes in the HPA

axis and its function could potentially affect the course of atopy as allergic rhinitis, asthma, and atopic dermatitis are all cortisol-responsive diseases.

7. Directions for Future Research

A link between family stress and mood and expression of atopic disease in youth is emerging in the literature, with the mechanism for this effect thought to be related to dysregulation of the HPA axis. Stress-related changes in SAM and HPA activity from both the intrauterine environment and early childhood may increase risk of childhood atopy above and beyond genetic risk. Given the negative financial and quality of life costs of childhood atopy, there is a vital need for ongoing research to better understand these modifiable risk factors.

To advance our understanding of the relation between psychosocial risk factors and the development of atopy in youth, it will be important for future research to improve upon the methodology of published studies. In particular, it will be essential for forthcoming research to utilize longitudinal designs, ideally beginning to gather psychosocial data with both parents early in pregnancy and following them and their children as the children age through preschool and into school. Atopic diagnoses should be confirmed by physicians or medical chart reviews, rather than obtained through parent report. Moreover, reliable and well-validated measures of psychological functioning should be used when measuring psychosocial risk factors. Finally, these studies need to be conducted in the United States, rather than specific to particular foreign countries, and should strive to include a sample that is broad in ethnic and racial characteristics. By doing so, the generalization of findings will be enhanced.

8. Clinical Applicability

Despite the need for increased research efforts, future research will need to investigate the impact of prevention and intervention strategies, as well as the potential benefits of psychopharmacological therapy. Some clinical implications can be derived from current findings. Specifically, the present literature suggests that prevention and intervention strategies aimed at reducing children's early exposure to stress and psychological difficulties in parents may prove beneficial in preventing or reducing the likelihood that their children will develop atopy. These strategies should be focused on parental stress management and mood symptom reduction via empirically validated approaches, such as cognitive behavioral therapy. At the very least, however, this paper suggests that pregnant women and new parents who report stress or psychological dysfunction likely would benefit from a referral for psychological services, and perhaps their young children will benefit as well. Thus, obstetricians and pediatricians should be aware of these potential clinical implications for the care of their patients.

References

[1] C. C. Johnson, D. R. Ownby, E. M. Zoratti, S. H. Alford, L. K. Williams, and C. L. M. Joseph, "Environmental epidemiology of pediatric asthma and allergy," *Epidemiologic Reviews*, vol. 24, no. 2, pp. 154–175, 2002.

[2] M. D. Klinnert, A. S. Kaugars, M. Strand, and L. Silveira, "Family psychological factors in relation to children's asthma status and behavioral adjustment at age 4," *Family Process*, vol. 47, no. 1, pp. 41–61, 2008.

[3] N. E. Lange, S. Bunyavanich, J. L. Silberg, G. Canino, B. A. Rosner, and J. C. Celedón, "Parental psychosocial stress and asthma morbidity in Puerto Rican twins," *Journal of Allergy and Clinical Immunology*, vol. 127, no. 3, pp. 734–740, 2011.

[4] L. C. Von Hertzen, "Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy," *Journal of Allergy and Clinical Immunology*, vol. 109, no. 6, pp. 923–928, 2002.

[5] H.-J. Wen, Y.-J. Wang, Y.-C. Lin et al., "Prediction of atopic dermatitis in 2-yr-old children by cord blood IgE, genetic polymorphisms in cytokine genes, and maternal mentality during pregnancy," *Pediatric Allergy and Immunology*, vol. 22, no. 7, pp. 695–703, 2011.

[6] R. Wright, P. Finn, J. P. Contreras et al., "Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy," *Journal of Allergy and Clinical Immunology*, vol. 113, no. 6, pp. 1051–1057, 2004.

[7] R. J. Wright, "Prenatal maternal stress and early caregiving experiences: implications for childhood asthma risk," *Paediatric and Perinatal Epidemiology*, vol. 21, no. 3, pp. 8–14, 2007.

[8] R. J. Wright and M. B. Enlow, "Maternal stress and perinatal programming in the expression of atopy," *Expert Review of Clinical Immunology*, vol. 4, no. 5, pp. 535–538, 2008.

[9] A. Buske-Kirschbaum, S. Fischbach, W. Rauh, J. Hanker, and D. Hellhammer, "Increased responsiveness of the hypothalamus-pituitary-adrenal (HPA) axis to stress in newborns with atopic disposition," *Psychoneuroendocrinology*, vol. 29, no. 6, pp. 705–711, 2004.

[10] A. Buske-Kirschbaum, K. von Auer, S. Krieger, S. Weis, W. Rauh, and D. Hellhammer, "Blunted cortisol responses to psychosocial stress in asthmatic children: a general feature of atopic disease?" *Psychosomatic Medicine*, vol. 65, no. 5, pp. 806–810, 2003.

[11] M. Z. Wamboldt, M. Laudenslager, F. S. Wamboldt, K. Kelsay, and J. Hewitt, "Adolescents with atopic disorders have an attenuated cortisol response to laboratory stress," *Journal of Allergy and Clinical Immunology*, vol. 111, no. 3, pp. 509–514, 2003.

[12] M. L. North and A. K. Ellis, "The role of epigenetics in the developmental origins of allergic disease," *Annals of Allergy, Asthma and Immunology*, vol. 106, no. 5, pp. 355–361, 2011.

[13] T. F. Oberlander, J. Weinberg, M. Papsdorf, R. Grunau, S. Misri, and A. M. Devlin, "Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses," *Epigenetics*, vol. 3, no. 2, pp. 97–106, 2008.

[14] M. P. Ogren and P. J. Lombroso, "Epigenetics: behavioral influences on gene function, part II: molecular mechanisms," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 47, no. 4, pp. 374–378, 2008.

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Research Article

Demographic Predictors of Peanut, Tree Nut, Fish, Shellfish, and Sesame Allergy in Canada

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Background. Studies suggest that the rising prevalence of food allergy during recent decades may have stabilized. Although genetics undoubtedly contribute to the emergence of food allergy, it is likely that other factors play a crucial role in mediating such short-term changes. *Objective*. To identify potential demographic predictors of food allergies. *Methods*. We performed a cross-Canada, random telephone survey. Criteria for food allergy were self-report of convincing symptoms and/or physician diagnosis of allergy. Multivariate logistic regressions were used to assess potential determinants. *Results*. Of 10,596 households surveyed in 2008/2009, 3666 responded, representing 9667 individuals. Peanut, tree nut, and sesame allergy were more common in children (odds ratio (OR) 2.24 (95% CI, 1.40, 3.59), 1.73 (95% CI, 1.11, 2.68), and 5.63 (95% CI, 1.39, 22.87), resp.) while fish and shellfish allergy were less common in children (OR 0.17 (95% CI, 0.04, 0.72) and 0.29 (95% CI, 0.14, 0.61)). Tree nut and shellfish allergy were less common in males (OR 0.55 (95% CI, 0.36, 0.83) and 0.63 (95% CI, 0.43, 0.91)). Shellfish allergy was more common in urban settings (OR 1.55 (95% CI, 1.04, 2.31)). There was a trend for most food allergies to be more prevalent in the more educated (tree nut OR 1.90 (95% CI, 1.18, 3.04)) and less prevalent in immigrants (shellfish OR 0.49 (95% CI, 0.26, 0.95)), but wide CIs preclude definitive conclusions for most foods. *Conclusions*. Our results reveal that in addition to age and sex, place of residence, socioeconomic status, and birth place may influence the development of food allergy.

1. Introduction

Among adults worldwide, 7.7% (Iceland) to 24.6% (US) are sensitized to food allergens [1]. Foods are the most common triggers for anaphylaxis, accounting for 33.2% to 56% of all cases [2, 3] with peanut, tree nut, fish, and shellfish responsible for the majority of fatal reactions [4]. Studies suggest an increasing prevalence of food allergies in the past two decades [5, 6], with a recent stabilization in developed countries [7, 8]. Although genetic factors undoubtedly contribute to the development of food allergies [9], it is evident that they are not fully responsible for these relatively short-term temporal trends in prevalence. Further, recent reports suggest that populations with similar genetic backgrounds may have different rates of food allergy, possibly due to different dietary habits [10], and alternatively, populations with different genetic backgrounds may have the same relative prevalence of food allergies [1]. It is evident that the development of food allergy results from an interplay of genetic, environmental, and demographic factors. However, little is known about which demographic factors are associated with food allergy. In the SCAAALAR study (Surveying

Canadians to Assess the Prevalence of Common Food Allergies and Attitudes towards Food LAbelling and Risk) launched in 2008, we determined the nationwide prevalence of peanut, tree nut, fish, shellfish, and sesame allergy [11]. In this manuscript, we evaluate potential demographic factors that may influence the prevalence of these potentially severe food allergies in the SCAAALAR population.

2. Methods

As described in detail elsewhere [11], households in the ten Canadian provinces were chosen by purchasing, from Info-Direct, a random selection of telephone numbers and their accompanying addresses from the electronic white pages. Interviews were conducted from May 2008 to March 2009 by trained interviewers from either McGill (Montreal, Quebec) or McMaster (Hamilton, Ontario) Universities, using computer-assisted telephone interview (CATI) software (WinCati 4.2, Copyright 1986–2004 Sawtooth Technologies Inc, Northbrook Illinois). Eligible respondents were 18 years or older and living in the household, with no language-mental-hearing barriers. They were queried on whether any of the household members had any of the above 5 food allergies as well as on potential demographic predictors of food allergy.

To optimize response rates and minimize bias, a maximum of 10 attempts were made to contact households during different days and times between the hours of 9:30 AM to 9:00 PM (local time) Monday through Friday and 10:30 AM to 5:00 PM on Saturdays and Sundays. Households were also advised of our survey a few weeks in advance of the phone call by a mailed information letter.

The study was approved by the Institutional Review Boards of the McGill University Health Centre and McMaster University.

3. Questionnaire

We used a standardized questionnaire developed by Sicherer et al. [5, 12] as in the US, and incorporated questions regarding sesame allergy. The questionnaire was translated into French and back-translated to English. If the eligible household respondent reported that he or she or any family member potentially had a food allergy, the respondent was queried on the history of the most severe allergic reaction, interval between exposure and symptom onset, if medical care was sought and if diagnosed by a physician. The eligible household respondent reported on the household sibship size, annual household income and the respondents' education level, marital status, and country of origin. The eligible household respondent also reported on the ages and gender of all household members.

4. Statistical Analysis

The prevalence of probable food allergy was estimated by including all with a convincing history and/or self-report of a physician diagnosis of allergy. A convincing history was defined as at least 2 mild signs/symptoms or 1 moderate or 1 severe sign/symptom that occurred within 120 minutes after ingestion or contact (or inhalation in those with fish/shellfish allergy). Mild reactions included pruritus, urticaria, flushing, or rhinoconjunctivitis; moderate: angioedema, throat tightness, gastrointestinal complaints, or breathing difficulties (other than wheeze); severe: wheeze, cyanosis, or circulatory collapse [7, 11, 13, 14].

Univariate and multivariate logistic regression analyses were used to estimate the associations between the presence of probable food allergy and potential predictive factors including sibship size, annual household income (low income level defined as an income at which families or unattached individuals spend at least 70% of before tax income on food, shelter, and clothing and is determined according to family size and location), location of household (urban defined as residing in Canadian metropolitan areas or in Canadian areas with a population $\geq$100,000), province of household (Atlantic provinces, Quebec, Ontario, Prairies, or British Columbia), education level of household respondent (completed college or university), marital status of household respondent (living with partner/married), immigration status of household respondent (Canadian born), ages of each household member (<18 years), and gender of each household member. Possible confounding factors were investigated by comparing univariate to multivariate results. Since the data were collected for randomly selected households rather than randomly selected individuals, all confidence intervals (CI) were corrected in order to account for clustering effects. In addition, a significant proportion of households (38%) did not provide any income data and hence multiple imputation techniques were applied, using all available data, in order to estimate the effect of low income over the largest possible sample. In the case of income-related questions, nonresponse may be due to nonignorable factors. Therefore, two sensitivity analyses were also performed in which the predicted incomes used for imputations were either doubled or halved.

5. Results

Three thousand six hundred sixty-six out of 10,596 households contacted responded (34.6% participation rate), of which 3613 completed the entire interview, providing data on 9667 participants.

Low income and immigrant populations were relatively underrepresented in SCAAALAR (8.9% of households in SCAAALAR were considered low income versus 14.5% in the Canadian population and 14.4% of household respondents in SCAAALAR were immigrants versus 19.4% in the Canadian population) while the SCAAALAR population had a higher proportion of household respondents with postsecondary education when compared to the general Canadian population (60.5% in SCAAALAR versus 32.9% in the Canadian population), the populations were similar with respect to urban versus rural location, province of residence, and marital status (Table 1).

Peanut, tree nut, and sesame allergy were more common in children (peanut: odds ratio (OR) 2.24 (95% CI,

Table 1: Multivariate logistic regression examining association between specific food allergies and respondent characteristics ($n = 8682^*$).

	Peanut odds ratio (OR) (95% CI)	Tree nut	Fish	Shellfish	Sesame
Age < 18 yo	2.24 (1.4, 3.59)	1.73 (1.11, 2.68)	0.17 (0.04, 0.72)	0.29 (0.14, 0.61)	5.63 (1.39, 22.87)
Male	1 (0.63, 1.58)	0.55 (0.36, 0.83)	0.96 (0.52, 1.78)	0.63 (0.43, 0.91)	1.04 (0.25, 4.23)
Urban	0.82 (0.5, 1.35)	0.99 (0.65, 1.5)	0.97 (0.51, 1.84)	1.55 (1.04, 2.31)	0.91 (0.18, 4.63)
Immigrant	0.62 (0.28, 1.38)	0.52 (0.25, 1.07)	0.45 (0.14, 1.46)	0.49 (0.26, 0.95)	0.73 (0.08, 6.65)
Postsecondary graduate	1.63 (0.94, 2.85)	1.9 (1.18, 3.04)	1.06 (0.56, 2)	0.69 (0.47, 1.01)	2.43 (0.56, 10.59)**

*This refers to participants providing complete data for the variables in this model; income level was provided by only 5,961 participants.
**Given the small number of sesame allergic individuals, the education variable is university graduate for this allergy.

1.40, 3.59), tree nut: OR 1.73 (95% CI, 1.11, 2.68), and sesame: OR 5.63 (95% CI, 1.39, 22.87)), while fish and shellfish allergy were more common in adults (OR 0.17 (95% CI, 0.04, 0.72) and OR 0.29 (95% CI, 0.14, 0.61), resp.). Tree nut and shellfish allergy were less common in males (OR 0.55 (95% CI, 0.36, 0.83) and OR 0.63 (95% CI, 0.43, 0.91), resp.). Shellfish allergy was more common in urban settings (OR 1.55 (95% CI, 1.04, 2.31)). Higher household education was associated with increased likelihood of allergy to peanut, tree, fish, and sesame although it reached significance only for tree nut (OR 1.9 (95% CI, 1.18, 3.04)). All food allergies were less common in immigrants although large CIs preclude definitive conclusions except for shellfish (OR 0.49 (95% CI, 0.26, 0.95)). Use of multiple imputation for income and the sensitivity analyses did not alter these associations.

6. Discussion

Consistent with other research, our study has demonstrated that peanut, tree nut, and sesame allergy were more common in children, fish and shellfish more common in adults, and tree nut and shellfish allergy less common in males [12, 15–18]. However, ours is the first North American study to examine the influence of education level, immigrant status, and geographic location on food allergy, and we found that most food allergies are more prevalent in the more educated and those born in Canada and shellfish allergy in those residing in urban settings.

Our results suggest that a higher educational level may be associated with an increased risk of food allergy. These results are consistent with other studies suggesting an increased risk for allergic diseases, including food allergies, in families with higher parental education [19]. However, the mechanisms underlying these relationships are not yet well understood. Given that a higher education level may be associated with changes in family lifestyle [20], the hygiene hypothesis may partially account for these findings. Consistent with the hygiene hypothesis, smaller family size, decreased exposure to pets and livestock, fewer infections during infancy, increased use of antibiotics and vaccinations, and improved sanitation might decrease microbial burden and lead predominantly to a type 2 T-helper cell response which is responsible for triggering allergic disorders [21]. Other factors may also explain this association between education and food allergy. It is possible that more educated parents may be more likely to have followed American Academy of Pediatrics' recommendations [22] regarding the restriction of potentially allergenic foods in early life. This guideline has recently been retracted as research suggests that delayed introduction may promote, rather than reduce, the development of food allergy [23]. Further, educated parents have higher health literacy and may be more likely to consult a physician for suspected food allergies [24]. Hence, the actual prevalence may not be higher in the more educated, but may merely appear increased because of greater likelihood of seeking a diagnosis.

The observed reduced risk of food allergy in immigrants might be due to genetic differences as well as environmental influences. Recent studies suggest an increased prevalence of allergic diseases commensurate with the length of stay in Westernized countries regardless of age at arrival, sex, or atopic status [25]. Further, it was reported that asthma symptoms in Chinese adolescents were lowest among residents of mainland China, were greater for those in Hong Kong and those who had immigrated to Canada, and were highest among those born in Canada [26]. It was also shown that individuals born in Western countries compared to those born in Asia have a higher risk of peanut and tree nut allergy although the risk for shellfish allergy was unrelated to the place of birth [27]. These observations suggest a crucial role for environmental factors in the pathogenesis of allergic diseases in immigrants. Certain Western dietary habits and lifestyles might contribute to the development of food allergies [28] including omega-3 fatty acids deficiency [29], decreased consumption of fresh fruits and vegetables [30], excess or inadequate vitamin D [31, 32], different food processing methods [33], delayed introduction of foods [10], low-dose cutaneous sensitization to peanut [34], and improved sanitation [35]. It is also possible that immigrants are less likely to consult a physician for a suspected allergy because of lower health literacy [36] and/or lack of a regular family doctor [37], resulting in an apparent, rather than a real decrease in allergy prevalence in this population.

Although a higher prevalence of asthma [38] and eczema [39] in urban settings was previously reported, no population-based studies have examined the association between urban/rural dwelling and food allergy. The higher prevalence of shellfish allergy in urban areas may be attributed to factors related to the hygiene hypothesis including less exposure to parasites and other infections [40], higher use of antibiotics,

less exposure to animals [41], less overcrowding (in a house) [42], higher use of processed food [43], and piped water intake (versus spring drinking water) [44]. It is possible that only shellfish allergy was associated with living in an urban setting as it is reported that city dwellers consume more shellfish [45], but not more of the other food allergens. It is also possible that individuals living in urban areas closer to the shellfish sources (i.e., coastal areas) are more likely to have shellfish allergy. However, the association between urban and seafood allergy remains robust even after controlling for coastal proximity through the use of an interaction term (coastal and urban, data not shown).

Gender differences were observed for tree nut and shellfish allergy. Higher rates of food allergy in postpubertal females are consistent with other studies suggesting that anaphylaxis is more common in adult females [2] potentially due to the effect of estrogens that enhance mast cell activation and allergic sensitization, and progesterone that inhibits histamine release, but potentiates IgE induction [46]. The reduced risk for tree nut and shellfish allergies in males may only be apparent and attributable to a lower rate of physician diagnosis in males as adult males are known to be less likely to have a regular doctor [37].

Our study has some potential limitations. As probable food allergy estimates are based on self-report of a convincing history or physician diagnosis, it is possible that the predictors identified in the regression analysis are not valid predictors of a confirmed food allergy (based on the corroboration of history and confirmatory tests). However, given that our probable peanut allergy estimates in Canadian and Quebec children (Canada: 1.68%; Quebec: 1.69%) are consistent with confirmed peanut allergy estimates in Montreal school children (1.63%) [7, 11], we believe that the associations identified for probable allergy are valid for confirmed allergy. Although our participation rate was only 34.6% with an underrepresentation of those of lower socioeconomic status and immigrants, this is consistent with other recent studies [16]. This low participation rate potentially resulted in selection bias with an overrepresentation of those with food allergy. However, given that our estimates for peanut allergy prevalence are consistent with our previous estimates in Montreal school children (as noted above) where the participation rate was 64.2% [7], we anticipate that such a bias is likely to be minimal. Yet, if such a bias does exist, it is likely to make the strength of the association between high socioeconomic status and allergy conservative. We anticipate that among the vulnerable populations, the presence of allergy will increase participation more than it would in the observed population. Hence, if the sample of the vulnerable populations was more representative, the prevalence of allergy in this sample would be even lower and the association between high socioeconomic status and allergy would be even stronger. Other limitations include the availability of data on education and birthplace on only a single household member (i.e., the eligible respondent), and our failure to explore other potential determinants. However, we have data on the education level and birthplace of the principal caregiver of the allergic individual and it is likely that the demographic characteristics of that caregiver play a major role in shaping the household lifestyle and the factors that may contribute to the emergence of food allergies in the household [47].

In conclusion, our results reveal that demographic determinants such as education level, birthplace, and urban dwelling may influence the development of food allergy. Further studies examining the prevalence and pathogenesis of food allergy in vulnerable populations and exploring genetic and other environmental determinants will help disentangle the numerous factors mediating the development of food allergy.

Abbreviations

SPT: Skin prick test
CI: Confidence interval
OR: Odds ratio.

Conflict of Interests

The authors declare that they have no competing interests.

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References

[1] P. Burney, C. Summers, S. Chinn, R. Hooper, R. Van Ree, and J. Lidholm, "Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: a EuroPrevall analysis," *Allergy*, vol. 65, no. 9, pp. 1182–1188, 2010.

[2] W. W. Decker, R. L. Campbell, V. Manivannan et al., "The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project," *Journal of Allergy and Clinical Immunology*, vol. 122, no. 6, pp. 1161–1165, 2008.

[3] M. Calvani, D. Di Lallo, A. Polo, A. Spinelli, D. Zappala, and M. Zicari, "Hospitalizations for pediatric anaphylaxis," *International Journal of Immunopathology and Pharmacology*, vol. 21, no. 4, pp. 977–983, 2008.

[4] K. Piromrat, S. Chinratanapisit, and S. Trathong, "Anaphylaxis in an emergency department: a 2-year study in a tertiary-care hospital," *Asian Pacific Journal of Allergy and Immunology*, vol. 26, no. 2-3, pp. 121–128, 2008.

[5] S. H. Sicherer, A. Muñoz-Furlong, and H. A. Sampson, "Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study," *Journal of Allergy and Clinical Immunology*, vol. 112, no. 6, pp. 1203–1207, 2003.

[6] J. Grundy, S. Matthews, B. Bateman, T. Dean, and S. H. Arshad, "Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts," *Journal of Allergy and Clinical Immunology*, vol. 110, no. 5, pp. 784–789, 2002.

[7] M. Ben-Shoshan, R. S. Kagan, R. Alizadehfar et al., "Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal," *Journal of Allergy and Clinical Immunology*, vol. 123, no. 4, pp. 783–788, 2009.

[8] C. Venter, S. Hasan Arshad, J. Grundy et al., "Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK," *Allergy*, vol. 65, no. 1, pp. 103–108, 2010.

[9] X. Hong, H. J. Tsai, and X. Wang, "Genetics of food allergy," *Current Opinion in Pediatrics*, vol. 21, no. 6, pp. 770–776, 2009.

[10] G. Du Toit, Y. Katz, P. Sasieni et al., "Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy," *Journal of Allergy and Clinical Immunology*, vol. 122, no. 5, pp. 984–991, 2008.

[11] M. Ben-Shoshan, D. W. Harrington, L. Soller et al., "A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada," *Journal of Allergy and Clinical Immunology*, vol. 125, no. 6, pp. 1327–1335, 2010.

[12] S. H. Sicherer, A. Muñoz-Furlong, and H. A. Sampson, "Prevalence of seafood allergy in the United States determined by a random telephone survey," *Journal of Allergy and Clinical Immunology*, vol. 114, no. 1, pp. 159–165, 2004.

[13] J. O. B. Hourihane, S. A. Kilburn, P. Dean, and J. O. Warner, "Clinical characteristics of peanut allergy," *Clinical and Experimental Allergy*, vol. 27, no. 6, pp. 634–639, 1997.

[14] S. H. Sicherer, A. W. Burks, and H. A. Sampson, "Clinical features of acute allergic reactions to peanut and tree nuts in children," *Pediatrics*, vol. 102, no. 1, article e6, 1998.

[15] S. H. Sicherer, A. Muñoz-Furlong, A. W. Burks, and H. A. Sampson, "Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey," *Journal of Allergy and Clinical Immunology*, vol. 103, no. 4, pp. 559–562, 1999.

[16] S. H. Sicherer, A. Muñoz-Furlong, J. H. Godbold, and H. A. Sampson, "US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up," *Journal of Allergy and Clinical Immunology*, vol. 125, no. 6, pp. 1322–1326, 2010.

[17] M. P. Ross, M. Ferguson, D. Street, K. Klontz, T. Schroeder, and S. Luccioli, "Analysis of food-allergic and anaphylactic events in the National Electronic Injury Surveillance System," *Journal of Allergy and Clinical Immunology*, vol. 121, no. 1, pp. 166–171, 2008.

[18] C. J. Derby, M. H. Gowland, and J. O. B. Hourihane, "Sesame allergy in Britain: a questionnaire survey of members of the Anaphylaxis Campaign," *Pediatric Allergy and Immunology*, vol. 16, no. 2, pp. 171–175, 2005.

[19] R. Pawlinska-Chmara, I. Wronka, and M. Muc, "Prevalence and correlates of allergic DISEASES among children," *Journal of Physiology and Pharmacology*, vol. 59, supplement 6, pp. 549–556, 2008.

[20] R. D. Semba, S. de Pee, K. Sun, M. Sari, N. Akhter, and M. W. Bloem, "Effect of parental formal education on risk of child stunting in Indonesia and Bangladesh: a cross-sectional study," *The Lancet*, vol. 371, no. 9609, pp. 322–328, 2008.

[21] S. Romagnani, "The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both?" *Immunology*, vol. 112, no. 3, pp. 352–363, 2004.

[22] American Academy of Pediatrics and Committee on Nutrition, "Hypoallergenic infant formulas," *Pediatrics*, vol. 106, no. 2, part 1, pp. 346–349, 2000.

[23] A. T. Fox, P. Sasieni, G. du Toit, H. Syed, and G. Lack, "Household peanut consumption as a risk factor for the development of peanut allergy," *Journal of Allergy and Clinical Immunology*, vol. 123, no. 2, pp. 417–423, 2009.

[24] S. Kendig, "Word power: the effect of literacy on health outcomes," *AWHONN Lifelines*, vol. 10, no. 4, pp. 327–331, 2006.

[25] R. C. Leung, J. B. Carlin, J. G. W. Burdon, and D. Czarny, "Asthma, allergy and atopy in Asian immigrants in Melbourne," *Medical Journal of Australia*, vol. 161, no. 7, pp. 418–425, 1994.

[26] H. Y. Wang, G. W. K. Wong, Y. Z. Chen et al., "Prevalence of asthma among Chinese adolescents living in Canada and in China," *CMAJ*, vol. 179, no. 11, pp. 1133–1142, 2008.

[27] L. P. C. Shek, E. A. Cabrera-Morales, S. E. Soh et al., "A population-based questionnaire survey on the prevalence of peanut, tree nut, and shellfish allergy in 2 Asian populations," *Journal of Allergy and Clinical Immunology*, vol. 126, no. 2, pp. 324.e7–331.e7, 2010.

[28] M. M. Lee, A. Wu-Williams, A. S. Whitemore et al., "Comparison of dietary habits, physical activity and body size among Chinese in north America and China," *International Journal of Epidemiology*, vol. 23, no. 5, pp. 984–990, 1994.

[29] P. N. Black and S. Sharpe, "Dietary fat and asthma: is there a connection?" *European Respiratory Journal*, vol. 10, no. 1, pp. 6–12, 1997.

[30] G. Lack, "Epidemiologic risks for food allergy," *Journal of Allergy and Clinical Immunology*, vol. 121, no. 6, pp. 1331–1336, 2008.

[31] C. E. Hayes, F. E. Nashold, K. M. Spach, and L. B. Pedersen, "The immunological functions of the vitamin D endocrine system," *Cellular and Molecular Biology*, vol. 49, no. 2, pp. 277–300, 2003.

[32] J. D. Milner, D. M. Stein, R. McCarter, and R. Y. Moon, "Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma," *Pediatrics*, vol. 114, no. 1, pp. 27–32, 2004.

[33] M. Worm, S. Hompes, E. M. Fiedler, A. K. Illner, T. Zuberbier, and S. Vieths, "Impact of native, heat-processed and encapsulated hazelnuts on the allergic response in hazelnut-allergic patients," *Clinical and Experimental Allergy*, vol. 39, no. 1, pp. 159–166, 2009.

[34] G. Lack, D. Fox, K. Northstone, and J. Golding, "Factors associated with the development of peanut allergy in childhood," *The New England Journal of Medicine*, vol. 348, no. 11, pp. 977–985, 2003.

[35] J. Douwes and N. Pearce, "Asthma and the westernization 'package'," *International Journal of Epidemiology*, vol. 31, no. 6, pp. 1098–1102, 2002.

[36] M. S. Zanchetta and I. M. Poureslami, "Health literacy within the reality of immigrants' culture and language," *Canadian Journal of Public Health*, vol. 97, supplement 2, pp. S26–S30, 2006.

[37] Y. Talbot, E. Fuller-Thomson, F. Tudiver, Y. Habib, and W. J. McIsaac, "Canadians without regular medical doctors: who are they?" *Canadian Family Physician*, vol. 47, pp. 58–64, 2001.

[38] D. Solé, V. E. Cassol, A. R. Silva et al., "Prevalence of symptoms of asthma, rhinitis, and atopic eczema among adolescents living in urban and rural areas in different regions of Brazil," *Allergologia et Immunopathologia*, vol. 35, no. 6, pp. 248–253, 2007.

[39] C. Flohr, "Is there a rural/urban gradient in the prevalence of eczema?" *British Journal of Dermatology*, vol. 162, no. 5, p. 951, 2010.

[40] D. T. Quyen, A. V. Irei, Y. Sato et al., "Nutritional factors, parasite infection and allergy in rural and suburban Vietnamese school children," *Journal of Medical Investigation*, vol. 51, no. 3-4, pp. 171–177, 2004.

[41] P. K. Vedanthan, P. A. Mahesh, R. Vedanthan, A. D. Holla, and A. H. Liu, "Effect of animal contact and microbial exposures on the prevalence of atopy and asthma in urban vs rural children in India," *Annals of Allergy, Asthma and Immunology*, vol. 96, no. 4, pp. 571–578, 2006.

[42] P. J. Cooper, M. E. Chico, L. C. Rodrigues et al., "Risk factors for atopy among school children in a rural area of Latin America," *Clinical and Experimental Allergy*, vol. 34, no. 6, pp. 845–852, 2004.

[43] D. Norbäck, Z. H. Zhao, Z. H. Wang, G. Wieslander, Y. H. Mi, and Z. Zhang, "Asthma, eczema, and reports on pollen and cat allergy among pupils in Shanxi province, China," *International Archives of Occupational and Environmental Health*, vol. 80, no. 3, pp. 207–216, 2007.

[44] A. Haileamlak, D. Dagoye, H. Williams et al., "Early life risk factors for atopic dermatitis in Ethiopian children," *Journal of Allergy and Clinical Immunology*, vol. 115, no. 2, pp. 370–376, 2005.

[45] C. Iandoli and M. Cozzolino, "Overview on aquaculture product differentiation," Ref Type: Electronic Citation, 2010, http://ressources.ciheam.org/om/pdf/c59/02600084.pdf.

[46] M. Burstein, A. Rubinow, and M. Shalit, "Cyclic anaphylaxis associated with menstruation," *Annals of Allergy*, vol. 66, no. 1, pp. 36–38, 1991.

[47] H. J. Wen, P. C. Chen, T. L. Chiang, S. J. Lin, Y. L. Chuang, and Y. L. Guo, "Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors," *British Journal of Dermatology*, vol. 161, no. 5, pp. 1166–1172, 2009.

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Research Article

L-Carnitine Improves the Asthma Control in Children with Moderate Persistent Asthma

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The objective. was to investigate L-Carnitine level and the effects of its supplementation in children with moderate persistent Asthma. *Methods*. Free and total serum carnitine levels were measured in 50 children having moderate persistent asthma and 50 healthy control children. The patients group was randomly divided into two subgroups. Subgroup A was supplemented with L-Carnitine for 6 months while subgroup B was used as a placebo controls. Both subgroups were assessed by pulmonary function tests (PFT) and childhood-asthma control test (C-ACT) before and 6 months after carnitine supplementation. *Results*. Total and free carnitine levels were significantly lower in patient group than in control group. PFT and C-ACT showed significant improvements in asthmatic children supplemented with L-Carnitine than in those who were not supplemented. *Conclusion*. L-Carnitine levels were initially lower in moderate persistent asthmatic children as compared to healthy control children. Asthmatic children who received L-Carnitine supplementation showed statistically significant improvement of C-ACT and PFT.

1. Introduction

Asthma is a common complex chronic inflammatory disorder of the airways characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper responsiveness, and an underlying inflammation. It is one of the most common chronic diseases of childhood, affecting more than 6 million children and more than 22 million persons in the United States [1]. The persistence or increase of asthma symptoms over time is accompanied by a progressive decline in lung functions [2]. The patho physiology of persistent asthma remains poorly understood. Even with the current therapies, the symptoms may be incompletely controlled, or they might have little effect on disease process [3, 4]. As pharmacologic therapy may have variable results in these asthmatic children, the search for metabolic or nutritional deficiencies contributing to the disease has continued. In instances where metabolic or nutritional deficiencies are a contributing factor to ongoing inflammatory processes in the bronchial tree, dietary supplementation of these deficiencies may provide benefit [5].

L-Carnitine is a cofactor that plays an essential role in the mitochondrial oxidation of long-chain fatty acids. It spares muscle glycogen, improves tolerance to physical activity, and reduces muscle fatigue [6]. It has been noted that L-Carnitine decreases leukotriene synthesis through inhibition of lipoxygenase enzyme [7]. L-Carnitine administration is beneficial to exercise and respiratory strength training in outpatients with stable, moderate-to-severe chronic obstructive pulmonary diseases [8]. L-Carnitine supplementation can increase serum carnitine levels, improve exercise capacity and correct the obstructive pattern in breath function tests in certain diseases [7, 9].

The role of L-Carnitine in development or persistence of pediatric asthma has not been investigated. This paper investigated the differences in serum L-Carnitine levels

in pediatric asthmatic patients as compared to healthy control children. In addition, it studied the effectiveness of L-Carnitine supplementation in improving symptom scores and pulmonary function testing in children moderate persistent pediatric asthma.

2. Study Patients

The study included 77 children between 6 and 12 years of age and diagnosed to have moderate persistent asthma. They were recruited from the Allergy and Pulmonology Unit, Paediatric Departments, New Children Hospital, Faculty of Medicine, Cairo University, Egypt. They were invited to participate in the study from March 2008 till May 2009. Fifty children out of 77 children completed the study, 10 refused to complete the study (as they were not able to swallow L-Carnitine capsules), and 17 failed to adhere to the study protocol (eight of them did not show up at the follow-up visits, 5 children did not take the asthma medications on a regular basis, and 4 suffered from infections during the pre study phase). Those 50 children were further randomly subdivided into two equal subgroups (A or B). Fifty healthy children of matched age and sex were included as a control group.

3. Definition of Moderate Persistent Asthma

The children were defined as having moderate persistent asthma according to National Heart, Lung, and Blood Institute Guidelines, if they have daily symptoms, nighttime awakenings more than 1 time/week but not nightly, some limitation of the normal activities, Forced Expiratory Volume in 1 second (FEV1) 60–80% of the predicted, Forced Expiratory Volume in 1 second/Forced Vital Capacity Ratio (FEV1/FVC) 75–80% of the predicted, daily use of a quick-relief inhaler, and/or exacerbations requiring systemic corticosteroids equal to or more than twice a year [1]. The standard care was allowed to be altered up or down during the supplementation phase according to the child condition.

4. Exclusion Criteria

(1) Any pulmonary or chronic systemic diseases other than asthma and rhinitis, for example, cystic fibrosis, bronchiectasis, tuberculosis, diabetes mellitus, and liver.

(2) Children with immunodeficiency or history of premature birth.

(3) Children with hypothyroidism or borderline thyroid functions.

(4) Other medications that may affect carnitine level: antibiotics use (particularly Ampicillins) and anticonvulsants for example Valproic acid.

(5) Recent exhaustion, infection (especially pneumonia), surgery, anaesthesia.

(6) Children who failed to have regular outpatient follow-up visits, a reliable caregiver, and willingness to complete at least 1 outpatient visit per month, and those who were not adherent to proper asthma medications.

5. Methodology

5.1. Study Design. There were two phases of the study; pre-clinical phase and active study phase during which children with moderate persistent asthma were recruited. During the 6-month preclinical phase the asthma control test, frequency of use of short acting B2 agonists, use of short courses of systemic steroids, the frequency of night time symptoms, frequency of acute asthma exacerbation, and the need for emergency department visit or hospitalization were recorded. During this phase every effort was done to maximize the asthma control and to decrease the severity of the asthma with the use of step up regimen according to National Heart, Lung, and Blood Institute Guidelines [1]. Children follow up and data collection were done at monthly intervals.

The active study phase was conducted as a randomized, double-blind, placebo-controlled trial over 6 consecutive months. The children were randomly allocated using computer-generated list of random numbers. At the beginning phase of this study, the total and free plasma carnitine levels were assessed in both the patient and control groups. One blood sample was collected from each of the control group, and two samples were collected from the asthmatic children; the first sample was obtained during acute asthma exacerbation, and the second was obtained three weeks after the attack. We considered the mean of the 2 samples for analysis.

The patient group was further subdivided into two subgroups. Subgroup A ($n = 25$) received L-Carnitine 350 mg capsules, 3 capsules each morning for 6 months. Subgroup B ($n = 25$) received 3 placebo identical appearing capsules containing lactose for a similar time. The parents were strictly instructed to supervise their children while taking the capsules and to report the occurrence of diarrhoea or gastric upset as a sign of overdose. In addition, children were instructed to swallow and not to bite or chew the capsules.

The children were checked at least once a month. They would also visit the clinic if they developed exacerbations or if it was necessary to maximize the asthma control. Recording of the childhood-asthma control test, the frequency of use of short acting B_2 agonists, use of short courses of systemic steroids, the frequency of night time symptoms, frequency of acute asthma exacerbation, and the need for emergency department visit or hospitalization were also done as well as any side effects related to the medications including L-Carnitine. At the end of the study, the total and the free plasma carnitine levels were reassessed in the patient subgroups.

Serum total and free carnitine levels were studied by the enzymatic spectrophotometric method (Shimadzu UV160A spectrophotometer, Japan). A venous blood sample was withdrawn from each child on serum gel blood-collection tubes (Sarstedt). The obtained samples were centrifuged at 3000×g for 15 minutes, and serum samples were kept at −20°C until analysis. Serum total and free carnitine levels

Table 1: Demographic data and associated comorbidities in patients and control groups.

	Asthmatic ($n = 50$)	Control ($n = 50$)	t	P
Age	9 ± 2	9.14 ± 2	0.27	>0.05
BMI	19 ± 2	18.5 ± 1.9	1.43	>0.05
M/F	1.1 : 1	01 : 01.1		
Age at diagnosis	3 ± 0.90	—	—	—
Urban/rural	28 : 22 (1.27 : 1)	27 : 23 (1.17 : 1)		
Associated nasal allergy	27 (54%)	2 (4%)	—	<0.001*
Atopic dermatitis	17 (34%)	5 (10%)		<0.001*
Immediate family history of asthma	18 (36%)	1 (2%)	—	<0.001*
Smoking parents	1 (2%)	7 (14%)		

(*) $P < 0.05$ is significant.

There was no significant difference in age and BMI between asthmatic children and the controls while there was significant increase in the incidence of associated nasal allergy, atopic dermatitis, and family history of asthma in asthmatic children than in the control group. On the other hand the incidence of smoking parents was higher in control group than in the asthmatic group.

were measured by an enzymatic UV test kit (Roche Diagnostics GmbH, Mannheim, Germany, CAT. no. 11242008001).

At the beginning of the study and at the end of treatment phase, the patients were assessed (using subjective, physiological & laboratory assessment) to avoid false positive or negative results as follows: *subjective* by childhood-asthma control Test (C-ACT) for children 4 to 12 years, *physiological* by pulmonary function test (PFT), and *laboratory* by sputum eosinophil and serum Immunoglobulin (Ig) E.

Childhood-Asthma Control Test (C-ACT). The C-ACT is a 7-item child- and caregiver-completed tool with a scoring range of 0–27; higher scores indicate better control. A score of 19 or less indicates that the asthma may not be well controlled. The C-ACT is intended for use in children up to the age of 12 years [10].

Pulmonary Function Tests (PFT). The children were weighed, and their heights were measured. Spirometry was performed for all children in the sitting position using a calibrated computerized spirometer (SpiroPro, CareFusion, San Diego, USA). Subjects were required to perform 3 acceptable Forced Vital Capacity (FVC) manoeuvres according to American Thoracic Society recommendations [1]. The maximum percentage in Forced Expiratory Volume in 1 second (FEV1) value from 3 readings was calculated.

The Kasr Al Eini Research Committee approved the study protocol. Verbal and written information were given with full explanation that the trial therapy is just an add-on therapy not replacing the traditional asthma therapy, and the children should continue their usual regimen of treatment. All the families were given the cell phone numbers of the investigators. They were instructed to call if there was any serious side effect of the L-Carnitine, any deterioration of the asthma condition or deterioration of the general condition of the enrolled child. A fully explained written consent was signed by the parents of the children who agreed to participate in the study.

5.2. Statistical Analysis. The primary end point of this trial was improvement of the lung functions and C-ACT. We hypothesized that the use of L-Carnitine supplementations will significantly improve the lung functions and C-ACT and can reduce the severity of inflammation in children with moderate persistent asthma with α level being set to be 0.05. The power level of the primary end point of the study was more than 90% and was still more than 85% after excluding the 27 children who could not complete the study (using: *Power & Precision* V3; http://www.Power-Analysis.com/). We used the paired value and looked at the mean of the results of each treatment group. Data were presented as mean (±SD) values. The two-way analysis of variance (ANOVA) was used to identify statistically significant differences in the different parameters before and after the treatment. For all analysis, a statistical significance of P value <0.05 was used. The confidence intervals were calculated as indicators of standardized mean differences between groups. Wilcoxon's Signed Rank test was used to assess the normality of distributions of the data. Correlation between the free and total serum carnitine level and the severity of asthma was done. The statistical analysis was performed using TexaSoft, WINKS SDA Software, Sixth Edition, Cedar Hill, Texas, 2007.

6. Results

Demographic data of the children enrolled in the study were shown in Table 1. There were no important differences in the demographic features of those children who completed the study versus those who did not. There was no significant difference between patient and the control group as regard to age, BMI, and sex. The free and total carnitine serum levels (Table 2) were significantly lower in children with moderate persistent asthma than in the control group ($P < 0.001$). The side effects of L-Carnitine supplementation encountered during the study are shown in Table 3. None of these side effects enforced the children to stop the medication. Table 4 demonstrates a significant positive correlation between both C-ACT and FEV1% predicted and the total and the free

Table 2: Laboratory findings in patients and control groups before starting the L-Carnitine therapy.

	Asthmatic ($n = 50$)	Control ($n = 50$)	t	P
Serum IgE (kU/L)	325 ± 103	100.8 ± 60.8	13	<0.001*
Blood eosinophils (%)	5.9 ± 2.1	2.0 ± 0.9	12.5	<0.001*
Free carnitine (umol/L)	30.3 ± 1.8	39.3 ± 3.8	14.5	<0.001*
Total carnitine (umol/L)	40.1 ± 2.6	49.5 ± 3.9	12.8	<0.001*

(*) $P < 0.05$ is significant.
The table showed serum IgE, blood eosinophils %, free and total serum carnitine in patient and control groups before starting the L-Carnitine therapy. The serum IgE and blood eosinophils were significantly higher in asthmatic than in control children. On the other hand, the free and total serum carnitine levels were significantly lower in asthmatic than in control children.

Table 3: Side effects of L-Carnitine treatment.

GIT symptoms	2 (8%)
Stuffy nose	1 (4%)
Hyperactivity	1 (4%)
Headache	2 (8%)
Insomnia	0%
Palpitation	0%
Hypertension	0%

The table showed that, the most encountered side effects of L-Carnitine were the gastrointestinal disorders and headache. Blocked nose and hyperactivity; both were recorded in one child. Insomnia, palpitation or hypertension was not reported. None of these side effects enforced the patients to stop the intake of the oral L-Carnitine.

serum carnitine level. However, there was no significant correlation between these levels and the FEV1/FVC ratio with carnitine levels.

Table 5 showed significant decrease in the emergency department visit, total hospital admissions, and blood eosinophils (%) between children supplemented with L-Carnitine compared to those asthmatic children with placebo or before supplementation, while there was no significant difference in serum IgE levels. Table 6 showed no significant difference in free and total carnitine serum levels among patient subgroups before L-Carnitine supplementation ($P > 0.05$). However, this difference became significant after six months of oral carnitine supplementation ($P > 0.001$). The results of PFT and C-ACT before and after carnitine supplementation are shown in Table 6. There was no significant difference in PFT and C-ACT between patient subgroups (subgroup A & B) before L-Carnitine supplementation ($P > 0.05$). However this difference became significant after 6 months of L-Carnitine supplementation for both PFT and C-ACT ($P < 0.001$). Also there was a significant improvement of both PFT and C-ACT after L-Carnitine supplementation in the subgroup A children ($P < 0.001$). On the other hand, when comparing PFT and C-ACT in subgroup B before and after placebo supplementation, there was no significant improvement in FEV1% predicted and C-ACT. However, there was significant improvement in FEV1/FVC ratio.

7. Discussion

The increased asthma prevalence in the last few decades is due to different factors including changes in the dietary habits. Carnitine deficiency due to fad diets or lack of access in children may lead to different problems including failure to thrive, recurrent infections, hypotonia, encephalopathy, cardiomyopathy, or nonketotic hypoglycaemia [11]. Since L-Carnitine has an essential role in the transport of long-chain fatty acids through the mitochondrial membrane in order to ensure efficient β-oxidation of fatty acids, it is important for activation of pulmonary surfactant synthesis [12].

In the current study, there were significant lower free and total carnitine serum levels in children with moderate persistent asthma than in the controls. These findings agreed with the results of Asilsoy et al. who found that serum carnitine levels were decreased in children with moderate asthma during exacerbation of asthma and shortly thereafter [13]. Whether the decrease in serum carnitine in children with moderate persistent asthma is a cause or an effect, needs to be further studied. In the study conducted by Asilsoy et al., they attributed the decrease of serum carnitine levels during the asthmatic attacks to the decrease in lung surfactant (during attack) and the use of body stores to replenish it (after attack).

Carnitine deficiency leads to toxic accumulation of long-chain fatty acids in the cytoplasm and of acyl CoA in the mitochondria. The accumulated saturated and monounsaturated fats may have different effects on airway inflammation [14]. Decreased serum carnitine was also documented in other respiratory problems like children with recurrent respiratory tract infections and neonates with respiratory distress syndrome [15, 16].

From our best knowledge, this study was the first to investigate the benefit of L-Carnitine supplementation in asthmatic children. In the current study, the PFT and the C-ACT were significantly improved in the asthmatic children who received L-Carnitine supplementation than in those who did not ($P < 0.001$). There was also a statistically significant improvement in PFT and C-ACT in subgroup A patients (who were supplemented with L-Carnitine) when compared to the presupplementation phase ($P < 0.001$).

There are no previous data about the effect of L-Carnitine supplementation for asthma management in humans. In the animal model, Uzuner et al. studied the effect of L-Carnitine supplementation in mice with laboratory-induced asthma. They found that L-Carnitine supplementation improved oxygen saturation and decreased urine leukotriene E4 and inflammation in lung tissues in the studied animals [17].

Table 4: Correlation between free and total carnitine levels with C-ACT, FEV1% of predicted and FEV1/FVC ratio in asthmatic children at the beginning of the study.

Variable ($n = 50$)		r	95% CI	P
C-ACT Mean ± SD 13.1 ± 1.43	Total S Carnitine 40.1±2.63	0.36	0.09, 0.58	<0.01*
	Free S Carnitine 30.3 ± 1.8	0.88	0.8, 0.9	<0.001*
FEV1 (% of predicted) 70.9 ± 3.7	Total S Carnitine	0.95	0.91, 0.97	<0.001*
	Free S Carnitine	0.7	0.52, 0.82	<0.001*
FEV1/FVC Mean ± SD 60.2 ± 4.5	Total S carnitine	0.26	−0.02, 0.5	>0.05
	Free S Carnitine	0.07	−0.2, 0.3	>0.05

C-ACT: Childhood-Asthma control test. FEV1/FVC: Forced Expiratory Volume in 1st second/Forced Vital Capacity Ratio. (*) $P < 0.05$ is significant, r correlation coefficient, CI confidence interval.
The table showed the correlation between serum carnitine (free and total) and C-ACT and some pulmonary function parameters in asthmatic children at the beginning of the study. C-ACT and FEV_1 (% of predicted) had significant positive correlations with total and free serum carnitine. However, there were no significant correlations between FEV_1/FVC and the levels of total and free serum carnitine.

Table 5: Emergency room visit, total hospital admissions, blood eosinophils, and serum IgE in patient subgroups before and after carnitine supplementation and the placebo group.

		Subgroup A (with L-Carnitine) ($n = 25$)	Subgroup B (Placebo) ($n = 25$)	t	P
Emergency room visit	bef.	3.1 ± 1.01	3.4 ± 1.0	1.2	>0.05
	aft	1.5 ± 0.6	2.6 ± 0.9	4.68	<0.001*
Total Hospital admissions	bef.	1.5 ± 0.6	1.8 ± 0.7	1.9	>0.05
	aft	0.44 ± 0.5	1.8 ± 0.6	7.5	<0.001*
Oral steroid	bef.	2.16 ± 0.74	2.12 ± 0.72	0.21	>0.05
	aft	1.2 ± 0.5	1.6 ± 0.5	2.8	<0.01*
Serum IgE (kU/L)	bef.	328 ± 89	322 ± 114	0.21	>0.05
	aft	253 ± 62	290 ± 106	1.6	>0.05
Blood eosinophils (%)	bef.	5.8 ± 2.1	6.04 ± 2.1	0.38	>0.05
	aft	3.1 ± 0.8	4.4 ± 1.2	4.2	<0.001*

(*) $P < 0.05$ is significant There were significant decreases in the frequency of emergency room visit, total hospital admissions, and the intake of oral steroids between L-Carnitine-supplemented children compared to placebo group during the study period. The blood eosinophils % decreased significantly after treatment with L-Carnitine in asthmatic group. It was significantly lower in L-Carnitine treatment group than in placebo group. Serum Ig E showed no significant difference in treatment and placebo group (both before and after treatment).

The beneficial effect of L-Carnitine in asthmatic children may be due to different mechanisms. It may be due to its antimicrobial effect, muscle strength effects, enhancing surfactant synthesis, antileukotriene activity, or through antagonising the harmful effects of fat on the respiratory tract. Olgun et al. found an effective antimicrobial effect of L-Carnitine on different bacterial strains. They claimed that some of the side effects of orally administered L-Carnitine on gastrointestinal system like diarrhoea could probably be related to antimicrobial effect on local bacteria [18].

Ergür et al. found that children with recurrent respiratory tract infections had low serum carnitine level [15]. Respiratory viral infections are important triggers of asthma attacks [19]. So children with low serum carnitine level may have recurrent viral respiratory tract infections and hence are more susceptible to develop asthma. Kavukçu et al. showed that carnitine can improve exercise tolerance and inspiratory muscle strength in COPD patients as well as reduce lactate production and increase rate of lactate removal [7].

Many studies proved that the surfactants of the asthmatic lungs are functionally impaired. The main mechanism of this impairment was thought to be due to the influx of inhibitory proteins into the airways, although changes in surfactant composition may occur [20]. Some studies proved the beneficial role of L-Carnitine supplementation in improving the synthesis and the functions of lung surfactants. Kurz et al., proved the beneficial role of L-Carnitine intake by pregnant women in decreasing the incidence of respiratory distress syndrome and even the mortality in premature newborns. They attributed these effects to the physiological action of L-Carnitine in surfactant synthesis activation [21].

Leukotrienes are among the mediators of inflammation in asthma and have a strong bronchoconstrictive effect. They are synthesized in the bronchial mucosa by eosinophils, basophils, and mast cells. They play an important role in airway eosinophilic inflammation, leukocyte trafficking, airway mucus secretion, airway oedema, collagen synthesis, and airway remodelling in asthmatic patients [22]. It has

Table 6: Free and total serum carnitine levels, pulmonary functions, and C-ACT in patient subgroups before and after carnitine supplementation and the placebo group.

		Subgroup A (with L-Carnitine) ($n = 25$)	Subgroup B (placebo) ($n = 25$)	t	P
Free carnitine (umol/L)	Bef.	30.3 ± 1.7	30.4 ± 1.8	0.17	>0.05
	Aft.	41 ± 5	31 ± 2	10	<0.001*
Total carnitine (umol/L)	Bef.	39.6 ± 2.3	40.6 ± 2.8	1.23	>0.05
	Aft.	50 ± 4	42 ± 3	47.56	<0.001*
FEV1% predicted	Bef.	70.5 ± 3.2	71.3 ± 4.2	t_1 0.66	>0.05
				t_2 15	<0.001*
	Aft.	76.2 ± 3.4	71.4 ± 4.6	t_3 3.5	< 0.01*
				t_4 0.96	>0.05
FEV1/FVC	Bef.	60.1 ± 4.5	60.2 ± 4.6	t_1 0.8	>0.05
				t_2 25	<0.001*
	Aft.	71 ± 4.4	61 ± 4.5	t_3 7.3	<0.001*
				t_4 3.2	<0.01*
C-ACT	Bef.	13.4 ± 1.5	12.8 ± 1.3	t_1 1.8	>0.05
				t_2 18	<0.001*
	Aft	16.5 ± 1.7	13.3 ± 1.4	t_3 7.1	<0.001*
				t_4 2.7	>0.05

C-ACT: Childhood-Asthma control test. FEV1: Forced Expiratory Volume in 1 second. FEV1/FVC: Forced Expiratory Volume in 1st second/Forced Vital Capacity Ratio.

t_1 between subgroup A & subgroup B before carnitine supplementation.

t_2 between subgroup A Before & after 6 months of carnitine supplementation.

t_3 between subgroup A & subgroup B after 6 months of carnitine supplementation to subgroup A.

t_4 between subgroup B before & after 6 months of followup.

(*) $P < 0.05$ is significant.

There was significant increase in total and free serum carnitine levels in L-Carnitine-supplemented group than before starting the treatment and also when compared with the placebo group. After L-Carnitine supplementation, the pulmonary function tests and C-ACT showed significant improvement in the Carnitine supplemented group when compared to presupplementation or the placebo group. However, the total and free serum carnitine levels did not show any significant change after treatment in placebo group. There was also statistically significant improvement in pulmonary function tests and C-ACT in placebo group before and after treatment.

been reported that L-Carnitine inhibits leukotriene synthesis by inactivation of lipoxygenase pathway and by altering the ratio of essential fatty acids. Borghi-silva et al. and Ahmad et al. demonstrated that L-Carnitine was able to prevent bronchospasm and improve the obstructive findings in PFT in children undergoing chronic haemodialysis [8, 23].

The improvement of FEV1/FVC in the subgroup supplied with placebo treatment was of statistical significance but the improvement was very subtle regarding the figure. This may be due to the regular attendance at the clinic and closer followup and better asthma care during the study period or due to the few sample cases. Also, FEV1% predicted is much more important than FEV1/FVC in following the severity and the improvement of the lung function.

The limitation of the study is that the selection of patients was confined to children with moderate persistent asthma. We did not choose children with mild asthma as they can be easily controlled, and we did not choose children with severe asthma as they were too sick to be included in this kind of trial. Whether the study finding of carnitine effect can be applied to other degrees of asthma severity or other asthma subtypes or phenotypes needs to be further studied.

Another limitation of this study is that we used a fixed dose of L-Carnitine. A dose effect of L-Carnitine supplement needs additional studies. An important limitation of the study is that despite the statistically significant improvement of C-ACT and PFT in the supplemented children, the children in the active treatment group still had unacceptably poor asthma control and were in need for more adequate asthma therapy. It is important to note that the L-Carnitine was investigated in the current study as add-on therapy and not replacing any of the traditional asthma medications.

8. Conclusion

L-Carnitine levels were initially lower in moderate persistent asthmatic children as compared to healthy control children. Asthmatic children who received L-Carnitine supplementation showed significant statistical improvement of C-ACT and PFT. The target serum level of L-Carnitine, the effect of its supplementation in different phenotypes and degrees of asthma severity, and the appropriate dosing need more studies.

References

[1] National Institute of Health, National Heart, Lung and Blood Institute, National Asthma Education, and Prevention Program, "Expert panel report 3: guidlines for diagnosis and management of asthma," Washington, DC, USA, NIH, 2007, http://www.nhlbi.nih.gov/guidelines/asthma.

[2] L. Antonicelli, C. Bucca, M. Neri et al., "Asthma severity and medical resource utilisation," *European Respiratory Journal*, vol. 23, no. 5, pp. 723–729, 2004.

[3] W. W. Busse, S. Banks-Schlegel, and S. E. Wenzel, "Pathophysiology of severe asthma," *Journal of Allergy and Clinical Immunology*, vol. 106, no. 6, pp. 1033–1042, 2000.

[4] M. K. Miller, C. Johnson, D. P. Miller, Y. Deniz, E. R. Bleecker, and S. E. Wenzel, "Severity assessment in asthma: an evolving concept," *Journal of Allergy and Clinical Immunology*, vol. 116, no. 5, pp. 990–995, 2005.

[5] M. A. Biltagi, A. A. Baset, M. Bassiouny, M. A. Kasrawi, and M. Attia, "Omega-3 fatty acids, vitamin C and Zn supplementation in asthmatic children: a randomized self-controlled study," *Acta Paediatrica, International Journal of Paediatrics*, vol. 98, no. 4, pp. 737–742, 2009.

[6] E. P. Brass, "Supplemental carnitine and exercise," *American Journal of Clinical Nutrition*, vol. 72, no. 2, pp. S618–S623, 2000.

[7] S. Kavukçu, M. Türkmen, Ş. Salman et al., "The effects of L-carnitine on respiratory function tests in children undergoing chronic hemodialysis," *Turkish Journal of Pediatrics*, vol. 40, no. 1, pp. 79–84, 1998.

[8] A. Borghi-Silva, V. Baldissera, L. M. M. Sampaio et al., "L-carnitine as an ergogenic aid for patients with chronic obstructive pulmonary disease submitted to whole-body and respiratory muscle training programs," *Brazilian Journal of Medical and Biological Research*, vol. 39, no. 4, pp. 465–474, 2006.

[9] S. Ahmad, "L-carnitine in dialysis patients," *Seminars in Dialysis*, vol. 14, no. 3, pp. 209–217, 2001.

[10] A. H. Liu, R. Zeiger, C. Sorkness et al., "Development and cross-sectional validation of the childhood asthma control test," *Journal of Allergy and Clinical Immunology*, vol. 119, no. 4, pp. 817–825, 2007.

[11] S. C. Winter, S. Szabo-Aczel, and C. J. R. Curry, "Plasma carnitine deficiency clinical observations in 51 pediatric patients," *American Journal of Diseases of Children*, vol. 141, no. 6, pp. 660–665, 1987.

[12] G. Seliger, E. Kantelhardt, C. van der Wal et al., "L-carnitine level in neonates—a large, retrospective analysis," *Archives of Perinatal Medicine*, vol. 13, no. 2, pp. 17–20, 2007.

[13] S. Asilsoy, Ö. Bekem, Ö. Karaman, N. Uzuner, and S. Kavukçu, "Serum total and free carnitine levels in children with asthma," *World Journal of Pediatrics*, vol. 5, no. 1, pp. 60–62, 2009.

[14] S. L. Huang and W. H. Pan, "Dietary fats and asthma in teenagers: analyses of the first nutrition and health survey in Taiwan (NAHSIT)," *Clinical and Experimental Allergy*, vol. 31, no. 12, pp. 1875–1880, 2001.

[15] A. T. Ergür, F. Tanzer, and Ö. Çetinkaya, "Serum free carnitine levels in children with recurrent pulmonary infections," *Acta Paediatrica Japonica*, vol. 39, no. 4, pp. 406–408, 1997.

[16] M. A. Ozturk, T. Gunes, E. Koklu, and A. Erciyes, "Free carnitine levels in respiratory distress syndrome during the first week of life," *American Journal of Perinatology*, vol. 23, no. 7, pp. 445–449, 2006.

[17] N. Uzuner, S. Kavukçu, O. Yilmaz et al., "The role of L-carnitine in treatment of a murine model of asthma," *Acta Medica Okayama*, vol. 56, no. 6, pp. 295–301, 2002.

[18] A. Olgun, O. Kisa, S. T. Yildiran, S. Tezcan, S. Akman, and M. K. Erbil, "Antimicrobial efficacy of L-carnitine," *Annals of Microbiology*, vol. 54, no. 1, pp. 95–101, 2004.

[19] D. Isaacs and P. Joshi, "Respiratory infections and asthma," *Medical Journal of Australia*, vol. 177, no. 6, pp. S50–S51, 2002.

[20] G. Devendra and R. G. Spragg, "Lung surfactant in subacute pulmonary disease," *Respiratory Research*, vol. 3, p. 19, 2002.

[21] C. Kurz, K. Arbeiter, A. Obermaier, H. Salzer, H. R. Salzer, and A. Lohninger, "L-carnitine-betamethasone combination therapy versus betamethasone therapy alone in prevention of respiratory distress syndrome," *Zeitschrift fur Geburtshilfe und Perinatologie*, vol. 197, no. 5, pp. 215–219, 1993.

[22] T. S. Hallstrand and W. R. Henderson Jr., "An update on the role of leukotrienes in asthma," *Current Opinion in Allergy and Clinical Immunology*, vol. 10, no. 1, pp. 60–66, 2010.

[23] S. Ahmad, A. Dasgupta, and M. A. Kenny, "Fatty acid abnormalities in hemodialysis patients: effect of L-carnitine administration," *Kidney International*, vol. 36, no. 27, pp. S243–S246, 1989.

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Review Article

Environmental Effects on Fractional Exhaled Nitric Oxide in Allergic Children

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Fractional exhaled nitric oxide (FeNO) is a non-invasive marker of airway inflammation in asthma and respiratory allergy. Environmental factors, especially indoor and outdoor air quality, may play an important role in triggering acute exacerbations of respiratory symptoms. The authors have reviewed the literature reporting effects of outdoor and indoor pollutants on FeNO in children. Although the findings are not consistent, urban and industrial pollution—mainly particles ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2)—as well as formaldehyde and electric baseboard heating have been shown to increase FeNO, whilst ozone (O_3) tends to decrease it. Among children exposed to Environmental Tobacco Smoke (ETS) with a genetic polymorphisms in nitric oxide synthase genes (NOS), a higher nicotine exposure was associated with lower FeNO levels. Finally, although more studies are needed in order to better investigate the effect of gene and environment interactions which may affect the interpretation of FeNO values in the management of children with asthma, clinicians are recommended to consider environmental exposures when taking medical histories for asthma and respiratory allergy. Further research is also needed to assess the effects of remedial interventions aimed at reducing/abating environmental exposures in asthmatic/allergic patients.

1. Introduction

Elevated levels of nitric oxide in exhaled air (fractional concentration of exhaled nitric oxide, FeNO) are considered a noninvasive marker of airway inflammation in asthma and respiratory allergy management [1]. Nitric oxide is produced endogenously in the airways from L-arginine by NO synthase. There are two constitutive and one inducible isoforms involved in airway inflammation; their expression is stimulated by inflammatory cytokines [2].

FeNO levels correlate with eosinophilic counts in induced sputum or bronchoalveolar lavage fluid and with eosinophil infiltration of the airways, especially of atopic subjects. Indeed, the interest in FeNO is based on the assumptions that FeNO is a useful noninvasive marker of asthma and asthma control [1]. In fact, in mild-to-moderate persistent asthmatic children followed by Childhood Asthma Research and Education (CARE) Network supported by NHLBI, a highly significant correlation of FeNO levels with blood eosinophilia was found [3].

FeNO assessment is simple to perform and acceptable for the population, especially in the pediatric age [4]. In addition, FeNO is faster and easier to obtain than other measurements of inflammation such as sputum eosinophils level [5]. For these reasons, some authors use it as a complementary tool to lung function tests in order to obtain a better control of clinical symptoms and asthma exacerbations [6].

There is extensive evidence that FeNO is elevated in patients with untreated asthma, whilst it is decreased as a consequence of corticosteroid therapy [2]. Besides, high FeNO levels can suggest a subclinical inflammation of the airways, even in the absence of symptoms and impairment of lung function [6]. Thus, FeNO could represent a helpful tool for rationalizing the anti-inflammatory therapy in patients with respiratory allergy. However, data on long-term benefits of incorporating this kind of measurement in treatment decisions are still missing [1].

In clinical practice, increased FeNO levels are used as predictors of failed steroid reduction in stable asthmatic children [7]. FeNO values have been related to the occurrence of disease exacerbation during a 1 yr of followup in moderate asthmatics by Gagliardo et al. [8], but not by Cabral et al. [5]. Such inconsistency has led the authors of a recent systematic review to not include FeNO among the useful clinical predictors of future asthma exacerbations for all the children with moderate-to-severe asthma undergoing ICS tapering [9].

In the last decades, there has been an increase in the prevalence of asthma and allergic diseases, particularly among children living in the urban areas of economically developed countries. This has led to suppose that environmental factors, especially indoor and outdoor air quality, may play an important role in the development of allergy and in triggering acute exacerbations of respiratory symptoms [10]. The role of air pollution in the epidemics of allergies is still debated, even if experimental studies have suggested that the effects of air pollutants on the development and the worsening of allergies are biologically plausible. Children are particularly vulnerable because they inhale a higher volume of air per body weight, their lungs are growing, their immune system is incomplete, and their defence mechanisms are still evolving, with respect to adults. If lung defences are breached, normal developmental and homeostatic processes can be disrupted. This could determine disturbances in lung development and acute damage that can, in turn, lead to a chronic reduction in lung function. Therefore, a damage to the developing lung may reduce the maximal attainable functional capacity, reducing the functional reserve in adulthood, thereby, enhancing susceptibility to the effects of ageing, infections as well as pollutants [11].

The aim of this review is to make a reappraisal of the current evidences on whether environmental factors, such as outdoor and indoor pollutants, affect FeNO in children.

2. Outdoor Pollutants and FeNO

Since airway inflammation is a hallmark of asthma, FeNO measurement is potentially useful to evaluate the impact of air pollution on the inflammatory state of airways in asthmatic children. Indeed, it is known that air pollution is associated with FeNO in elderly adults with asthma [12], in healthy adults [13], and in schoolchildren [14].

There is extensive evidence that outdoor pollutants present in urban areas do have adverse effects on the respiratory health of children [15]. Children in general, mainly those suffering from asthma, are particularly sensitive to the effects of outdoor pollutants such as ozone (O_3), particulate matter (PM_{10}, $PM_{2.5}$), nitrogen dioxide (NO_2), and sulphur dioxide (SO_2) [16].

Although the mechanisms involved in the bronchial inflammation due to pollution exposure are not yet fully clarified, it is known that the type of air pollutant plays a main role. In this sense, the oxidative stress, induced by reactive oxygen species (ROS), may activate some transcription factors, followed by cytokines secretion and inflammatory cells recruitment. At last, NO is produced by epithelial cells through the induction of inducible NO synthase (iNOS) [17]. Furthermore, experimental evidences suggest that PM organic components have adjuvant effects on airway inflammation, partly through exposure to redox-active chemicals and oxidative stress [18]. PM organic components can also decrease lung function in both elderly adults with COPD and children with asthma [19].

Delfino et al. [2] found that personal (i.e., measured by wearable monitors) and ambient air pollution correlate with increased FeNO concentration from the lower airways of children with asthma. In particular, in two pollutant models, the most robust positive association with FeNO levels was found for personal and ambient elemental carbon and nitrogen dioxide, and for personal but not ambient $PM_{2.5}$. The association between PM and airway inflammation may be missed using ambient particle mass concentration, which may not adequately represent causal pollutant components from fossil fuel combustion. Therefore, the contrasting results for personal versus ambient air pollution could suggest that protecting public health using only a particle mass-based standard may be not sufficient. Supplemental measurements of particle composition and ultrafine particles are needed to better assess the health impact of particulate air pollution.

Rusconi et al. [20] evaluated lung function and markers of inflammation and oxidative stress in children and adolescents with and without asthma or wheezing symptoms living in a petrochemical polluted area versus those living in a reference area in Sardinia. They found that children living in the polluted area showed decreased lung function (FEV_1, FEF_{25--75}) and increased levels of FeNO in conjunction with the increased level of certain pollutants, particularly PM_{10} and SO_2. More recently, Renzetti et al. [10] have found significantly decreased FeNO concentrations after relocating to a rural environment asthmatic children who previously had more active airway inflammation, while living in a highly polluted urban environment.

Similar results were found by Flamant-Hulin et al. [21] who showed significantly increased FeNO levels in both asthmatic and nonasthmatic schoolchildren exposed to high concentrations of formaldehyde, acetaldehyde and $PM_{2.5}$. Stronger associations were found in nonasthmatic children who were atopic, suggesting that they are more sensitive to air pollution than nonatopic children. In other words, atopy and asthma appear as cofactors in determining elevated FeNO levels. In this sense, atopic status is strongly associated with high FeNO levels, even in asymptomatic individuals. The relation between atopy and FeNO levels indicates that

FeNO measurements may help to clarify the relevant role of sensitization in the complex interplay of multiple factors determining the translation into clinical allergy.

Liu et al. [22] demonstrated an important decrement in small airway function and an increase in airway oxidative stress in asthmatic children in association with exposure to SO_2, NO_2, and $PM_{2.5}$, but they did not find statistically significant changes in FeNO associated with these pollutants. The authors advance some possible interpretations for their findings: need of a larger sample size to detect significant changes in airway inflammation and measurement of FeNO at low flow rate (0.05 L/sec) to capture inflammation in lower airways. Another explanation might be related to the severe inflammation of the airways that overwhelmed the effects of air pollution, particularly at low concentrations of exposure. FeNO had a statistically significant negative association with O_3. This result is counterintuitive because laboratory studies showed that high levels of O_3 cause inflammation in the airways of human subjects. Therefore, a sound interpretation for this negative association remains to be found. Indeed, Kim et al. [23], in an occupational setting, found a significantly inverse relationship between $PM_{2.5}$ exposure and FeNO concentrations, the latter decreasing while $PM_{2.5}$ concentrations increased.

More recently, Berhane et al. [24] have shown that short-term increases in $PM_{2.5}$, PM_{10}, and O_3 were significantly associated with higher FeNO levels, being PM_{10} effects significantly higher in the warm season. In addition, the effects of $PM_{2.5}$ and PM_{10} had relatively shorter lag structures compared to those of O_3 that had a longer lag structure (23 days) prior to FeNO measurement. The biologically plausible reasons for the lagged effects of ambient air pollutants on FeNO might depend on the different levels of exposures to pollutants across geographical regions and seasons and on the variable degree of susceptibility of subjects, in terms of asthma and/or allergy status. The authors suggest that current level of ambient pollutants determine a potential increase of nitrosative stress in both healthy and susceptible children, leading to an increase of FeNO.

3. Indoor Pollutants and FeNO

Since people generally spend the majority of their time indoors, there is growing scientific evidence that indoor pollution plays a significant role in affecting health. Indoor environment contributes significantly to human exposure to pollutants through complex interrelationships with outdoor pollution [25]. Indoor airborne pollutants are known to trigger allergic responses in asthmatic patients with consequent airway inflammation [26]. Studies in both adults and children showed that sensitization to indoor allergens is associated with an increase in FeNO [27]. In a review by Sofia et al. it is suggested that FeNO can be used as a marker for adverse respiratory health effects caused by indoor air pollution [28].

Allergen sensitization may play an important role in elevating NO production in the airways. In a study conducted by Cibella et al. [4], only sensitizations to *Dermatophagoides* and to cat dander were found to influence FeNO levels. This result was confirmed in other studies [29, 30]. Similarly, Leuppi et al. [31] showed that in atopic children an increased FeNO level is associated with sensitization to perennial allergens, possibly through long-lasting inflammatory stimuli, but not with seasonal allergen. Spanier et al. found that cat and dog sensitizations were associated with increased FeNO [29]. Differently, Kovesi and Dales [32] found that dog ownership, but not cat ownership, was associated with changes in FeNO levels.

Numerous factors related to housing have been associated with airway inflammation in children. Kovesi and Dales reported that, compared with forced air and hot water radiant heat, electric baseboard heating is associated with a higher FeNO [32]. The authors, based on others' report that forced air heating is linked to lower indoor dust mite levels, speculate that the increased levels of indoor dust mite associated with electric heating may increase the likelihood of allergic sensitization and FeNO. In addition, it has been found that electric baseboard heating is related to higher formaldehyde concentrations in houses [33], which, in turn, is associated with increased FeNO levels in children [34]. As far as the exposure to indoor PM sources is concerned, a recent work found that self-reported exposure to the use of woodstoves, candles, or gas cookers was not significantly associated with increased levels of FeNO [35, 36].

Pasquale et al. [36] tested the hypothesis that chlorine exposure is associated with increased concentrations of exhaled NO, as a marker of eosinophilic airway inflammation, in children regularly attending (for 1 to 2 hours a week) swimming pools. FeNO level was similar in children who regularly attended a swimming pool and in those who did not, whereas it was higher both in children with upper airway infections in the last week and in those who had a history of asthmatic symptoms. This suggests that intermittent exposure to chlorine derivatives does not induce eosinophilic airway inflammation.

In addition, two studies evaluated the influence on FeNO of exposure to polyvinyl chloride (PVC) material which today represents a common indoor pollutant. Tuomainen et al. [37] did not observe changes in FeNO levels in exposed individuals. On the contrary, Kolarik et al. [38] found a significant increase of FeNO compared to the reference condition (clean outdoor air), suggesting that exposure to plastic materials can be associated with a subclinical inflammation of the airways.

4. Smoking and FeNO

Many studies investigated the effects of smoking on FeNO values in both adults and children. There is consistent evidence that active smoking and acute cigarette smoke exposure lead to a transient decrease in FeNO levels in healthy and asthmatic adults [39, 40]. As far as we know, no study has yet demonstrated a link between passive smoke and FeNO values in healthy children. In asthmatic children, results are discordant probably due to methodological biases (small sample sizes, heterogeneous study populations, lack

of control for potential confounding factors) [41]. Different studies have not found a significant association of FeNO and environmental tobacco smoke (ETS) exposure in children with asthma [32, 42]. In particular, Laoudi et al. [41] observed lower FeNO levels in exposed asthmatic children than in unexposed children. This could be explained by different mechanisms according to the type of exposure. Acute exposure induces a marked but transient reduction in FeNO levels related to a negative feedback of iNOS activity, since tobacco smoke contains high concentrations of NO. In the case of daily exposure, the mechanism is still unknown, but one plausible hypothesis is that the progressive negative feedback leads to the inhibition of iNOS gene expression.

Genetic differences may explain some of the conflicting results in studies evaluating the effects of tobacco exposure on FeNO levels. Spanier et al. found that a NO synthase gene (NOS3) polymorphism (a mutation in exon 7) modifies the effect of nicotine exposure on FeNO. The authors noticed that this polymorphism determines decreased FeNO levels in children exposed to increasing nicotine concentrations, possibly through a decreased enzyme activity due to a combination of genetic and environmental factors [43].

More recently, Salam et al. [45] have shown that common variants in the NO synthesis pathway genes contribute to variation in FeNO levels in children. Particularly, the authors found that four NOS2A single nucleotide polymorphisms (SNPs) and one ARG2 SNP are significantly associated with lower FeNO. They also noticed that the ARG2 SNP modify the effect of NOS2A on FeNO. Therefore, FeNO levels depend on variants in both ARG2 and NOS2A. This gene-gene interaction may be due to a competition for a common substrate, L-arginine, since arginase can inhibit iNOS expression reducing NO synthesis. Some of the observed genetic influences were stronger in children with asthma. Therefore, asthma status can be considered an important factor for determining the contributions of these genetic variants to FeNO levels.

5. Variations and Inconsistencies in FeNO Measurements in Children Exposed to Environmental Pollutants

Most of referred data show that FeNO assessment is a complementary tool to evaluate the effects of environmental pollutants exposure in children. Nevertheless, some variations exist among the studies. Such variations are mainly related to the population studied (i.e., genetic variation, atopic versus nonatopic, and asthmatic versus nonasthmatic), including the treatment effects (i.e., inhaled steroid in asthmatics), and to the variable pollutants exposure (i.e., personal versus ambient, level of exposure, and short term versus long term).

Up to date, there are only few data about the influences of genetic variations of NO synthesis pathway on FeNO levels, suggesting that the genetic factors play a key role in determining FeNO levels and have to be considered to understand interindividual differences, especially when there are host susceptibility factors, such as asthma and/or atopy.

Previous studies found that atopy status is *per se* able to significantly influence FeNO levels, even in asymptomatic individuals [21, 31]. In our experience, a significant relation exists between FeNO levels and number of positive skin tests, and the highest FeNO levels are observed in atopic children with physician-diagnosed asthma. Thus, the association of asthma and atopy appears to be the most consistent predictor of increased FeNO level [4].

Earlier studies showed that FeNO levels are raised in asthmatic children, especially if asthma is uncontrolled and during asthma exacerbation. Instead, FeNO levels are reduced after corticosteroid treatment [1, 44]. Therefore, asthma condition may be an effect modifier in the relationship air pollution FeNO; it is associated with high FeNO levels according to several authors [2, 10, 45], with decreased FeNO according to others [22, 43].

The contrasting results of FeNO values for ambient and personal air pollution may be related to the individual susceptibility and to the considered pollutant. In this sense, Berhane et al. [24] underline that current levels of ambient pollution have the potential to increase nitrosative stress in both healthy and susceptible children. Heterogeneity is increased by the different level of exposure reported in the studies; anyway, it allows investigating a dose-response effect, mainly at the proximity level of individuals [2]. Indeed, the use of multipollutant models might improve in the final interpretation of interaction of pollution exposure with FeNO values.

In agreement with Berhane et al. [24], we think that the inconsistencies on FeNO level interpretation about the duration of the lags might be overcome including the time-activity patterns to avoid the misclassification of exposure assignments.

Finally, in light of the evidence that the variations in FeNO measurements show many inconsistencies in children exposed to environmental pollutants, further research is warranted to examine whether FeNO could be used as a useful tool to identify the most susceptible children to adverse respiratory effects from exposure to pollutants.

6. Conclusion

Since many factors such as atopy, sex, season, and corticosteroid treatment influence FeNO values [4, 29], clinicians and researchers should know an individual FeNO baseline in asthmatic children management before studying the effect of other determinants. In addition, clinicians should take into account some indoor pollution factors, like indoor allergens [4, 31, 32], mainly Dermatophagoides and pets, electric baseboard heating [32], higher formaldehyde concentrations in houses [34], using of woodstoves, candles or gas cookers [35, 36], chlorine, or PVC exposure [36, 38] for which increase FeNO values are found in children. Furthermore, the possibility that a low FeNO level in an asthmatic child is related to ETS exposure should be considered by the clinicians [41–43, 45].

As environmental interventions are an important component of asthma management, FeNO might be useful to

integrate the control of environmental triggers into asthma management [29]. Assuming that the inflammatory response of the airways to airborne irritants is reversible, it may be expected that limiting air pollution will reduce airway inflammation [10]. Therefore, FeNO assessment may help in the management of asthmatic patients when they are exposed to major changes in environmental disease-related factors [46, 47].

Even considering that we reviewed this topic from a public health perspective, the literature impacts into the clinical practice should include the more recent findings on the higher FeNO levels significantly associated with the short-term increases in $PM_{2.5}$, PM_{10}, and O_3. Therefore, we would recommend clinicians to obtain more complete information on outdoor and indoor exposure of susceptible subjects for the sake of an accurate interpretation of the FeNO levels in the real life management of allergic asthmatic children. The observed reduction of the FeNO levels in asthmatic children after one week relocation to the rural environment [10], the lower level of FeNO in children living in the reference area in comparison to those living in the high polluted area [20], as well as the higher FeNO levels in children living in homes with high average of formaldehyde levels versus those living at a lower concentration [34] suggest that FeNO assessment might be a useful marker also to monitor the variation in airway inflammation due to the pollution exposure.

In light of the reviewed evidence, we would recommend that further research is carried out firstly by organizing a cross-sectional multicentre epidemiological study in different countries characterized by different genetic background and level of environmental pollutants in order to better investigate the effect of gene and environment interactions on FeNO levels; such study design would also help obtaining reliable reference values of FeNO. Subsequently, nested case-control studies should be performed in order to assess the impact of remedial interventions regarding the previously cited factors affecting a FeNO concentration; such study design would allow clinicians to implement a public health perspective in the individual-physician relationship. Lastly, it would be helpful to expand the medical histories of children enrolled in pharmaceutical clinical trials, through collecting information on exposome, in order to reduce the residual variability of therapeutic treatment.

Conflict of Interests

The authors have no conflict of interests to disclose in the subject matter.

References

[1] M. W. H. Pijnenburg and J. C. De Jongste, "Exhaled nitric oxide in childhood asthma: a review," *Clinical and Experimental Allergy*, vol. 38, no. 2, pp. 246–259, 2008.

[2] R. J. Delfino, N. Staimer, D. Gillen et al., "Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma," *Environmental Health Perspectives*, vol. 114, no. 11, pp. 1736–1743, 2006.

[3] R. C. Strunk, S. J. Szefler, B. R. Phillips et al., "Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children," *Journal of Allergy and Clinical Immunology*, vol. 112, no. 5, pp. 883–892, 2003.

[4] F. Cibella, G. Cuttitta, S. La Grutta, G. Passalacqua, and G. Viegi, "Factors that influence exhaled nitric oxide in Italian schoolchildren," *Annals of Allergy, Asthma and Immunology*, vol. 101, no. 4, pp. 407–412, 2008.

[5] A. L. B. Cabral, W. M. Vollmer, R. M. Barbirotto, and M. A. Martins, "Exhaled nitric oxide as a predictor of exacerbation in children with moderate-to-severe asthma: a prospective, 5-month study," *Annals of Allergy, Asthma and Immunology*, vol. 103, no. 3, pp. 206–211, 2009.

[6] M. Verini, N. P. Consilvio, S. Di Pillo et al., "FeNO as a marker of airways inflammation: the possible implications in childhood asthma management," *Journal of Allergy*, vol. 2010, Article ID 691425, 7 pages, 2010.

[7] A. Zacharasiewicz, N. Wilson, C. Lex et al., "Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children," *American Journal of Respiratory and Critical Care Medicine*, vol. 171, no. 10, pp. 1077–1082, 2005.

[8] R. Gagliardo, S. La Grutta, P. Chanez et al., "Non-invasive markers of airway inflammation and remodeling in childhood asthma," *Pediatric Allergy and Immunology*, vol. 20, no. 8, pp. 780–790, 2009.

[9] H. L. Petsky, C. J. Cates, T. J. Lasserson et al., "A systematicreview and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils)," *Thorax*. In Press.

[10] G. Renzetti, G. Silvestre, C. D'Amario et al., "Less air pollution leads to rapid reduction of airway inflammation and improved airway function in asthmatic children," *Pediatrics*, vol. 123, no. 3, pp. 1051–1058, 2009.

[11] World Health Organization, *Effects of Air Pollution on Children's Health and Development: A Review of the Evidence*, WHO Regional Office for Europe, Copenhagen, Denmark, 2005, http://www.euro.who.int/__data/assets/pdf_file/0010/74728/E86575.pdf.

[12] K. L. Jansen, T. V. Larson, J. Q. Koenig et al., "Associations between health effects and particulate matter and black carbon in subjects with respiratory disease," *Environmental Health Perspectives*, vol. 113, no. 12, pp. 1741–1746, 2005.

[13] J. G. C. van Amsterdam, B. P. J. Verlaan, H. van Loveren et al., "Air pollution is associated with increased level of exhaled nitric oxide in nonsmoking healthy subjects," *Archives of Environmental Health*, vol. 54, no. 5, pp. 331–335, 1999.

[14] P. H. Fischer, P. A. Steerenberg, J. D. Snelder, H. van Loveren, and J. G. C. van Amsterdam, "Association between exhaled nitric oxide, ambient air pollution and respiratory health in school children," *International Archives of Occupational and Environmental Health*, vol. 75, no. 5, pp. 348–353, 2002.

[15] T. Nicolai, D. Carr, S. K. Weiland et al., "Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children," *European Respiratory Journal*, vol. 21, no. 6, pp. 956–963, 2003.

[16] W. J. Gauderman, E. Avol, F. Gilliland et al., "The effect of air pollution on lung development from 10 to 18 years of age," *The New England Journal of Medicine*, vol. 351, no. 11, pp. 1057–1067, 2004.

[17] D. H. Yates, "Role of exhaled nitric oxide in asthma," *Immunology and Cell Biology*, vol. 79, no. 2, pp. 178–190, 2001.

[18] N. Li, M. Hao, R. F. Phalen, W. C. Hinds, and A. E. Nel, "Particulate air pollutants and asthma: a paradigm for the

role of oxidative stress in PM-induced adverse health effects," *Clinical Immunology*, vol. 109, no. 3, pp. 250–265, 2003.

[19] C. A. Trenga, J. H. Sullivan, J. S. Schildcrout et al., "Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study," *Chest*, vol. 129, no. 6, pp. 1614–1622, 2006.

[20] F. Rusconi, D. Catelan, G. Accetta et al., "Asthma symptoms, lung function, and markers of oxidative stress and inflammation in children exposed to oil refinery pollution," *Journal of Asthma*, vol. 48, no. 1, pp. 84–90, 2011.

[21] M. Flamant-Hulin, D. Caillaud, P. Sacco, C. Penard-Morand, and I. Annesi-Maesano, "Air pollution and increased levels of fractional exhaled nitric oxide in children with no history of airway damage," *Journal of Toxicology and Environmental Health A*, vol. 73, no. 4, pp. 272–283, 2010.

[22] L. Liu, R. Poon, L. Chen et al., "Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children," *Environmental Health Perspectives*, vol. 117, no. 4, pp. 668–674, 2009.

[23] J. Y. Kim, R. Hauser, M. P. Wand, R. F. Herrick, C. J. Amarasiriwardena, and D. C. Christiani, "The association of expired nitric oxide with occupational particulate metal exposure," *Environmental Research*, vol. 93, no. 2, pp. 158–166, 2003.

[24] K. Berhane, Y. Zhang, W. S. Linn et al., "The effect of ambient air pollution on exhaled nitric oxide in the children's health study," *European Respiratory Journal*, vol. 37, no. 5, pp. 1029–1036, 2011.

[25] G. Viegi, M. Simoni, A. Scognamiglio et al., "Indoor air pollution and airway disease: state of the art," *The International Journal of Tuberculosis and Lung Disease*, vol. 8, no. 12, pp. 1401–1415, 2004.

[26] P. J. Franklin, R. Taplin, and S. M. Stick, "A community study of exhaled nitric oxide in healthy children," *American Journal of Respiratory and Critical Care Medicine*, vol. 159, no. 1, pp. 69–73, 1999.

[27] S. J. Langley, S. Goldthorpe, M. Craven, J. Morris, A. Woodcock, and A. Custovic, "Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma," *Journal of Allergy and Clinical Immunology*, vol. 112, no. 2, pp. 362–368, 2003.

[28] M. Sofia, M. Maniscalco, G. D'Onofrio, P. Carratù, and A. Vatrella, "Exhaled nitric oxide as a marker of adverse respiratory health effect in environmental disease," *Monaldi Archives for Chest Disease*, vol. 57, pp. 182–187, 2002.

[29] A. J. Spanier, R. W. Hornung, R. S. Kahn, M. B. Lierl, and B. P. Lanphear, "Seasonal variation and environmental predictors of exhaled nitric oxide in children with asthma," *Pediatric Pulmonology*, vol. 43, no. 6, pp. 576–583, 2008.

[30] S. Raja, Y. Xu, A. R. Ferro, P. A. Jaques, and P. K. Hopke, "Resuspension of indoor aeroallergens and relationship to lung inflammation in asthmatic children," *Environment International*, vol. 36, no. 1, pp. 8–14, 2010.

[31] J. D. Leuppi, S. H. Downs, S. R. Downie, G. B. Marks, and C. M. Salome, "Exhaled nitric oxide levels in atopic children: relation to specific allergic sensitisation, AHR, and respiratory symptoms," *Thorax*, vol. 57, no. 6, pp. 518–523, 2002.

[32] T. A. Kovesi and R. E. Dales, "Effects of the indoor environment on the fraction of exhaled nitric oxide in school-aged children," *Canadian Respiratory Journal*, vol. 16, no. 3, pp. e18–e23, 2009.

[33] N. L. Gilbert, D. Gauvin, M. Guay et al., "Housing characteristics and indoor concentrations of nitrogen dioxide and formaldehyde in Quebec City, Canada," *Environmental Research*, vol. 102, no. 1, pp. 1–8, 2006.

[34] P. Franklin, P. Dingle, and S. Stick, "Raised exhaled nitric oxide in healthy children is associated with domestic formaldehyde levels," *American Journal of Respiratory and Critical Care Medicine*, vol. 161, no. 5, pp. 1757–1759, 2000.

[35] L. G. Hersoug, L. L. N. Husemoen, S. F. Thomsen, T. Sigsgaard, B. H. Thuesen, and A. Linneberg, "Association of indoor air pollution with rhinitis symptoms, atopy and nitric oxide levels in exhaled air," *International Archives of Allergy and Immunology*, vol. 153, no. 4, pp. 403–412, 2010.

[36] M. F. Pasquale, M. Da Frè, F. Rusconi, G. Bonetto, S. Zanconato, and E. Baraldi, "Swimming pool attendance and exhaled nitric oxide in children," *Journal of Allergy and Clinical Immunology*, vol. 118, no. 4, pp. 958–960, 2006.

[37] A. Tuomainen, H. Stark, M. Seuri et al., "Experimental PVC material challenge in subjects with occupational PVC exposure," *Environmental Health Perspectives*, vol. 114, no. 9, pp. 1409–1413, 2006.

[38] B. Kolarik, L. Lagercrantz, and J. Sundell, "Nitric oxide in exhaled and aspirated nasal air as an objective measure of human response to indoor air pollution," *Indoor Air*, vol. 19, no. 2, pp. 145–152, 2009.

[39] S. A. Kharitonov, R. A. Robbins, D. Yates, V. Keatings, and P. J. Barnes, "Acute and chronic effects of cigarette smoking on exhaled nitric oxide," *American Journal of Respiratory and Critical Care Medicine*, vol. 152, no. 2, pp. 609–612, 1995.

[40] C. P. McSharry, I. C. McKay, R. Chaudhuri, E. Livingston, I. Fraser, and N. C. Thomson, "Short and long-term effects of cigarette smoking independently influence exhaled nitric oxide concentration in asthma," *Journal of Allergy and Clinical Immunology*, vol. 116, no. 1, pp. 88–93, 2005.

[41] Y. Laoudi, L. Nikasinovic, F. Sahraoui, A. Grimfeld, I. Momas, and J. Just, "Passive smoking is a major determinant of exhaled nitric oxide levels in allergic asthmatic children," *Allergy*, vol. 65, no. 4, pp. 491–497, 2010.

[42] A. J. Spanier, R. Hornung, M. Lierl, and B. P. Lanphear, "Environmental exposures and exhaled nitric oxide in children with asthma," *Journal of Pediatrics*, vol. 149, no. 2, pp. 220–226, 2006.

[43] A. J. Spanier, R. S. Kahn, R. W. Hornung et al., "Environmental exposures, nitric oxide synthase genes, and exhaled nitric oxide in asthmatic children," *Pediatric Pulmonology*, vol. 44, no. 8, pp. 812–819, 2009.

[44] P. J. Franklin and S. M. Stick, "The value of FeNO measurement in asthma management: the motion against FeNO to help manage childhood asthma—reality bites," *Paediatric Respiratory Reviews*, vol. 9, no. 2, pp. 122–126, 2008.

[45] M. T. Salam, T. M. Bastain, E. B. Rappaport et al., "Genetic variations in nitric oxide synthase and arginase influence exhaled nitric oxide levels in children," *Allergy*, vol. 66, no. 3, pp. 412–419, 2011.

[46] S. Vahlkvist, M. Sinding, K. Skamstrup, and H. Bisgaard, "Daily home measurements of exhaled nitric oxide in asthmatic children during natural birch pollen exposure," *Journal of Allergy and Clinical Immunology*, vol. 117, no. 6, pp. 1272–1276, 2006.

[47] A. Bodini, D. Peroni, A. Loiacono et al., "Exhaled nitric oxide daily evaluation is effective in monitoring exposure to relevant allergens in asthmatic children," *Chest*, vol. 132, no. 5, pp. 1520–1525, 2007.

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Review Article

Managing Anxiety Related to Anaphylaxis in Childhood: A Systematic Review

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Objectives. This paper reviews the relationship between anxiety and anaphylaxis in children and youth, and principles for managing anxiety in the anaphylactic child and his or her parents. *Methods*. A review of the medical literature (Medline) was done using the keywords "anxiety," "anaphylaxis," and "allergy," limited to children and adolescents. Findings were organized into categories used in the treatment of childhood anxiety disorders, then applied to managing anxiety in the anaphylactic child. *Results*. Twenty-four relevant papers were identified. These varied widely in methodology. Findings emphasized included the need to distinguish anxiety-related and organic symptoms, ameliorate the anxiety-related impact of anaphylaxis on quality of life, and address parental anxiety about the child. *Conclusion*. Children with anaphylaxis can function well despite anxiety, but the physical, cognitive, and behavioral aspects of anxiety associated with anaphylactic risk must be addressed, and parents must be involved in care in constructive ways.

1. Introduction

Anxiety symptoms are common in children with anaphylactic conditions and in their parents. Children with anxiety disorders are at increased risk for allergies, including those associated with anaphylaxis [1], and anaphylaxis itself can provoke anxiety. Given the life-threatening nature of anaphylaxis, this anxiety is understandable especially within the first few months after diagnosis or after a reaction. Some anxiety in the face of anaphylaxis may even be adaptive, as anxious children are less likely to take risks with respect to their anaphylactic conditions than children who are not anxious [2].

In some cases, however, anxiety becomes debilitating and imposes unnecessary restrictions on the anaphylactic child's life, preventing the child from engaging in important daily activities at home, at school, or socially. Anxiety associated with such daily impairment is not considered normative [3]. For example, a child with an insect sting allergy might completely avoid the outdoors; a child with a severe food allergy might follow an overly restrictive diet or avoid friends' homes for fear of encountering an allergen; a young anaphylactic child might refuse to stay at school without a parent for fear of having a reaction there. Prominent symptoms of anxiety (e.g., hyperventilation or blushing) may also mimic anaphylactic reactions, often resulting in further anxiety and impairment [4–6].

Anxiety that is persistent, extreme, and results in restriction of activities that is not medically warranted must be addressed in order to return the child to a normative developmental course. Few guidelines exist on how to do this. Therefore, this paper reviews studies focusing on the relationship between anxiety and anaphylaxis in children and key clinical recommendations related to managing anxiety in the child and his or her parents.

2. Materials and Methods

A review of the medical literature (Medline Search) was done using the keywords "anxiety" and "anaphylaxis," limited to papers focusing on children and adolescents. The search yielded 17 papers, but 6 were excluded: 4 did not investigate any aspect of children's or parents' anxiety; 2 were reviews that did not contain new data. The remaining 11 papers were deemed relevant to this paper. These varied widely in

methodology, but none were excluded for methodological reasons, given the paucity of studies. Scrutiny of these papers revealed additional citations that used the term "severe allergy" rather than anaphylaxis. Therefore, the original search was repeated using the term "allergy" instead of anaphylaxis, but only those papers that included children who might have anaphylactic reactions (mainly food and insect sting allergies) were included. This strategy yielded 13 additional papers, resulting in a total of 24 papers. Key findings and recommendations from each of these papers are summarized in Table 1.

For the discussion, findings and recommendations were then further organized in relation to physiological, cognitive, behavioral, or parental aspects of anxiety. This was done because psychological interventions developed for children with anxiety disorders (e.g., cognitive behavioral therapy [7]) generally target these aspects. Focusing on these aspects allowed concepts relevant to interventions developed for childhood anxiety disorders to be applied to the special challenge of ameliorating anxiety in the context of pediatric anaphylaxis.

3. Results and Discussion

Findings and interventions relevant to four aspects of anxiety (physiological, cognitive, behavioral, and parental), derived from the literature on pediatric anaphylaxis and on treatment of childhood anxiety disorders, will now be described. Successful management of anxiety in the anaphylactic child usually requires emphasis on those aspect(s) which predominate in a given child or family.

3.1. Physiological Aspects of Anxiety. Recurrent, unexplained flushing [4], asthmatic attacks [6], anxiety-related syncope, and anxiety attacks [5] can all be mistaken for anaphylactic reactions in children and youth. For example, hyperventilation associated with anxiety can often cause tingling in the lips and extremities, prompting food allergic children to fear that they have come in contact with an allergen. Anxiety reactions that mimic anaphylaxis have also been noted during large-scale vaccination campaigns [5]. Education of children, families, school personnel, and public health providers is therefore important to improve their ability to distinguish anxiety symptoms from those of anaphylaxis, ensuring appropriate treatment [4–6]. When there is doubt, it is prudent to err on the side of caution and treat for anaphylaxis. However, when there are recurrent reactions in situations where the risk of allergen exposure is low, an anxious etiology should be suspected.

Children who become anxious in response to having an anaphylactic condition can often benefit from learning relaxation techniques such as slow, deep breathing, or progressive muscle relaxation (reviewed in [8]). These techniques must be practiced daily for a few weeks at nonanxious times (e.g., at bedtime) in order to become usable at anxious times. "Box breathing" is a particularly useful technique for reducing hyperventilation. In this technique, the child breathes in four stages and draws the sides of a box with his or her index finger in the process. These stages include breathing in, holding the breath, breathing out, and waiting for the next breath. The child is asked to count to 3 at each stage before moving on to the next, then count to 4 at each stage, and so on until breathing slowly.

When anxiety symptoms subside, it is important to return the child quickly to his or her usual daily activities [8]. This practice has two benefits: it distracts the child from focusing further on any remaining symptoms, and it prevents reinforcement of avoidant behaviors that exacerbate anxiety in the long run. For example, if the child experiences anxiety symptoms at school, he or she can be helped to calm down by an adult in the school office, and then returned to class after a few minutes. Calling parents to come and remove the child from school is generally not helpful and may promote school avoidance. Of course, if there is a possibility of a true anaphylactic reaction, emergency medical services should be contacted.

3.2. Cognitive Aspects of Anxiety. Nut allergic children report a lower quality of life than their peers, and even than diabetic children [9, 10]. Children with anaphylactic conditions are especially vulnerable to worry and psychological distress relative to those with less severe allergies [11–13]. Separation anxiety is a particular concern in this population [14].

As mentioned above, some worry about having an anaphylactic reaction is natural and may be protective [2]. Unlike ordinary worries of childhood about low-risk events (e.g., worries about tests or examinations), worries about anaphylaxis focus on a life-threatening, high-risk event. Reassurance focused on minimizing this risk is therefore not helpful. Instead, reassurance must focus on the child's own ability to manage the risk. Education of the child and his or her parents about the degree of risk in various situations with emphasis on what the child can do to increase safety is an important first step towards reducing anxiety [2, 5, 14–22]. Then, the child should be engaged as a participant in a clear, concise plan for managing anaphylactic risk [22]. Such participation generally reduces children's sense of helplessness when living with an anaphylactic condition [14].

Young children may be limited in their ability to manage anaphylactic risk, as they are highly dependent on adults. However, they can still be engaged in practices that improve environmental safety (e.g., reminding people to read product labels; eliminating allergens from the home environment) [14]. Knowing when to ask an adult for help is another important skill for the young allergic child. Consistency in allergy management between environments (e.g., ensuring that the school and extended family members take the same precautions that the parents take) may further reduce the child's anxiety, as anxious children are typically reassured by predictability [7].

Adolescents, on the other hand, are often vulnerable to peer pressure and may cognitively minimize their allergic risk [15, 19]. High-risk behaviors with respect to anaphylaxis are particularly common among adolescents expressing little concern about their condition and among adolescents in social situations involving peers [19]. Inability to remember an anaphylactic reaction may also contribute to risk taking in adolescents [15]. Allergic youth with high health competence

Table 1: Key findings and recommendations of included studies.

Study	Method	Key findings	Recommendations
Akeson et al., 2007 [15]	Qualitative study of anaphylactic adolescents and their parents.	Adolescents perceived anaphylaxis as "no big deal" and could not remember a reaction; parents reported anxiety about "handing over" management of anaphylaxis to adolescents.	Tailored information for transition from parental to self-management needed; regular reviews and reinforcement about avoidance and emergency management needed; offer peer support via workshops.
Avery et al., 2003 [9]	Peanut allergic and diabetic children compared on a quality of life questionnaire.	Peanut allergic children reported lower quality of life and higher anxiety; epinephrine injectors and eating in familiar places seemed to reduce anxiety.	Anxiety may promote better adherence to allergen avoidance; epinephrine injectors may ease excessive anxiety.
Cummings et al., 2010 [10]	Nut allergic children and mothers completed questionnaires on anxiety and quality of life.	Children had lower quality of life relative to norms; mothers and children were less anxious when prescribed epinephrine injectors, regardless of their adherence to precautions.	Prescribe epinephrine injectors to reduce anxiety; provide additional education/advice to improve adherence and reduce risk taking.
DunnGalvin et al., 2009 [27]	Comparison of parents of food allergic children who enrolled child in immunotherapy study with those who did not.	Parents who enrolled their children reported higher anxiety, but similar quality of life.	Study samples may be biased towards anxious parents; avoid taking advantage of anxious parents' vulnerability when recruiting for studies.
DunnGalvin et al., 2008 [28]	Evaluation of quality of life questionnaire for parents of food allergic children.	The Food Allergy QoL-Parent Form shows excellent reliability and validity.	Consider using this questionnaire to assess health-related quality of life in parents of food allergic children.
Eigenmann et al., 2006 [25]	Survey of food allergic patients after a negative food challenge.	25% of patients continued to avoid the food, fearing persistence of allergy.	Reassess food consumption in patients with negative food challenge; repeat challenge if avoidance continues.
Friedman et al., 1994 [4]	Case series of 10 patients with recurrent unexplained flushing.	Several were originally diagnosed as anaphylactic, but eventually found to have somatization disorders.	Recognition of this presentation is needed to avoid unwarranted examinations and procedures.
Hawkes et al., 2010 [29]	Retrospective review of cases admitted to hospital for MMR immunization in Ireland.	Children often admitted due to history of egg allergy, even though risk of anaphylactic reaction is very low in this population.	Advise routine community vaccination for children with egg allergy; educate physicians about their low anaphylaxis risk.
Herbert and Dahlquist, 2008 [11]	Comparison of food allergic and nonallergic adolescents/young adults on self-report measures.	Perceived autonomy, anxiety, depression, and parental behavior did not differ between groups; those with anaphylaxis reported more worry and parental overprotection than those with less severe allergies.	Recognize that anaphylactic individuals and their parents are at particular risk for psychological distress; further study is needed.
Hu et al., 2008 [16]	Survey and qualitative interviews with parents of food allergic children.	Parents found consumer organizations good sources of practical information and support, but some nonspecific advice and contact with other anxious parents were unhelpful.	Clinicians should guide parents as to what aspects of consumer organizations are most helpful.
Khetsuriani et al., 2010 [5]	Review of adverse events in a measles-rubella vaccination campaign in Georgia.	79 severe adverse events; 37 of these had symptoms of syncope or anxiety attack, and all but one of these was initially diagnosed anaphylactic.	Risk communication strategies for care providers and the public are needed during public vaccination campaigns.
King et al., 2009 [14]	Quality of life reports from children with peanut allergy, parents, and siblings.	Mothers reported poorer quality of life and higher anxiety than fathers; separation anxiety greater in children with peanut allergy than their siblings.	Be aware that child's allergy management may fall to mothers, increasing their personal and family stress; foster allergy self-care for children to reduce anxiety.
Lebovidge et al., 2006 [12]	Development and evaluation of a questionnaire regarding parental response to children's food allergies.	Factor analysis revealed anxiety/distress, psychosocial impact of allergy, parental coping/competence, and family support factors. Greatest anxiety if child had many allergies or had anaphylaxis.	This measure may be a useful screening tool to identify parents of allergic children who are most vulnerable to anxiety and high psychosocial impact of child's allergy.

Table 1: Continued.

Study	Method	Key findings	Recommendations
Lyons and Forde, 2004 [17]	Comparison of adolescents/young adults with/without food allergy on self-report questionnaire.	Allergy had less impact on allergic individuals' lives than others thought; allergic youth with high health competence reported greatest anxiety; few subjects knew the meaning of the term "anaphylaxis."	Health education is needed in this population; increased vigilance among health competent individuals may increase anxiety or anxious individuals may self-diagnose food allergy; more research is needed.
Mandell et al., 2005 [2]	Qualitative interviews of parents of anaphylactic children.	Repeated cycles of adaptation to episodic anxiety-provoking (i.e., anaphylaxis-related) events challenge families to regain a sense of control.	Recognize patterns of family adaptation to anaphylaxis; help families maintain an optimal balance between protective and debilitating anxiety.
Oude et al., 2002 [23]	Randomized controlled trial of patients receiving either immunotherapy or epinephrine injector for yellow jacket allergy.	Quality of life reported as improved in immunotherapy group but not in epinephrine injector group.	Provide venom immunotherapy to improve quality of life and decrease anxiety in this population.
Powers, 2004 [6]	Single case report of reaction to jellyfish sting reported as anaphylaxis.	Individual had asthmatic attack due to anxiety induced by the jellyfish sting.	Emergency workers should treat presenting symptoms rather than assuming that anaphylaxis has occurred.
Primeau et al., 2000 [18]	Comparison of quality of life and family relations in parents of children with peanut allergy versus rheumatological disease.	Parents of peanut allergic children reported that children had more disruption in daily life and the condition had more impact on the family.	Accurate diagnosis of peanut allergy, support for families, and offering more peanut-free products would help these children and families.
Roberts-Thompson et al., 1985 [13]	Retrospective review of 98 cases of bee sting anaphylaxis.	Most reactions occurred in children; considerable anxiety present in some subjects.	Provide venom immunotherapy to alleviate anxiety.
Sampson et al., 2006 [19]	Internet questionnaire for 174 food allergic adolescents and young adults.	High-risk behavior associated with less "concern," and with social situations involving peers.	Education of food allergic teens and also of their peers is needed to reduce risk of anaphylaxis.
Sicherer et al., 2001 [20]	Comparison of 253 parents of food allergic children versus established norms on psychosocial function questionnaire.	Low health perception of child, high emotional impact on parent, high limitation of family activities reported, especially if child had multiple food allergies.	Be aware of these psychological effects on child and family; provide family support and education; raise public awareness of the issue; advocate for food labeling.
Somers, 2011 [21]	Case report of 11-year old with peanut allergy.	Subject had very restricted diet due to fear of anaphylaxis, affecting weight gain; tense family interactions around meals.	Offer nutritional guidance; use 24-hour food recall; offer behavioral guidelines for parents; get child involved in food preparation to increase confidence.
Vargas et al., 2011 [22]	Qualitative study of parents of food allergic children.	Parents wanted (1) concise information on symptoms, cross-contamination of foods, label reading, epinephrine injectors, and advocacy; (2) education of professionals and community.	Parents of newly diagnosed children could benefit from a food allergy management curriculum; clear, concise materials would likely reduce anxiety.
Zijlstra et al., 2010 [24]	Parental anxiety measured before and after allergic children underwent food challenges.	Parental state anxiety decreased with food challenge regardless of result; parental trait anxiety was unchanged.	Food challenges may help alleviate parental anxiety about their children's allergies.

with respect to their condition, however, reported greater anxiety than those with low health competence [17] suggesting that education about anaphylaxis may result in a more realistic assessment of risk. Akeson and colleagues [15] have also emphasized the need to regularly review precautions and emergency management with adolescents in order to facilitate the transition from parental to self-management of anaphylactic risk.

Some aspects of the medical management of anaphylaxis can also affect children's and parents' anxiety. For example, use of epinephrine injectors has been found to reduce food allergic children's anxiety [9, 10]. On the other hand,

children allergic to yellow jacket stings were found to be less anxious after venom immunotherapy than before, but continued to be anxious if given an epinephrine injector without immunotherapy [23]. Parental anxiety has been found to decrease after food challenges, regardless of challenge results [24].

3.3. Behavioral Aspects of Anxiety. Behavioral aspects of anxiety usually consist of unnecessary avoidance of certain situations or excessive clinginess with parents [14, 21, 25]. For example, some children with food allergies severely restrict food intake beyond what is medically necessary, adversely affecting their weight and nutrition [21], and some children anaphylactic to insect stings avoid all outdoor activities [13]. Other children continue to avoid certain foods despite a negative food challenge to those foods [25]. Repeating food challenges is reassuring in some but not all cases [25].

To begin to address unnecessary avoidance, obtain a detailed account of regularly avoided situations or foods (e.g., a 24-hour food recall) [21] or of situations where the child relies excessively upon his or her parents. Then, encourage daily practice approaching these situations or foods in small steps, beginning with a step that the child considers relatively easy (reviewed in [26]). In the case of food restriction, for example, the child may be involved in food preparation to increase confidence before being asked to eat a food that makes him or her anxious [21]. If a child with insect sting anaphylaxis avoids the outdoors, going outdoors in the winter (i.e., when there are no flying insects about) may be an easy first step. Although such practice is initially anxiety provoking, it results in cognitive desensitization to the feared stimulus, reducing anxiety over time [7]. If the child insists on parental accompaniment in this process, it is usually wise to allow it initially but then fade parental support gradually as the child gains confidence. Practice sessions should be long enough for the child's anxiety to peak and then begin subsiding (usually at least 20 minutes), as premature escape from the situation interferes with desensitization.

To motivate the child's participation, it is often helpful to chart progress, providing praise and points or stickers for every attempt (reviewed in [26]). Providing a small reward every five or every ten points can increase motivation further. Adolescents may respond better to an extra privilege (e.g., extra "screen time" for their favorite computer activities; a little extra time to stay out with friends) than a tangible reward. Nutritional and/or behavioral guidelines may be needed for parents in order to optimize their participation in the child's anxiety desensitization program [21].

After a child becomes confident with the first step, he or she can begin practicing a step that is just slightly more anxiety provoking, with additional incentives for doing so if needed. Having mastered that step, the child then continues with further steps until there are no longer any situations or foods that are being unnecessarily avoided [7, 26].

3.4. Parental Aspects of Anxiety. Most authors cited in Table 1 noted anxiety in the parents of children with anaphylactic conditions, though some suggest that study recruitment may be somewhat biased towards more anxious parents [27]. Nevertheless, parental anxiety is common enough in this population that at least two relevant questionnaires have recently been developed and evaluated for parents of allergic children [12, 28]. Lebovidge and colleagues [12] developed a screening tool to identify parents of allergic children who are most vulnerable to anxiety. DunnGalvin and colleagues [28] suggest using The Food Allergy QoL-Parent Form to assess health-related quality of life in parents of food allergic children, including parental anxiety. Parents of food allergic children report that their child's allergy has a substantial impact on their quality of life [18, 20]. In one study this impact was reported as greater than that of having a child with rheumatological disease [18].

Studies of parental anxiety concluded that those whose children had multiple allergies or had anaphylaxis were most anxious [2, 12]. Consistent with these findings, adolescents with anaphylaxis reported more parental overprotection than those with less severe allergies [11]. Mothers may be especially vulnerable to anxiety about the child, as much of the management of children's allergies typically falls to their mothers [14]. Professionals, however, may also suffer excessive anxiety in response to even a remote risk of anaphylaxis. For example, family practitioners in Ireland frequently hospitalize children with egg allergies for routine vaccinations, even though this is not considered medically necessary [29].

Recommendations for addressing excessive parental anxiety include ongoing education and advice about realistic versus unrealistic risks (endorsed by all authors in this paper), especially in the form of clear, concise materials for families [22]; acknowledgment of psychological distress in families [11]; tailored information for families of adolescents to inform the transition from parental to self-management of allergy [14, 15]; recognizing patterns of family adaptation after an anaphylactic event [2], including the fact that anxiety in the first few months is normative; providing guidance for parents regarding optimal use of consumer organizations [16]; providing epinephrine injectors and instruction on how to use them to families of food allergic children with anaphylactic risk [9, 10]; providing venom immunotherapy to children with insect sting anaphylaxis [13, 23]; offering more peanut-free products for children with peanut allergy [18]; advocating for food labeling and public awareness of severe allergies and anaphylaxis [20, 22].

Working with anxious parents of children with anaphylactic conditions can be frustrating for professionals, especially when parents are difficult to reassure. However, it is important to enlist parents as allies in managing the child's allergy and to emphasize their ability to ensure safety, to model healthy coping, and to promote healthy coping in their child (reviewed in [8]). Putting oneself in the parents' shoes is often helpful, as it allows empathy for the parents' anxiety and sense of helplessness. Doing so can also help clarify the aspects of allergy management that are most difficult for a given family, thus guiding further intervention.

Moreover, guidance for parents of allergic children should not be limited to a single discussion. The parents' role with respect to the child's allergy will change over time, as the child develops, so ongoing professional support and

communication are needed. For example, parents must learn developmentally appropriate degrees of child independence at various ages, how best to influence child behavior at different ages (see above), and how best to advocate for one's child as he or she progresses through the school system. Policies regarding the allergic child and the use of epinephrine injectors may vary from school to school, so ongoing parental advocacy is needed. Siblings may respond adversely to the extra attention often required by the anaphylactic child [8], so parents may also need guidance on how to manage sibling interactions. Support groups related to child allergies may be helpful for some parents [16], and ongoing communication with families improves access to these and other resources.

Furthermore, some children with anaphylactic conditions develop mental health problems that are not entirely allergy related. For example, children who exhibit anxious behaviors that predate a diagnosis of anaphylaxis may have anxiety disorders in addition to anaphylaxis-related anxiety [8]. Children with anaphylactic conditions can also have mental health problems that interfere with allergy management. For example, children with attention or learning problems may have difficulty remembering appropriate precautions or may be prone to misplacing epinephrine injectors or other allergy-related medications. Therefore, specialist referral for concurrent mental health problems can be helpful if these are present.

4. Conclusions

Children and adolescents with anaphylactic conditions can learn to function well at home, at school, and socially when their anxiety is not excessive, developing into well-adjusted young adults. For this to occur, however, the physical, cognitive, and behavioral aspects of anxiety that may be associated with anaphylactic risk must be addressed, and parents must be involved in the child's care in constructive ways. Ongoing professional support and communication with these youth and their families is needed to ensure optimal psychological as well as medical outcomes.

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References

[1] P. A. Kovalenko, C. W. Hoven, P. Wu, J. Wicks, D. J. Mandell, and Q. Tiet, "Association between allergy and anxiety disorders in youth," *Australian and New Zealand Journal of Psychiatry*, vol. 35, no. 6, pp. 815–821, 2001.

[2] D. Mandell, R. Curtis, M. Gold, and S. Hardie, "Anaphylaxis: how do you live with it?" *Health and Social Work*, vol. 30, no. 4, pp. 325–335, 2005.

[3] American Psychiatric Association, *Diagnostic and Statistical Manual of the American Psychiatric Association*, Text Revision (DSM-IV-TR), American Psychiatric, Washington, DC, USA, 4th edition, 2000.

[4] B. S. Friedman, P. Germano, J. Miletti, and D. D. Metcalfe, "A clinicopathologic study of ten patients with recurrent unexplained flushing," *Journal of Allergy and Clinical Immunology*, vol. 93, no. 1, pp. 53–60, 1994.

[5] N. Khetsuriani, P. Imnadze, L. Baidoshvili et al., "Impact of unfounded vaccine safety concerns on the nationwide measles-rubella immunization campaign, Georgia, 2008," *Vaccine*, vol. 28, no. 39, pp. 6455–6462, 2010.

[6] D. W. Powers, "A bad way to end a vacation," *Emergency Medical Services*, vol. 33, no. 6, p. 46, 2004.

[7] S. N. Compton, J. S. March, D. Brent, A. M. Albano, V. R. Weersing, and J. Curry, "Cognitive-bahvioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 43, no. 8, pp. 930–959, 2004.

[8] S. Monga and K. Manassis, "Treating anxiety in children with life-threatening anaphylactic conditions," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 45, no. 8, pp. 1007–1010, 2006.

[9] N. J. Avery, R. M. King, S. Knight, and J. O. B. Hourihane, "Assessment of quality of life in children with peanut allergy," *Pediatric Allergy and Immunology*, vol. 14, no. 5, pp. 378–382, 2003.

[10] A. J. Cummings, R. C. Knibb, M. Erlewyn-Lajeunesse, R. M. King, G. Roberts, and J. S. A. Lucas, "Management of nut allergy influences quality of life and anxiety in children and their mothers," *Pediatric Allergy and Immunology*, vol. 21, no. 4, pp. 586–594, 2010.

[11] L. J. Herbert and L. M. Dahlquist, "Perceived history of anaphylaxis and parental overprotection, autonomy, anxiety, and depression in food allergic young adults," *Journal of Clinical Psychology in Medical Settings*, vol. 15, no. 4, pp. 261–269, 2008.

[12] J. S. Lebovidge, K. D. Stone, F. J. Twarog et al., "Development of a preliminary questionnaire to assess parental response to children's food allergies," *Annals of Allergy, Asthma and Immunology*, vol. 96, no. 3, pp. 472–477, 2006.

[13] P. J. Roberts-Thomson, P. Harvey, and S. Sperber, "Bee sting anaphylaxis in an urban population of South Australia," *Asian Pacific Journal of Allergy and Immunology*, vol. 3, no. 2, pp. 161–164, 1985.

[14] R. M. King, R. C. Knibb, and J. O. B. Hourihane, "Impact of peanut allergy on quality of life, stress and anxiety in the family," *Allergy*, vol. 64, no. 3, pp. 461–468, 2009.

[15] N. Akeson, A. Worth, and A. Sheikh, "The psychosocial impact of anaphylaxis on young people and their parents," *Clinical and Experimental Allergy*, vol. 37, no. 8, pp. 1213–1220, 2007.

[16] W. Hu, R. Loblay, J. Ziegler, and A. Kemp, "Attributes and views of families with food allergic children recruited from allergy clinics and from a consumer organization," *Pediatric Allergy and Immunology*, vol. 19, no. 3, pp. 264–269, 2008.

[17] A. C. Lyons and E. M. E. Forde, "Food allergy in young adults: perceptions and psychological effects," *Journal of Health Psychology*, vol. 9, no. 4, pp. 497–504, 2004.

[18] M. N. Primeau, R. Kagan, L. Joseph et al., "The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut allergic children," *Clinical and Experimental Allergy*, vol. 30, no. 8, pp. 1135–1143, 2000.

[19] M. A. Sampson, A. Muñoz-Furlong, and S. H. Sicherer, "Risk-taking and coping strategies of adolescents and young adults

with food allergy," *Journal of Allergy and Clinical Immunology*, vol. 117, no. 6, pp. 1440–1445, 2006.

[20] S. H. Sicherer, S. A. Noone, and A. Muñoz-Furlong, "The impact of childhood food allergy on quality of life," *Annals of Allergy, Asthma and Immunology*, vol. 87, no. 6, pp. 461–464, 2001.

[21] L.S. Somers, "Peanut allergy: case of an 11-year-old boy with a selective diet," *Journal of the American Dietetic Association*, vol. 111, pp. 301–306, 2011.

[22] P. A. Vargas, S. H. Sicherer, and L. Christie, "Developing a food allergy curriculum for parents," *Pediatric Allergy and Immunology*, vol. 22, no. 6, pp. 575–582, 2011.

[23] J. N. Oude Elberink, J. G. R. De Monchy, S. Van Der Heide, G. H. Guyatt, and A. E. J. Dubois, "Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom," *Journal of Allergy and Clinical Immunology*, vol. 110, no. 1, pp. 174–182, 2002.

[24] W. T. Zijlstra, A. E. Flinterman, L. Soeters et al., "Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy," *Pediatric Allergy and Immunology*, vol. 21, no. 2, pp. 439–445, 2010.

[25] P. A. Eigenmann, J. C. Caubet, and S. A. Zamora, "Continuing food-avoidance diets after negative food challenges," *Pediatric Allergy and Immunology*, vol. 17, no. 8, pp. 601–605, 2006.

[26] K. Manassis, *Keys to Parenting Your Anxious Child*, Barron's Educational Series, Hauppauge, NY, USA, 2nd edition, 2007.

[27] A. DunnGalvin, W. C. Chang, S. Laubach et al., "Profiling families enrolled in food allergy immunotherapy studies," *Pediatrics*, vol. 124, no. 3, pp. e503–e509, 2009.

[28] A. DunnGalvin, B. M. J. De BlokFlokstra, A. W. Burks, A. E. J. Dubois, and J. O. B. Hourihane, "Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity," *Clinical and Experimental Allergy*, vol. 38, no. 6, pp. 977–986, 2008.

[29] C. P. Hawkes, S. Mulcair, and J. O. B. Hourihane, "Is hospital based MMR vaccination for children with egg allergy here to stay?" *Irish Medical Journal*, vol. 103, no. 1, pp. 17–19, 2010.

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Review Article

Eosinophilic Esophagitis in Pediatrics: The Worst of all Possible Allergy Worlds ?

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Eosinophilic esophagitis (EoE) is a relatively uncommon allergic disease. Presenting with variable gastrointestinal symptoms, the definitive diagnosis is made after esophageal visualization and histological confirmation of excessive esophageal eosinophils. The scientific discovery of the pathophysiology of EoE has been aided by its relationship to other common and well-recognized allergic diseases. Similarities and important differences have emerged to distinguish EoE as a significant pediatric allergic disease with unique medical care requirements.

1. Introduction

From an early description as a pathological sidebar in 1977 [1] eosinophilic esophagitis (EoE) has become an important allergic disease. Currently, as a pediatric disease entity, EoE requires the diagnostic acumen of multiple specialists, including allergists, gastroenterologists, pathologists, and radiologists. It presents with a spectrum of symptoms depending on age and has a natural history of such short duration that the prognosis for patients and their families is difficult to predict.

Eosinophilic esophagitis has the lowest prevalence in the allergic disease family and ranked most to least common: allergic rhinitis, asthma, atopic dermatitis, food allergy, and EoE. Children with EoE often have other preexisting allergic diseases, and, presumptively, young children with EoE likely will develop other allergic disease(s) with age. The pathophysiological understanding of the allergic disease family has grown exponentially in the past decade, which is equally true of EoE [2].

In this paper we will contrast and compare the known pathophysiology and clinical circumstances of each of the allergic diseases and EoE and suggest that EoE has disadvantages to patients greater than or equal to its allergy family members. An excellent consensus paper with recommendations for treating children and adults with EoE has been recently published [3].

2. Food Allergy versus Eosinophilic Esophagitis

By every indicator IgE-mediated food allergy has increased in the past decade. In almost all cases, symptoms of IgE-mediated food allergy are readily defined and generally temporally approximate to the food ingested, but not persistent or chronic. The diagnosis is relatively straightforward, using a clinical history supported by appropriate allergy skin tests or specific IgE blood tests. As long as the inciting food is avoided, symptoms are totally gone, and daily therapy is not indicated. With the exception of peanuts and tree nuts, food allergy generally resolves itself by late adolescence. The exact reason for the clinical presence of an allergy to a specific food(s) is still unknown, considering many children allergic to a specific food(s) have concomitant specific food serum IgE levels (or positive skin tests) to tolerated foods.

In EoE an associated food allergy has been shown to have both pathophysiological and clinical relevance. In contrast to IgE-mediated food allergy where the avoidance of the allergenic food(s) is almost always clinically beneficial, even an elemental diet does not induce remission in all subjects with EoE. And compared to conventional IgE-mediated food allergy, deciding on the food protein avoidance regimen in EoE involves both standard skin testing and in some cases allergy patch testing [4]. The scant data on patch testing suggests that the range of food protein "allergy" in EoE far exceeds conventional IgE-mediated food allergy

mechanisms. Despite the information gained using these techniques (skin testing and patch testing) in some situations complete food protein avoidance is necessary for effective control of symptoms [5]. And finally, in contrast to food allergy, current evidence does not support the eventual tolerance of allergic food(s) and the total resolution of EoE [6]. Although morbidity with EoE is relatively high, mortality, as compared to food allergy, has not been reported.

3. Eosinophilic Esophagitis and Atopic Dermatitis

Atopic dermatitis (AD) pathophysiology is a complex interaction of intrinsic dermal/epidermal dysfunction and humoral (IgE) and cellular (T-cell) reactivity to the environment. In particular, abnormal filaggrin protein(s) (an epidermal component) has been linked to severe AD phenotypes [7], with a resultant loss of epidermal integrity, thus allowing interaction between the external environment and the heightened immune response. Recent research has suggested a diminished filaggrin protein in EoE, resulting in decreased esophageal barrier function [8].

Atopy is a common finding in pediatric atopic dermatitis and EoE, although nonatopic forms of AD and EoE are not uncommon. IgE-mediated sensitization to food protein(s) is commonly enhanced in both disease conditions, and the elimination of sensitized foods has been a cornerstone of therapy in EoE and a frequent discussion point in AD. Multiple studies investigating food avoidance as an effective therapy for AD have not been convincing, despite the fact that IgE-mediated food sensitization is common in AD.

The clinical relevance of avoiding IgE-mediated sensitized foods in AD patients is limited. Preceding the use of patch testing in EoE for foods was a movement to isolate clinically relevant food allergies in AD using a delayed (48–72 hours) food response [9]. Although in limited use currently, these strategies suggest a more complex immune response to food protein than through a Type 1 immune reaction in both EoE and AD. The limited studies of patch testing in EoE suggest a stronger association with disease activity and/or therapeutic responsiveness to certain food protein, especially milk [10]. Also, food protein exposure in AD has several pathways to sensitization, including contact, airborne, and even transplacental or via breast milk, while in EoE food protein exposure may be through a systemic route with esophageal transmural migration, or possibly by direct contact during food ingestion.

Environmental allergen sensitization is common to both AD and EoE, but studies do not exist that compare rates of environmental sensitization in children with a single disease state (EoE or AD), or each disease at different ages. It is generally held that young AD patients eventually develop environmental allergen sensitization and often second or third allergic diagnoses, but similar studies showing the development of other allergic diseases have not been done with early onset EoE. Conventional allergy immunotherapy, often issued in allergic rhinitis and allergic asthma, is not commonly utilized for AD and has not been reported for EoE.

The prognosis of AD in children is considered good, with many children having resolution of active disease by adolescence. The current longitudinal data for pediatric-onset EoE from a single center was not optimistic for improvement [6], strongly suggesting a persistent course, possibly into adulthood.

4. Eosinophilic Esophagitis versus Allergic Rhinitis

Allergic rhinitis is a relatively straightforward and common allergic disease which usually starts in childhood. The exposure and sensitization to an airborne allergen is then recentered to an intranasal allergy response on re-exposure. Although not commonly emphasized, the late phase allergic is largely responsible for chronicity of symptoms. Subepithelial thickening and remodeling are apparently present, but do not usually receive the same consideration as do the same processes in the lower airway.

Food allergens only extremely rarely are involved in allergic rhinitis, although a corollary process, pollen-food allergy syndrome, may occasionally coexist. Allergic rhinitis therapy is directed by and enhanced with appropriate skin testing, with good clinical correlation. Avoidance can be helpful, topical therapy with intranasal corticosteroids is often successful, and allergy immunotherapy is a mainstay. Complications arising from allergic rhinitis are uncommon, but life-long disease is common.

In comparison to allergic rhinitis, EoE is uncommon, sometimes indolent, or under recognized, with only an occasional association with seasonal worsening. Eosinophilic esophagitis patients can have positive skin tests to both seasonal and nonseasonal allergens, but clinical esophageal symptomatology to environmental allergens, in comparison to nasal symptoms as seen with allergic rhinitis, is less obvious. Food allergy, both immediate and possibly non-IgE mediated, is common to EoE, unlike allergic rhinitis.

Recent data strongly suggests a significant role for remodeling/fibrosis in EoE [11] and even smooth muscle hyperplasia and possibly hyperresponsiveness [12]. Therapy for EoE often hinges on topical inhaled corticosteroids, but avoidance of food allergens can be partially (or even near totally) remissive. Immunotherapy for EoE has not been studied to date, and, in large part, therapeutic regimens are empiric, without the long time honored benefit of placebo-controlled trials required in new allergic rhinitis therapies. Like allergic rhinitis, the pediatric EoE patient may have long-lasting disease, although the opportunity for serious, life-altering sequela is likely much higher in EoE.

5. Eosinophilic Esophagitis versus Asthma

The occasionally used term "asthma of the esophagus" places EoE in the same realm of disease pathophysiology of the frequently cited "most common chronic disease of children" asthma if not so much for its frequency but to its impact on morbidity. The rapidly advancing basic research studies in EoE, with a several decades of asthma pathophysiology as

a guide, have quickly moved EoE into position of significant biological complexity.

Asthma has run a gamut of pathophysiological causes, smooth muscle constriction, bronchial hyperresponsiveness, eosinophilic inflammation, specific T-cell hyperactivity, and extensive cytokine production, although many of the processes currently recognized date to work by Slater in the early 1800s and Osler by the turn of the century [13]. EoE was first described only 4 decades ago. Like asthma, EoE has a hierarchy of recognized histological consequences, the discovery of which has been compressed into a mere decade of research.

Asthma in young children is usually associated with nonallergic triggers, especially viral illnesses, while asthma that continues into grade school and later-onset asthma usually has allergic comorbidity. Food allergy is a frequent comorbid process, but avoidance of food protein never induces remission of active disease. Asthma is usually associated with wheezing or recurrent cough and is usually considered early after its onset. The presence of wheezing is readily apparent to most parents and is a tell-tale symptom for health care providers. The rapid response to beta-agonists in a clinical setting, or in a pulmonary function laboratory, provides confirmation of likelihood for asthma. Current asthma guidelines provide a literature-supported, evidence-based approach for medical and supportive management, with advancing complexity for difficult-to-manage patients. Unfortunately, asthma has always maintained an imposing morbidity among the allergic diseases, although the rate of asthma deaths has decreased this decade. The natural history of pediatric asthma supports a reasonable chance for sustained remission, although fixed airway flow changes may persist.

EoE has a spectrum of presentations in children, with a different face with advancing age of onset. No one symptom clearly dominates, unlike the recurrence of wheezing or chronic cough seen in asthma. The relative infrequency, as compared to asthma, may delay the diagnosis. In some situations, the presence of EoE is totally unknown until an incidental finding on an endoscopy for an unrelated concern or only after the retrieval of a stuck esophageal foreign body. The incidence of "silent" EoE is unknown. In contrast the medical literature has thousands of epidemiological studies, using multiple methods of ascertainment, looking at "hidden" asthma. Unlike asthma, the definitive diagnosis requires an invasive procedure, with the subsequent initiation of largely empirical medical and/or food protein avoidance therapy(s). Any prescribed therapeutic intervention does not generally allow for a certain response, or easily determined benefit, without a repeat endoscopy. A published report in pediatric EoE patients followed for over one decade does not support a reasonable chance of remission [6]. Mortality from eosinophilic esophagitis has not been reported, in contrast to asthma, currently at over 3000 deaths per year.

6. Summary

Eosinophilic esophagitis certainly matches the biological complexity of atopic dermatitis and asthma. Asthma, allergic rhinitis, food allergy, and to a less extent atopic dermatitis, have long recognized and/or easily undertaken medical protocols, which are further supported by evidence-based research. The long-term clinical impact of EoE is yet, largely, unknown, but studies suggest extended chronicity, while the other allergic diseases, especially atopic dermatitis and most food allergies, have a very reasonable likelihood of remission. Subject to some debate, the incidence of EoE is likely increasing, as are all other allergic diseases. The potential for morbidity in EoE appears to be high, but without current reports of mortality, unlike food allergy or asthma. Overall, EoE is a complex allergic disease, with long-term concerns, *with minimal pediatric placebo-controlled trials* [14, 15] to guide therapy, and no readily apparent method of following clinical progress, except repeated invasive testing procedures. Extensive information has been gained on its pathophysiology, *aided* by years of sequential understanding of the other allergic diseases.

References

[1] J. W. Dobbins, D. G. Sheahan, and J. Behar, "Eosinophilic gastroenteritis with esophageal involvement," *Gastroenterology*, vol. 72, no. 6, pp. 1312–1316, 1977.

[2] C. Blanchard, E. M. Stucke, B. Rodriguez-Jimenez et al., "A striking local esophageal cytokine expression profile in eosinophilic esophagitis," *Journal of Allergy and Clinical Immunology*, vol. 127, no. 1, pp. 208–e7, 2011.

[3] C. A. Liacouras, G. T. Furuta, I. Hirano et al., "Eosinophilic esophagitis: updated consensus recommendations for children and adults," *Journal of Allergy and Clinical Immunology*, vol. 128, no. 1, pp. 3–20, 2011.

[4] J. M. Spergel, T. Andrews, T. F. Brown-Whitehorn, J. L. Beausoleil, and C. A. Liacouras, "Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests," *Annals of Allergy, Asthma and Immunology*, vol. 95, no. 4, pp. 336–343, 2005.

[5] J. E. Markowitz, J. M. Spergel, E. Ruchelli, and C. A. Liacouras, "Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents," *American Journal of Gastroenterology*, vol. 98, no. 4, pp. 777–782, 2003.

[6] J. M. Spergel, T. F. Brown-Whitehorn, J. L. Beausoleil et al., "14 years of eosinophilic esophagitis: Clinical features and prognosis," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 48, no. 1, pp. 30–36, 2009.

[7] N. Morar, W. O. C. M. Cookson, J. I. Harper, and M. F. Moffatt, "Filaggrin mutations in children with severe atopic dermatitis," *Journal of Investigative Dermatology*, vol. 127, no. 7, pp. 1667–1672, 2007.

[8] C. Blanchard, E. M. Stucke, K. Burwinkel et al., "Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis," *The Journal of Immunology*, vol. 184, no. 7, pp. 4033–4041, 2010.

[9] E. Isolauri and K. Turjanmaa, "Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis," *Journal of Allergy and Clinical Immunology*, vol. 97, no. 1 I, pp. 9–15, 1996.

[10] J. M. Spergel, T. Brown-Whitehorn, J. L. Beausoleil, M. Shuker, and C. A. Liacouras, "Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis," *Journal of Allergy & Clinical Immunology*, vol. 119, no. 2, pp. 509–511, 2007.

[11] J. P. Li-Kim-Moy, V. Tobias, A. S. Day, S. Leach, and D. A. Lemberg, "Esophageal subepithelial fibrosis and hyalinization are features of eosinophilic esophagitis," *Journal of Pediatric Gastroenterology and Nutrition*, 2011.

[12] S. S. Aceves, D. Chen, R. O. Newbury, R. Dohil, J. F. Bastian, and D. H. Broide, "Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF-β1, and increase esophageal smooth muscle contraction," *Journal of Allergy and Clinical Immunology*, vol. 126, no. 6, pp. 1198–1204, 2010.

[13] E. R. McFadden Jr., "A century of asthma," *American Journal of Respiratory and Critical Care Medicine*, vol. 170, no. 3, pp. 215–221, 2004.

[14] A. Straumann, S. Conus, L. Degen et al., "Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis," *Gastroenterology*, vol. 139, no. 5, pp. 1526–1537, 2010.

[15] M. R. Konikoff, R. J. Noel, C. Blanchard et al., "A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis," *Gastroenterology*, vol. 131, no. 5, pp. 1381–1391, 2006.

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Review Article

An Overlapping Syndrome of Allergy and Immune Deficiency in Children

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Recurrent airway inflammations in children are an important clinical problem in pediatric practice. An essential challenge is differentiation between allergic background and immune deficiency, which is a difficult task taking into consideration individual predisposition to atopy, immune system maturation in the early childhood, as well as exposition to environmental allergens and microbial antigens. In this paper relationship between selected elements of innate and adaptive immunity, such as pattern-recognition receptors, complement components, dendritic cells, as well as immunoglobulins, and regulatory T lymph cells has been discussed. Particular attention has been paid to these mechanisms of the immune response which, depending on settings and timing of activation, predispose to allergy or contribute to tolerogenic phenotype. In the context of multifactorial conditioning of the innate and adaptive immunity governing the ultimate response and associations between allergy and immune deficiencies, these phenomena should be considered as pathogenetically not precluding, but as an overlapping syndrome.

1. Introduction

Development of the immune response in childhood is a dynamic process initiated within the fetal period and expanding in time through months and even years of child's life. Physiological phenomenon of immune system maturation, type and timing of activating allergens, and microbial antigens in conjunction with genetic predisposition to allergy are of crucial importance in determination of the proallergic or tolerogenic phenotype. Clinically, these considerations apply particularly to diagnostic and therapeutic dilemmas regarding recurrent airway inflammations in children, in which major questions concern differentiation between allergy and immune deficiency. Establishing a diagnosis is an essential challenge including common clinical manifestations, reciprocal impact of different clinical entities, overlapping pathomechanisms of allergic background, and defects of innate and adaptive immune responses, as well as deficiencies in factors playing a hitherto unexpected immunoregulatory role.

2. Maturation of the Immune System

Physiological phenomenon of maturation of the immune system, initiated within the fetal period, is dynamic in its character and is expanding in time through the first months and even years of child's life. Hence, within the neonatal period, infancy and early childhood dysfunction of numerous components of the immune system is observed.

Within the neonatal period, considerable immaturity characterizes the system of monocytes-macrophages. It consists in decreased expression of costimulatory molecules and diminished ability to differentiation into dendritic cells as well as weak production of IL-12 by monocytes [1]. Macrophages exhibit diminished response to IFNγ, decreased activity upon phagocytosis [1], and impairment of intracellular killing [2].

In neonates, the immaturity concerns function of dendritic cells. This consists in downregulated expression of costimulatory molecules by myeloid (mDC) and of plasmacytoid (pDC)dendritic cells, defective maturation and synthesis

of cytokines—IFNγ and IL-12 as the response to signaling pathways downstream of Toll-like receptors engagement, particularly TLR4 and TLR9 and CD40 molecule as well as impaired ability to stimulate the immune response by pDC. The proposed mechanisms to explain the dysfunction of neonatal DC comprise intrinsic immaturity, defective interaction between dendritic cells and T lymphocytes as well as modulatory effect of natural regulatory T cells (nTreg). These cells, playing an important role during pregnancy and maintaining maternal tolerance to the fetus, are present in high numbers in neonates and are critical in maintaining homeostasis, immunological tolerance, and preventing autoimmunity. Neonatal nTregs exert their immunosuppressive function by the mechanism of interaction between molecules CTLA-4 and CD80/CD86 on antigen-presenting cells and by secretion of L-10 and TGFβ [1].

Functional alterations of neonatal antigen-presenting cells may in turn lead to secondary defects of adaptive T-cell response. In neonates occurs a T-cell functional deficiency manifesting as downregulated expression of TCR/CD3 complex, adhesion molecules and CD40 ligand (CD40L, CD154), impaired cytotoxic activity of CD8+ T cells as well as decreased cytokine synthesis. Expression of a range of cytokines playing an essential role in the immune response, such as IL-4, IL-5, IFNγ, TNFα, and IL-12, is a dynamic process and their production increases with child's age [3]. Hodge et al. demonstrated a diminished number of neonatal T lymph cells and NK cells exhibiting expression of β chain of the IL-2 receptor. Moreover, the production level of cytokines such as IL-1α, IL-1β, and TNFα was lower compared to adults, pointing to decreased capacity to mount effective inflammatory response. On the contrary, the level and kinetics of expression of other functional molecules—CD71, HLA-DR; and CD152—were comparable to that in adults [4].

Predominance of the Th2-dependent immune response prevailing within the fetal period and expanding through the neonatal period and infancy [5–7] may be among others as a result of exerted activity of regulatory T cells, suppressing the proinflammatory Th1-mediated response [8]. Moreover, mechanisms of the innate immune response profiling development of the adaptive response towards advantageous Th1-or Th2-mediated immunity contribute to the predisposition or to the protection from asthma and allergy. Dose, settings, and timing of exposure to antigens are of crucial importance in modulating the immune response profile within the child's early life [9, 10].

Immaturity of the effector mechanisms and suppressive activity of the transplacentally transmitted maternal IgG antibodies contribute to the consequent deficiency of specific humoral response [5]. In neonates, rapid increase of the immunoglobulin M active in primary immune response to antigens, relatively high concentration of IgG of maternal origin and weak production of child's own immunoglobulins IgG and IgA manifest as dysgammaglobulinemia and reflect distinct dynamics of different isotype synthesis. In infants between the second and sixth months of life hypogammaglobulinemia continues as a result of still weak production of own and the breakdown of maternal immunoglobulin G. Delayed maturation of the humoral response manifests frequently as transient hypogammaglobulinemia of infancy (THI), which abates typically until the end of the second year of life [11], but may be prolonged even up to the fifth or sixth year of life [12] and hitherto the evaluation, if the immune defect in a child is transient or is signaling a permanent primary immune deficiency, may be difficult. In the recent study of Keles et al. [13], evaluating clinical and immunological features of THI children, asthma was the leading health problem present in 52% of patients.

3. Allergic Diseases Coexisting with Immune Deficiencies

3.1. Antibody Production Defects. To the clinical problem of concomitant occurrence of allergic diseases and primary immune deficiencies in children drew attention Klemola, who reported symptoms of atopic diseases in 50% of children with selective IgA deficiency (sIgAD) [14]. Interestingly, it was noted a better correlation between the prevalence and severity of the clinical course of allergic diseases in children within the first two years of life and a low normal IgA concentration in serum than a concentration of IgE increased above the normal value for age [15]. In the prospective study evaluating the same group of children at the age of four years, it was observed an association between occurrence of allergic diseases and asthma and decreased IgA and IgG4 subclass in serum as well as secretory salivary IgA [16]. The Papadopoulou study revealed not solely a higher prevalence of atopy in a group of children with selective IgA deficiency compared to a control group, but also pointed to the more frequent coexisting bronchial hyperreactivity and hypersensitivity to *Dermatophagoides pteronyssinus* in children with sIgAD [17]. The results of the study performed by Kutukculer et al. [18] indicated that partial IgA deficiency and IgG subclass deficiency are transient in 52% and 51% children, respectively, and that increases in serum immunoglobulins to age-related normal levels occur up to the sixth year of life. Exactly, in this group of children atopic diseases proved to occur more frequently than among children with complete selective IgA deficiency (in 41% and 24% patients, resp.). An analysis of correlation between clinical and immunological phenotypes was done in the recent report of Iranian authors [19] on the group of patients aged 4–32 years, showing IgA concentration below 62 mg/dl. Recurrent airway inflammations were the most frequent clinical problems, referring to 94% of patients. Allergic diseases-asthma, atopic dermatitis, allergic rhinitis, and conjunctivitis were diagnosed in 84% of patients, indicating the fact that not only a predisposition to infections resulting from an immunodeficiency solely, but also an allergic background considerably affects the clinical manifestation of the disease. Interestingly, an asthmatic phenotype was present exclusively in patients with selective IgA deficiency amounting 62% of the study group. On the contrary, in 38% of patients, who suffered from a complex immunodeficiency consisting in IgA deficiency, IgG subclass deficiency, deficiency of specific antibodies against polysaccharide antigens (sAbDs), and

infections of the respiratory tract predominated as clinical manifestations and exclusively in this group of patients occurrence of bronchiectases was observed. Moraes et al. [20] in the study on the group of 41 severe asthmatic children showed an association between the degree of asthma control and recurrent airway infections as well as deficiencies within the immune system. In children with poor asthma control more frequently than in children with sufficiently controlled asthma (66% versus 55% of children) a deficiency of one or more IgG subclasses and IgG3 or IgG4 deficiency were diagnosed as well as solely in this group of children, a combined IgA and IgG subclass deficiency was revealed.

Single reports in the literature concerning selective immunoglobulin M deficiency (sIgMD) in pediatric population and in adults point to the recurrent respiratory tract infections as the predominant clinical feature. Allergic diseases and asthma coexist with this immune deficiency in 7-8% of affected children [21] and as much as 33% of adult patients [22].

Interestingly, an association between allergic diseases and immune deficiencies was observed in patients manifesting profound defects of antibody production. Shabestari et al. [23] reported a case of a boy with Bruton's agammaglobulinemia in whom concentrations of main classes of immunoglobulins were decreased within all isotypes including IgE (<0,1 IU/ml), B lymph cells bearing antigens CD19 and CD20 amounted less than 1% of normal value for age and the disease was confirmed by *BTK* gene mutation. Recurrent episodes of respiratory infections with obstruction of the lower airways were the most important clinical symptoms, and in additional diagnostic examinations, positive skin prick tests with alimentary and airborne allergens as well as bronchial hyperreactivity in spirometry were noted. A bias towards Th2-mediated immune response was also documented in patients with common variable immunodeficiency (CVID) through investigation of cytokine levels and demonstration of increased IL-4 and IL-10 production [24]. A high incidence of asthma, usually diagnosed after the initial presentation, was seen in 83% of pediatric patients with CVID as it was reported by Ogershok et al. [25].

3.2. Complement Deficiencies. Associations between allergic background of respiratory symptoms and immune defects are not exclusively confined to a dysregulation of immunoglobulin production and impaired balance between Th1 and Th2 lymph cells compartments. These phenomena are also determined by the activity of complement pathway components, establishing links between innate and adaptive immune responses. Although each pathway is activated by distinct pathway recognition receptors (PRRs), they all culminate in activation of C3 component, a central step in complement activation. Activation of C3 leads to the generation of anaphylatoxins C3a and C5a, which through binding their receptors on inflammatory cells proved to induce pathophysiological features of allergic inflammation. In support of this proallergic role of C3, its deficiency was shown on an animal model to have a protective effect against antigen-induced bronchial hyperreactivity [26, 27]. C5a, in turn, in allergic inflammation plays a dual role, both promoting and protective, depending on the inflammatory cells and cytokine environment upon its activation. Immunological role of C5a component consists principally in modulation of the adaptive immune response through altering the phenotype and function of antigen-presenting dendritic cells [28]. A deficiency in C5a leads to a shift of the proportion of the myeloid dendritic cells (mDCs) to plasmacytoid dendritic cells (pDCs), and to the consequent development of Th2-dependent effector phase. In this condition of a lack of C5a also an increase of the production of Th2-specific chemokines, CCL17 and CCL22 by pulmonary mDCs occurs, enhancing homing of Th2 lymph cells [29]. Impairment of the immune tolerance results from a defective stimulation of pDCs and absence of regulatory T-cell induction, corroborating a concept of a tolerogenic role of C5a and protective effect during allergen sensitization. A recognition of pattern-associated molecular patterns (PAMPs) leads to the activation of complement pathway by lectin proteins. A decreased level of a mannose-binding lectin (MBL), playing an important role in opsonization, was found in a group of asthmatic children [30]. Moreover, an association was shown between an allelic variant of *MBL2* gene leading to decreased MBL concentration in serum and higher risk of asthma in children presenting with recurrent and chronic *Chlamydia pneumonia* infection [31]. In adults an allelic MBL variant was not only associated with predisposing effect to asthma, but also correlated with a decrease in lung function [32].

Ficolins M, L, and H (1, 2, and 3, resp.), structurally similar to collectins, MBL, and surfactant protein A and D initiate the lectin pathway of complement activation through serin proteases MASPs [33]. Cedzynski et al. reported an association between relative L-ficolin deficiency and recurrent respiratory infections coexisting with asthma in children [34].

Deficiencies of humoral innate and adaptive immune responses associated with proallergic effect are displayed on Figure 1.

3.3. Phagocyte Defect. Fitzpatrick et al. [35] demonstrated impaired alveolar macrophage phagocytosis in children with poorly controlled asthma. These findings suggest that a functional deficiency of innate immunity contributes to a defective antimicrobial response and recurrent airway inflammation resulting in exacerbations of asthma. This phenomenon of impaired phagocytosis may be explained by an alternative mechanism of macrophage activation potentiated by IL-4 in the Th2 microenvironment, where inhibition of phagocytosis associated with defective phagosome formation and concomitant increased proinflammatory cytokine secretion was observed by Varin et al. [36].

4. Role of Regulatory T Lymphocytes

Natural Treg cells of a CD4+CD25+ phenotype are best characterized by an intracellular marker, a transcription factor Foxp3, playing an essential role in development and

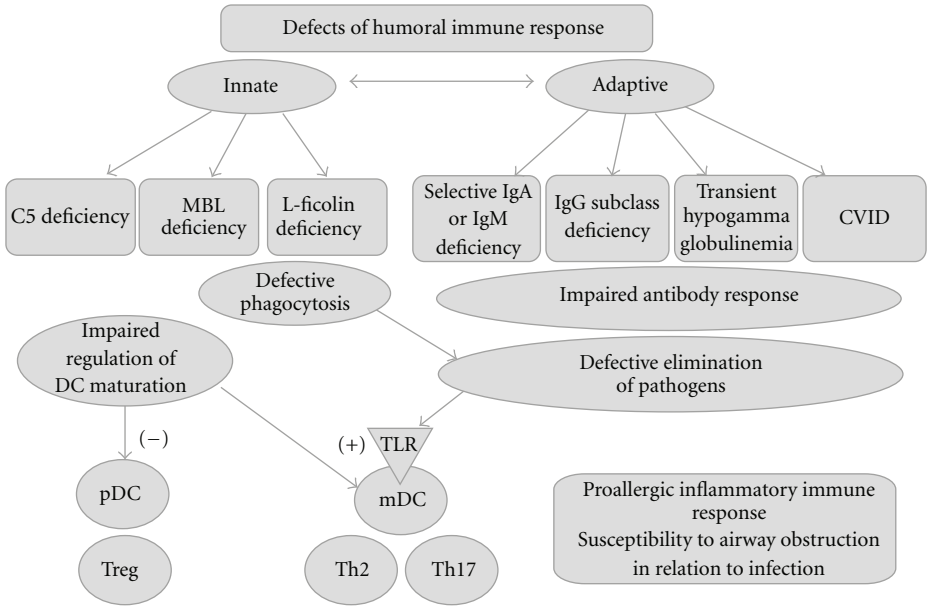

Figure 1: Humoral defects of innate and adaptive immune responses associated with proallergic effect.

activity of these cells [37–40]. Inducible regulatory T lymph cells (iTreg, Tr1) arise as a result of activation of mature T cells in the settings lacking an optimal exposure to antigen or costimulation as well as in the environment of inhibitory cytokines and are characterized by IL-10 and TGFβ production. Naïve CD4+ T cells may also develop into Tr1 cells in the presence of chronic stimulation with allergens infectious and tumor antigens. However, the suppressive function is not strictly Treg-specific and all CD4+ T cells exhibit suppressive activity in different degree. Mechanisms determining types of immune response and their mutual relationship as a result of transcription factors and cytokine activities towards CD4+ T cell subsets are displayed on Figure 2.

For T regulatory lymphocytes, the following nonexclusive functions are proposed: prevention of autoimmunity by establishing and maintaining immunological tolerance to self-antigens, induction of maternal tolerance to the fetus, induction of tolerance against alimentary antigens, and suppression of pathogen-induced immunopathology [38, 39].

In allergic diseases and asthma, activation of CD4+ T cells plays a key role and allergic inflammation in the airways is mediated by subpopulations of effector Th2 and Th17 cells. Regulatory T cells, both nTregs having CD4+CD25+ phenotype and antigen-induced IL-10 secreting Tr1 cells achieve their regulatory effect by different pathways, inhibiting dendritic cells activity, suppressing effector Th2 and Th17 cells, suppressing mast cells and basophils, as well as decreasing migration of inflammatory cells to target tissues [41–44]. They also downregulate IgE synthesis and stimulate class switching towards anti-inflammatory isotypes—IgG4 subclass and, in a lesser extent, to IgA. Induction of IgA synthesis is first of all determined by activation of B lymphocytes through Toll-like receptors TLR9 and TLR7 pathway [45]. Hartl et al. [46] reported significantly decreased number of CD4+CD25+ T cells and lower concentration of cytokines IL-10 and TGFβ in bronchoalveolar lavage fluid of asthmatic as compared to healthy children. Likewise, in patients manifesting symptoms of atopic diseases, Saito [47] demonstrated a smaller proportion of cells Foxp3+CD4+ than in asymptomatic individuals in the control group, having similar concentrations of IFNγ and IgE in serum as well as blood eosinophil count. These above-mentioned findings suggest that development of symptoms of allergic diseases is determined by mutual relationship between proinflammatory Th2 and Th17 lymph cells subsets and regulatory T cells. Recently, novel distinct populations of effector T helper cells involved in tissue inflammation have been demonstrated, namely Th9 cells, characterized by IL-9 and IL-10 secretion [48], and Th22 cells with IL-22 secretion and low expression levels of IL-17 [49, 50].

A deficiency of regulatory T cells resulting from *FOXP3* gene mutation is an essential factor in pathogenesis of IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) [51]. In a range of primary immune deficiency diseases an immunological dysregulation may be consequent to functional regulatory T cells impairment and predominating Th2-dependent immune response, as it was demonstrated in patients with common variable immunodeficiency, a disorder predisposing to autoimmunity [52, 53]. A Th17 cells deficiency is a crucial immune abnormality in the hyperimmunoglobulin E syndrome (HIES), a complex immunodeficiency with a constellation of diverse clinical manifestations, unique predisposition to staphylococcal and mycotic infections, and heterogeneous genetic origin. In autosomal dominant hyper-IgE syndrome (AD-HIES) hypomorphic mutations in *STAT3* (signal transducer and activator of transcription) gene has been demonstrated [54], leading to impaired Th17 cells differentiation and

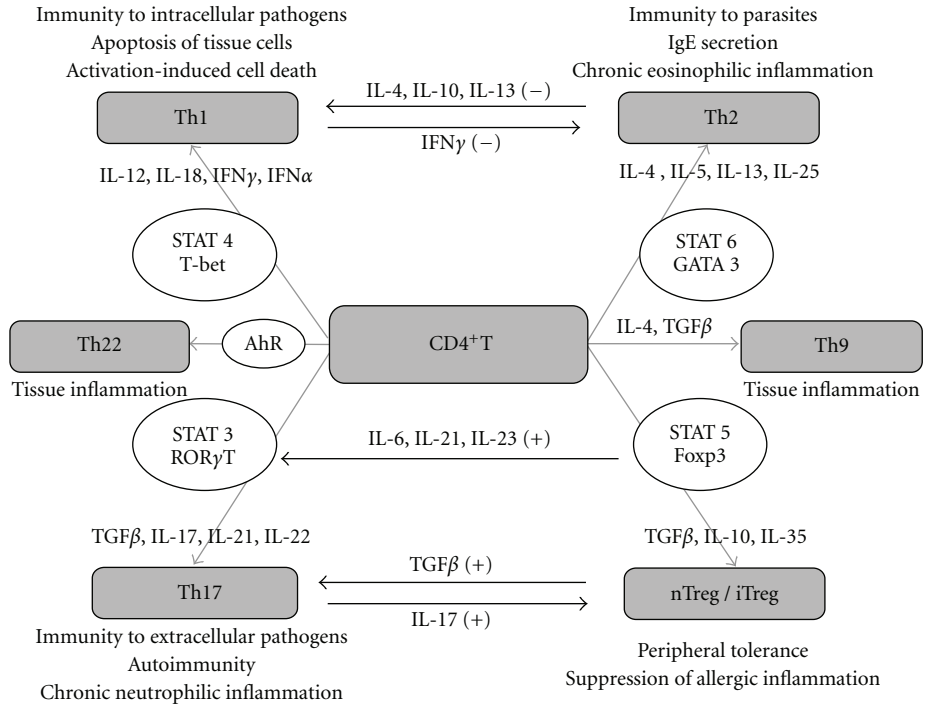

Figure 2: Mechanisms determining types of immune response and their mutual relationship as a result of transcription factors and cytokine activities towards CD4+ T cell subsets.

defective multiple cytokine signaling, resulting in impaired upregulation of antimicrobial peptides [55]. Patients affected with autosomal recessive hyper-IgE syndrome (AR-HIES) due to DOCK8 (dedicator of cytokinesis 8) [56] or *Tyk2* (tyrosine kinase 2) gene mutation [57] share common features of HIES, such as elevated serum IgE concentration and eosinophilia as well as predisposition to staphylococcal and candidal infections however, different infection profile and clinical features suggest a distinct disease entity.

Primary immune deficiencies of different genetic background associated with T-cell dysfunction and aberrant IgE production are displayed in Table 1.

5. Immunomodulatory Role of Pattern Recognition Receptors (PRRs)

Toll-like receptors (TLRs), along with retinoid acid-inducible gene-I-like receptors (RLRs) and nucleotide-binding oligomerization domain- (NODs) like receptors (NLR) are crucial elements of innate arm of immunity, recognizing pathogen-associated molecular patterns (PAMPs), and molecular structures specific for microbial pathogens. They are expressed in different cellular compartments, such as cell surface, endosome, lysosome or cytoplasm, and activate specific signaling pathways leading to expression of genes that tailor immune responses to particular microbes [58]. Toll-like receptors TLR1, TLR2, TLR4, TLR6, and TLR10 detect extracellular pathogen-associated signatures, while TLR3, TLR7, TLR8, and TLR9 recognize ligands derived from intracellular viral and bacterial pathogens.

In B lymph cells, Toll-like receptors activation results in upregulation of activation markers, proliferation, cytokine secretion, terminal differentiation, and immunoglobulin secretion. It has been demonstrated that TLR9 stimulation of B cells with CpG motifs induces IgG class switch recombination (CSR). This effect results in inhibition of the IL-4 and CD40-dependent IgG1/IgE class switch and suppression of IgE production as well as simultaneous stimulation of IgA synthesis [59].

Extensive interactions and crosstalk among TLRs and other surface receptors is a characteristic feature of TLRs [60]. Both microbial antigens and allergens represent important trigger factors with effect on antigen-presenting cells and effector cells involved in allergic reactions. Therefore, it is likely that not separate but concomitant stimulation of both receptor types, namely, Toll-like receptors and high-affinity receptor for IgE (FcεRI) may occur under physiological conditions and in particular in the context of allergic and infectious diseases. Potential counterregulation and interaction of TLRs with IgE receptor-mediated immune response along with integrated signal from different receptor networks may therefore compose mechanisms which promote development of allergy [60].

Different TLRs, in particular TLR2 and TLR4 have been demonstrated to be expressed on mast cells, which can be activated to secrete diverse mediators and cytokines by IgE as well as specific antigens and products derived from either pathogens or the host during innate and adaptive immune responses [61, 62]. Depending on the type of ligand, TLR2 displays modulatory effect on FcεRI-mediated signaling

Table 1: Primary immune Deficiencies and their genetic background, associated with T-cell dysfunction and aberrant IgE production.

Primary immune deficiencies with elevated IgE		
T-cell dysfunction	Immune deficiency	Genetic background
Treg cell deficiency	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)	Forkhead box protein 3 (Foxp3) signal transducer and activator of transcription 5b (STAT5b)CD25
Treg cell dysfunction	Wiskott-Aldrich syndrome (WAS)	Wiskott-Aldrich syndrome protein (WASP)
Treg cell deficiency T-cell oligoclonality	Omenn syndrome (OS)	recombination activation genes (RAG1,RAG2) Artemis IL-7R zeta-associated protein, 70 kD (ZAP-70,) DNA ligase
Reduced NK cell cytotoxicityskewed Th1 phenotype	Comel-Netherton syndrome (CNS)	Serin protease inhibitor Kazal type (SPINK) lymphoepithelial Kazal type inhibitor (LEKTI)
T-cell oligoclonality	DiGeorge syndrome (DGS)—atypical complete form	Microdeletion 22q11
Reduced Th17 cells Treg cell dysfunctionmultiple cytokine signaling defect	Hyperimmunoglobulin E syndrome (HIES)	Signal transducer and activator of transcription 3 (STAT3) dedicator of cytokinesis 8 (DOCK8) tyrosine kinase 2 (Tyk2)

and downregulation of FcεRI and attenuation of the IgE-dependent mast cell degranulation has been demonstrated in context to lipoteichoic acid [63]. These data point to the immunomodulatory function of mast cell TLR2 depending on the stimulating bacterial product.

Interestingly, counterregulation of FcεRI, and TLR9 has been demonstrated on plasmacytoid dendritic cells. The capacity of pDC to release type 1 interferon (IFN-α and IFN-β) after TLR9 stimulation with specific ligands, unmethylated CpG motifs is substantially decreased after FcεRI aggregation and allergen challenge in vitro, indicating a cross talk also among these receptors, TLR9 and FcεRI [64]. Summarizing, costimulation of effector cells on the level of TLRs and FcεRI may lead to diverse ultimate effect, either protective or promoting allergic response and effective or impaired antimicrobial immune responses under specific conditions.

6. Effects of Vitamin D on Immune Functions

There is an emerging evidence of the role of vitamin D not only confined to calcium and bone homeostasis, but also to its pleiotropic and immunomodulatory effect on both innate and adaptive immune responses. The active form of vitamin D, $1,25(OH)_2D$ binds to the vitamin D receptor (VDR), a nuclear receptor and ligand-activated transcription factor, expressed in many tissues and regulating cellular differentiation and function of many cell types, including the immune system. VDR expression is found, among others, in macrophages, dendritic cells, NK cells, T cells, and B cells. Upon activation, VDR elicits in these cells a potent anti-proliferative, prodifferentiative, and immunomodulatory effects on both transcription-dependent and transcription-independent actions [65]. Vitamin D inhibits the function of T lymphocytes both directly and via effects on antigen-presenting cells, particularly of Th1-associated cytokine production and IL-17 production by Th17 lymph cells involved in autoimmune and allergic processes, including asthma. The effect on Th2-mediated immune response is more complex and the reports point to both its inhibition and enhancement [66]. Vitamin D shows an inhibitory effect on dendritic cells by downregulating expression of costimulatory molecules CD40 and CD80/86, decreasing secretion of immunostimulatory IL-12. Concurrently, it leads to increased production of anti-inflammatory IL-10 by dendritic cells and CD4+CD25+ Treg cells.

In the lungs airway, epithelial cells have been found to express high levels of 1alpha-hydroxylase, the vitamin D-activating enzyme. Calcitriol has also been shown to inhibit the synthesis and release of certain cytokines, such as RANTES (regulated on activation, normal T-cell expressed and secreted), PDGF (platelet-derived growth factor), and matrix metalloproteinases from bronchial smooth muscle cells, thereby leading to decreased inflammation and smooth muscle cell proliferation [67]. Additionally, on animal model, vitamin D receptors have been found in fetal type II alveolar epithelial cells, which may according to recent evidence play a role in the induction of regulatory T cells [68]. In several clinical studies, association of vitamin D with allergy and asthma has been investigated. In 2007, two simultaneously published reports [69, 70] have demonstrated higher risk of recurrent wheeze in children born from women with low vitamin D intake during pregnancy. Brehm et al. [71] showed a correlation between low levels

of vitamin D and markers of asthma severity in children including hospitalizations, the use of medications, and airway hyperresponsiveness.

Therefore, vitamin D has been found to act as an immunomodulator relevant to pathomechanisms of antimicrobial response and allergy. In this context, vitamin D deficiency might be considered as an immunodeficiency state predisposing to airway infections and to decreased tolerogenic phenotype, with effect on complex interactions between genetic and environmental factors leading to development of asthma.

7. Concluding Remarks

Multidirectional interactions and precise control of elements of the immune response determine homeostasis between effector mechanisms and tolerance. Above-mentioned associations between numerous elements of the immune system, the innate as well as adaptive immune response, and mechanisms predisposing to the development of allergy suggest complex considering of the clinical problem of recurrent airway inflammations in children. The above-mentioned findings point to the pathogenetic relationship between allergy and immune deficiencies which better than mechanisms of atopy correlate with symptomatology of the allergic diseases in children. These observations regarding mainly young children and infants presenting transient deficiencies of the immune response indicate a delayed maturation of immunological components as a phenomenon of crucial importance. A dysregulation of the immune response contributing to the defective antigen elimination in the early childhood of the predisposed individual may be considered as the critical risk factor preceding development of allergy. The immune deficiencies and allergy have mutual impact and are thus not precluding phenomena, but should be considered as a specific overlapping syndrome.

References

[1] P. A. Velilla, M. T. Rugeles, and C. A. Chougnet, "Defective antigen-presenting cell function in human neonates," *Clinical Immunology*, vol. 121, no. 3, pp. 251–259, 2006.

[2] F. Saito, H. Kuwata, E. Oiki et al., "Inefficient phagosome maturation in infant macrophages," *Biochemical and Biophysical Research Communications*, vol. 375, no. 1, pp. 113–118, 2008.

[3] C. Härtel, N. Adam, T. Strunk, P. Temming, M. Müller-Steinhardt, and C. Schultz, "Cytokine responses correlate differentially with age in infancy and early childhood," *Clinical and Experimental Immunology*, vol. 142, no. 3, pp. 446–453, 2005.

[4] S. Hodge, G. Hodge, R. Flower, and P. Han, "Cord blood leucocyte expression of functionally significant molecules involved in the regulation of cellular immunity," *Scandinavian Journal of Immunology*, vol. 53, no. 1, pp. 72–78, 2001.

[5] B. Morein, G. Blomqvist, and K. Hu, "Immune responsiveness in the neonatal period," *Journal of Comparative Pathology*, vol. 137, no. 1, pp. S27–S31, 2007.

[6] A. Gasparoni, L. Ciardelli, A. Avanzini et al., "Age-related changes in intracellular Th1/Th2 cytokine production, immunoproliferative T lymphocyte response and natural killer cell activity in newborns, children and adults," *Biology of the Neonate*, vol. 84, no. 4, pp. 297–303, 2003.

[7] A. Kotiranta-Ainamo, J. Rautonen, and N. Rautonen, "Imbalanced cytokine secretion in newborns," *Biology of the Neonate*, vol. 85, no. 1, pp. 55–60, 2004.

[8] B. Adkins, "Heterogeneity in the CD4 T cell compartment and the variability of neonatal immune responsiveness," *Current Immunology Reviews*, vol. 3, no. 3, pp. 151–159, 2007.

[9] M. Belderbos, O. Levy, and L. Bont, "Neonatal innate immunity in allergy development," *Current Opinion in Pediatrics*, vol. 21, no. 6, pp. 762–769, 2009.

[10] N. W. J. Schröder, "The role of innate immunity in the pathogenesis of asthma," *Current Opinion in Allergy and Clinical Immunology*, vol. 9, no. 1, pp. 38–43, 2009.

[11] V. Moschese, S. Graziani, M. A. Avanzini et al., "A prospective study on children with initial diagnosis of transient hypogammaglobulinemia of infancy: results from the Italian Primary Immunodeficiency Network," *International Journal of Immunopathology and Pharmacology*, vol. 21, no. 2, pp. 343–352, 2008.

[12] N. Kutukculer and N. Gulez, "The outcome of patients with unclassified hypogammaglobulinemia in early childhood," *Pediatric Allergy and Immunology*, vol. 20, no. 7, pp. 693–698, 2009.

[13] S. Keles, H. Artac, R. Kara, B. Gokturk, A. Ozen, and I. Reisli, "Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: similarities and differences," *Pediatric Allergy and Immunology*, vol. 21, no. 5, pp. 843–851, 2010.

[14] T. Klemola, "Deficiency of immunoglobulin A," *Annals of Clinical Research*, vol. 19, no. 4, pp. 248–257, 1987.

[15] B. R. Ludviksson, T. H. Eiriksson, B. Ardal, A. Sigfusson, and H. Valdimarsson, "Correlation between serum immunoglobulin A concentrations and allergic manifestations in infants," *Journal of Pediatrics*, vol. 121, no. 1, pp. 23–27, 1992.

[16] B. R. Luovíksson, G. J. Arason, O. Thorarensen, B. Árdal, and H. Valdimarsson, "Allergic diseases and asthma in relation to serum immunoglobulins and salivary immunoglobulin A in pre-school children: a follow-up community-based study," *Clinical and Experimental Allergy*, vol. 35, no. 1, pp. 64–69, 2005.

[17] A. Papadopoulou, D. Mermiri, S. Taousani, M. Triga, P. Nicolaidou, and K. N. Priftis, "Bronchial hyper-responsiveness in selective IgA deficiency," *Pediatric Allergy and Immunology*, vol. 16, no. 6, pp. 495–500, 2005.

[18] N. Kutukculer, N. E. Karaca, O. Demircioglu, and G. Aksu, "Increases in serum immunoglobulins to age-related normal levels in children with IgA and/or IgG subclass deficiency," *Pediatric Allergy and Immunology*, vol. 18, no. 2, pp. 167–173, 2007.

[19] A. Aghamohammadi, T. Cheraghi, M. Gharagozlou et al., "IgA deficiency: correlation between clinical and immunological phenotypes," *Journal of Clinical Immunology*, vol. 29, no. 1, pp. 130–136, 2009.

[20] C. De Moraes Lui, L. C. Oliveira, C. L. Diogo, M. Kirschfink, and A. S. Grumach, "Immunoglobulin G subclass concentrations and infections in children and adolescents with severe asthma," *Pediatric Allergy and Immunology*, vol. 13, no. 3, pp. 195–202, 2002.

[21] M. F. Goldstein, A. L. Goldstein, E. H. Dunsky, D. J. Dvorin, G. A. Belecanech, and K. Shamir, "Pediatric selective IgM immunodeficiency," *Clinical and Developmental Immunology*, vol. 2008, Article ID 624850, 10 pages, 2008.

[22] L. Yel, S. Ramanuja, and S. Gupta, "Clinical and immunological features in igm deficiency," *International Archives of Allergy and Immunology*, vol. 150, no. 3, pp. 291–298, 2009.

[23] M. S. Shabestari and N. Rezaei, "Asthma and allergic rhinitis in a patient with BTK deficiency," *Journal of Investigational Allergology and Clinical Immunology*, vol. 18, no. 4, pp. 300–304, 2008.

[24] N. Rezaei, A. Aghamohammadi, G. A. Kardar, M. Nourizadeh, and Z. Pourpak, "T- helper 1 and 2 cytokine assay in patients with common variable immunodeficiency," *Journal of Investigational Allergology and Clinical Immunology*, vol. 18, no. 6, pp. 449–453, 2008.

[25] P. R. Ogershok, M. B. Hogan, J. E. Welch, W. T. Corder, and N. W. Wilson, "Spectrum of illness in pediatric common variable immunodeficiency," *Annals of Allergy, Asthma and Immunology*, vol. 97, no. 5, pp. 653–656, 2006.

[26] S. M. Drouin, D. B. Corry, J. Kildsgaard, and R. A. Wetsel, "Cutting edge: the absence of C3 demonstrates a role for complement in Th2 effector functions in a murine model of pulmonary allergy," *Journal of Immunology*, vol. 167, no. 8, pp. 4141–4145, 2001.

[27] D. M. Walters, P. N. Breysse, B. Schofield, and M. Wills-Karp, "Complement factor 3 mediates particulate matter-induced airway hyperresponsiveness," *American Journal of Respiratory Cell and Molecular Biology*, vol. 27, no. 4, pp. 413–418, 2002.

[28] J. Köhl, R. Baelder, I. P. Lewkowich et al., "A regulatory role for the C5a anaphylatoxin in type 2 immunity in asthma," *Journal of Clinical Investigation*, vol. 116, no. 3, pp. 783–796, 2006.

[29] J. Köhl and M. Wills-Karp, "Complement regulates inhalation tolerance at the dendritic cell/T cell interface," *Molecular Immunology*, vol. 44, no. 1–3, pp. 44–56, 2007.

[30] H. K. Thórarinsdóttir, B. R. Lúdvíksson, T. Víkingsdóttir et al., "Childhood levels of immunoglobulins and mannan-binding lectin in relation to infections and allergy," *Scandinavian Journal of Immunology*, vol. 61, no. 5, pp. 466–474, 2005.

[31] A. Nagy, G. T. Kozma, M. Keszei, A. Treszl, A. Falus, and C. Szalai, "The development of asthma in children infected with Chlamydia pneumoniae is dependent on the modifying effect of mannose-binding lectin," *Journal of Allergy and Clinical Immunology*, vol. 112, no. 4, pp. 729–734, 2003.

[32] J. Aittoniemi, H. Soranummi, A. T. Rovio et al., "Mannose-binding lectin 2 (MBL2) gene polymorphism in asthma and atopy among adults," *Clinical and Experimental Immunology*, vol. 142, no. 1, pp. 120–124, 2005.

[33] X. L. Zhang and M. A. M. Ali, "Ficolins: structure, function and associated diseases," *Advances in Experimental Medicine and Biology*, vol. 632, pp. 105–115, 2008.

[34] M. Cedzynski, A. P. M. Atkinson, A. S. Swierzko et al., "L-ficolin (ficolin-2) insufficiency is associated with combined allergic and infectious respiratory disease in children," *Molecular Immunology*, vol. 47, no. 2-3, pp. 415–419, 2009.

[35] A. M. Fitzpatrick, F. Holguin, W. G. Teague, and L. A. S. Brown, "Alveolar macrophage phagocytosis is impaired in children with poorly controlled asthma," *Journal of Allergy and Clinical Immunology*, vol. 121, no. 6, pp. 1372–1378.e3, 2008.

[36] A. Varin, S. Mukhopadhyay, G. Herbein, and S. Gordon, "Alternative activation of macrophages by IL-4 impairs phagocytosis of pathogens but potentiates microbial-induced signalling and cytokine secretion," *Blood*, vol. 115, no. 2, pp. 353–362, 2010.

[37] L. F. Lu and A. Rudensky, "Molecular orchestration of differentiation and function of regulatory T cells," *Genes and Development*, vol. 23, no. 11, pp. 1270–1282, 2009.

[38] A. Corthay, "How do regulatory t cells work?" *Scandinavian Journal of Immunology*, vol. 70, no. 4, pp. 326–336, 2009.

[39] N. Cools, P. Ponsaerts, V. F. I. Van Tendeloo, and Z. N. Berneman, "Regulatory T cells and human disease," *Clinical and Developmental Immunology*, vol. 2007, Article ID 89195, 10 pages, 2007.

[40] S. Nandakumar, C. W. T. Miller, and U. Kumaraguru, "T regulatory cells: an overview and intervention techniques to modulate allergy outcome," *Clinical and Molecular Allergy*, vol. 7, article no. 5, 2009.

[41] S. Finotto, "T-cell regulation in asthmatic diseases," *Chemical Immunology and Allergy*, vol. 94, pp. 83–92, 2008.

[42] O. Palomares, G. Yaman, A. K. Azkur, T. Akkoc, M. Akdis, and C. A. Akdis, "Role of Treg in immune regulation of allergic diseases," *European Journal of Immunology*, vol. 40, no. 5, pp. 1232–1240, 2010.

[43] C. A. Akdis and M. Akdis, "Mechanisms and treatment of allergic disease in the big picture of regulatory T cells," *Journal of Allergy and Clinical Immunology*, vol. 123, no. 4, pp. 735–746, 2009.

[44] M. Akdis, K. Blaser, and C. A. Akdis, "T regulatory cells in allergy," *Chemical Immunology and Allergy*, vol. 91, pp. 159–173, 2006.

[45] F. Meiler, S. Klunker, M. Zimmermann, C. A. Akdis, and M. Akdis, "Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors," *Allergy*, vol. 63, no. 11, pp. 1455–1463, 2008.

[46] D. Hartl, M. Griese, T. Nicolai et al., "Pulmonary chemokines and their receptors differentiate children with asthma and chronic cough," *Journal of Allergy and Clinical Immunology*, vol. 115, no. 4, pp. 728–736, 2005.

[47] H. Saito, "Essentials for starting a pediatric clinical study (2): role of environment and immunity in the development of childhood allergic and immunologic disorders," *Journal of Toxicological Sciences*, vol. 34, no. 2, pp. SP313–SP319, 2009.

[48] A. S. Adamson, K. Collins, A. Laurence, and J. J. O'Shea, "The Current STATus of lymphocyte signaling: new roles for old players," *Current Opinion in Immunology*, vol. 21, no. 2, pp. 161–166, 2009.

[49] M. Jutel and C. A. Akdis, "T-cell subset regulation in atopy," *Current Allergy and Asthma Reports*, vol. 11, no. 2, pp. 139–145, 2011.

[50] S. Trifari and H. Spits, "IL-22-producing CD4+ T cells: Middle-men between the immune system and its environment," *European Journal of Immunology*, vol. 40, no. 9, pp. 2369–2371, 2010.

[51] H. J. J. Van Der Vliet and E. E. Nieuwenhuis, "IPEX as a result of mutations in FOXP3," *Clinical and Developmental Immunology*, vol. 2007, Article ID 89017, 5 pages, 2007.

[52] J. Genre, P. R. Errante, C. M. Kokron, M. Toledo-Barros, N. O. S. Câmara, and L. V. Rizzo, "Reduced frequency of $CD4^{+}CD25^{HIGH}FOXP3^{+}$ cells and diminished FOXP3 expression in patients with Common Variable Immunodeficiency: a link to autoimmunity?" *Clinical Immunology*, vol. 132, no. 2, pp. 215–221, 2009.

[53] K. M. Melo, K. I. Carvalho, F. R. Bruno et al., "A decreased frequency of regulatory T cells in patients with common variable immunodeficiency," *PLoS One*, vol. 4, no. 7, Article ID e6269, 2009.

[54] S. M. Holland, F. R. DeLeo, H. Z. Elloumi et al., "STAT3 mutations in the hyper-IgE syndrome," *New England Journal of Medicine*, vol. 357, no. 16, pp. 1608–1619, 2007.

[55] J. D. Milner, J. M. Brenchley, A. Laurence et al., "Impaired TH17 cell differentiation in subjects with autosomal dominant

hyper-IgE syndrome," *Nature*, vol. 452, no. 7188, pp. 773–776, 2008.

[56] K. R. Engelhardt, S. McGhee, S. Winkler et al., "Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome," *Journal of Allergy and Clinical Immunology*, vol. 124, no. 6, pp. 1289–1302.e4, 2009.

[57] Y. Minegishi, M. Saito, T. Morio et al., "Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity," *Immunity*, vol. 25, no. 5, pp. 745–755, 2006.

[58] T. Kawai and S. Akira, "The roles of TLRs, RLRs and NLRs in pathogen recognition," *International Immunology*, vol. 21, no. 4, pp. 317–337, 2009.

[59] I. Bekeredjian-Ding and G. Jego, "Toll-like receptors—sentries in the B-cell response," *Immunology*, vol. 128, no. 3, pp. 311–323, 2009.

[60] N. Novak, T. Bieber, and W. M. Peng, "The immunoglobulin E-toll-like receptor network," *International Archives of Allergy and Immunology*, vol. 151, no. 1, pp. 1–7, 2009.

[61] S. J. Galli and M. Tsai, "Mast cells in allergy and infection: versatile effector and regulatory cells in innate and adaptive immunity," *European Journal of Immunology*, vol. 40, no. 7, pp. 1843–1851, 2010.

[62] V. Kumar and A. Sharma, "Mast cells: emerging sentinel innate immune cells with diverse role in immunity," *Molecular Immunology*, vol. 48, no. 1–3, pp. 14–25, 2010.

[63] M. Yoshioka, N. Fukuishi, S. Iriguchi et al., "Lipoteichoic acid downregulates FcεRI expression on human mast cells through Toll-like receptor 2," *Journal of Allergy and Clinical Immunology*, vol. 120, no. 2, pp. 452–461, 2007.

[64] N. Novak, J. P. Allam, T. Hagemann et al., "Characterization of FcεRI-bearing $CD123^+$ blood dendritic cell antigen-2^+ plasmacytoid dendritic cells in atopic dermatitis," *Journal of Allergy and Clinical Immunology*, vol. 114, no. 2, pp. 364–370, 2004.

[65] V. P. Walker and R. L. Modlin, "The vitamin D connection to pediatric infections and immune function," *Pediatric Research*, vol. 65, no. 5, pp. 106R–113R, 2009.

[66] N. E. Lange, A. Litonjua, C. M. Hawrylowicz, and S. Weiss, "Vitamin D, the immune system and asthma," *Expert Review of Clinical Immunology*, vol. 5, no. 6, pp. 693–702, 2009.

[67] M. S. Sandhu and T. B. Casale, "The role of vitamin D in asthma," *Annals of Allergy, Asthma and Immunology*, vol. 105, no. 3, pp. 191–199, 2010.

[68] M. Gereke, S. Jung, J. Buer, and D. Bruder, "Alveolar type II epithelial cells present antigen to CD4+ T cells and induce Foxp3+ regulatory T cells," *American Journal of Respiratory and Critical Care Medicine*, vol. 179, no. 5, pp. 344–355, 2009.

[69] C. A. Camargo Jr., S. L. Rifas-Shiman, A. A. Litonjua et al., "Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age," *American Journal of Clinical Nutrition*, vol. 85, no. 3, pp. 788–795, 2007.

[70] G. Devereux, A. A. Litonjua, S. W. Turner et al., "Maternal vitamin D intake during pregnancy and early childhood wheezing," *American Journal of Clinical Nutrition*, vol. 85, no. 3, pp. 853–859, 2007.

[71] J. M. Brehm, J. C. Celedón, M. E. Soto-Quiros et al., "Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica," *American Journal of Respiratory and Critical Care Medicine*, vol. 179, no. 9, pp. 765–771, 2009.

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Clinical Study

Induction of Specific Immunotherapy with Hymenoptera Venoms Using Ultrarush Regimen in Children: Safety and Tolerance

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Background & Objective. Ultrarush induction for specific venom immunotherapy has been shown to be reliable and efficacious in adults. In this study its safety and tolerance in children was evaluated. *Methods.* Retrospective analysis of 102 ultrarush desensitizations carried out between 1997 and 2005 in 94 children, aged 4 to 15 years. Diagnosis and selection for immunotherapy were according to recommendations of the European Academy of Allergy and Clinical Immunology. Systemic adverse reactions (SARs) were described using the classification of H. L. Mueller. *Results.* All patients reached the cumulative dose of 111.1 μg hymenoptera venom within 210 minutes. Six patients (6%) had allergic reactions grade I; 2 patients (2%) grade II and 5 patients (5%) grade III. Three patients (3%) showed unclassified reactions. SARs did not occur in the 15 patients aged 4 to 8 years and they were significantly more frequent in girls (29%) compared with boys (12%) ($P = 0.034$, multivariant analysis) and in bee venom extract treated patients (20%) compared to those treated with wasp venom extract (8%) (OR 0.33, 95% Cl 0.07–1.25). *Conclusion.* Initiation of specific immunotherapy by ultrarush regimen is safe and well tolerated in children and should be considered for treating children with allergy to hymenoptera venom.

1. Introduction

Hypersensitivity to hymenoptera venom affects approximately 1%–5% of the general population. In Switzerland the prevalence is estimated to be 3.5% in the general population and 0.4%–0.8% in children aged 4 to 16 years. It is one of the three most common causes of immediate type anaphylactic reactions, the other two major causes being drugs and foods [1]. A field sting in a hymenoptera venom allergic patient can cause a spectrum of reactions ranging from severe local swelling to anaphylactic shock with circulatory collapse. Several cases of death are attributed to hymenoptera allergy yearly, mostly in adults.

Specific immunotherapy (SIT) is the only known causal treatment for venom-allergic patients [2, 3]. In subjects with a history of generalized reactions to insect sting SIT results in up to 95% rate of protection in wasp venom allergic patients and 80% in bee venom allergic patients [4]. Different protocols have been published for the stepwise increase of the dose of the insect venom during initiation of subcutaneous specific immunotherapy [5–9]: the conventional regime, with injections using increasing doses every one to two weeks over a period of 2 to 4 months, rush immunotherapy extending over approximately 1 week and ultrarush protocols, in which the maintenance dose is achieved in 1-2 days. The latter has been shown to be effective and time-saving in adults [5]. The aim of this retrospective study was to investigate the safety and tolerance of ultrarush induction in desensitization in children.

A systemic grading of reactions to immunotherapy is necessary in order to evaluate the safety of the treatment and in order to compare various regimens [10]. In this study we chose to use a modified version of the classification of generalized allergic reactions introduced by H. L. Mueller in

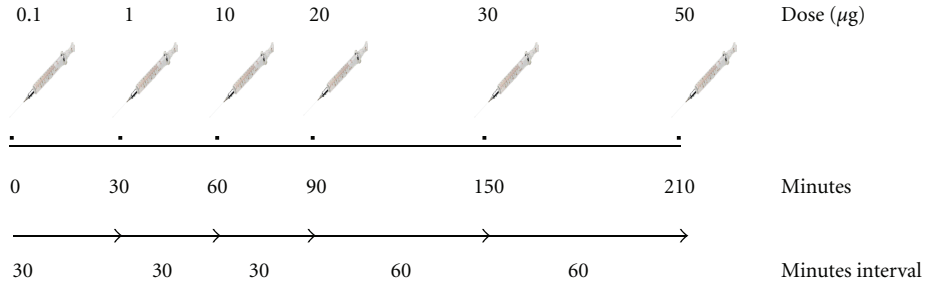

Figure 1: Ultrarush induction regimen in desensitization with subcutaneous venom injections.

1966 [11]. This classification is presented in Table 2 for quick reference.

2. Methods

2.1. Patients. Medical records of 94 children treated with the ultrarush induction regime in the intensive care unit of the University Children's Hospital of Zurich between January 1997 and December 2005 were analysed retrospectively; the clinical data is summarized in Table 1. Indication for SIT was a combination of an immediate systemic allergic reaction grade III or IV after a hymenoptera field sting and detection of specific IgE antibodies to the venom, as recommended by the European Academy of Allergy and Immunology Subcommittee on insect venom allergy [4, 6]. Patients with less severe reactions were included when the risk of exposure was very high, for example, when a wasp nest was in close proximity to the home, or when the fear from getting a sting caused anxiety and a significant limitation in the quality of life.

The study population included 24 girls and 70 boys; 61 of the patients were allergic to bee venom, 33 to wasp-venom; and 8 boys to both. These 8 boys were considered twice in the evaluation. The patients were divided into three groups according to age: group A included 15 patients aged 4 to 8 years, in group B there were 60 subjects aged 8 to 12 years and in group C 27 patients aged 12 to 15 years. The classification of generalized allergic reactions according to H. L. Mueller which was used to define the adverse reactions is shown in Table 2.

2.2. Tests. Sensitization was detected by skin prick tests with 10, 100, and 300 μg/mL purified insect venom extract (Pharmalgen, ALK) and/or intradermal tests with 0.00001, 0.001, 0.01, 0.1, and 1.0 μg/mL purified venom extract (ALK-SQ, ALK-Scherax, Germany). The tests were considered positive if a weal of at least 3 mm in diameter occurred after 15 minutes, and, in the case of intradermal tests, a reaction was considered positive at a concentration of 1 μg/mL or less. Positive (1% histamine hydrochloride) and negative (sodium-chloride 0.9%) control tests were performed. In addition levels of specific IgE were determined in serum (Pharmacia ImmunoCAP System, Sweden); they were considered negative when less than 0.35 kU/L.

2.3. Induction of Specific Immunotherapy Using the Ultrarush Regime. The ultrarush induction regime is described in Figure 1. All patients were treated with a standardized purified venom preparation (ALK Pharmalgen, Trimedal) given in subcutaneous injections. The cumulative dose of 111.1 μg hymenoptera venom was reached after 210 minutes using at least 6 injections. In the case of side effects, the interval between the doses was extended. The patients were observed in the intensive care unit with intravenous access, continuous measurements of the oxygen saturation, and repeated measurements of the blood pressure. Three hours after the last injection the patients were discharged to home. Booster injections were given later as follows: on day 7 two doses of 50 μg (ALK Pharmalgen, Trimedal) were given with an interval of 30 minutes, and 3 and 7 weeks after the ultrarush procedure the patients received 100 μg of Alutard (Aluminiumhydroxid-depot-preparation, ALK) subcutaneously. During the entire therapy the children did not receive premedication with antihistamines.

If both wasp and bee venoms sensitizations were required; they were administered in separate protocols a few days apart.

3. Results

Between January 1997 and December 2005 94 children, aged 4 to 15.1 years, including 70 males and 24 females, underwent induction of specific immunotherapy using ultrarush regime in the intensive or intermediate care unit of the University Children's Hospital of Zurich. A total of 102 ultrarush immunotherapy induction procedures were performed, in all of which the cumulative dose of 111.1 μg was reached. 61 patients were treated with bee venom, 33 with wasp venom, and 8 boys with both. Average duration of the procedure was 3.5 hours with a range of 2.5 to 5.5 hours.

3.1. Adverse Reactions. All patients had local swelling and redness of the upper arm with a diameter of less than 10 cm. As summarized in Table 3, Systemic side effects were observed in 16 subjects (16%), 11 of them required treatment. 6 patients (6%) showed an allergic reaction grade I, 2 girls (2%) grade II, and 5 patients (5%) developed a grade III reaction, 1 of these 5 subjects recovered spontaneously. No grade IV reactions occurred. 3 (3%) patients showed a reaction which could not be classified according to Mueller, namely, prickle of the tongue and throat and dizziness. Severe adverse reactions occurred mainly after injection of 50 μg venom (9 subjects) and more often in bee venom (13

Table 1: Clinical data of children undergoing ultrarush venom immunotherapy.

No. patients	Total 94	Bee venom ultrarush	Wasp venom ultrarush
Age in years			
Range	4.0–15.1		
Mean, median	10.4, 10.5		
Gender			
Boys	78 (76.5 %)	47 (46.1%)	31 (30.4%)
Girls	24 (23.5 %)	18 (17.6%)	6 (5.9%)
Allergen			
Bee venom	57 (55.9 %)	65 (63.7%)	
Wasp venom	29 (28.4 %)		37 (36.3 %)
Both	8 (7.8 %)		
Grade of reaction to field sting			
I	1 (1.0%)	1	0
II	20 (19.6%)	13	7
III	60 (58.8%)	37	23
IV	15 (14.7%)	9	6
Other (Sensitisation)	6 (5.9%)	5	1

Table 2: Classification of allergic reactions after HL Mueller, modified.

	Reaction
Large local reaction	Swelling at site of sting with diameter >10 cm, lasting >24 h
Grade I	Generalized urticaria, itching, malaise, anxiety
Grade II	Any of the above, plus two or more of the following: angiooedema (grade II also if alone), constriction in chest, nausea, vomiting, diarrhoea, abdominal pain, dizziness
Grade III	Any of the above, plus two or more of the following: dyspnoea, wheezing, stridor (any of these alone are grade III), dysphagia, dysarthria, hoarseness, weakness, confusion, fear of death
Grade IV	Any of the above, plus two or more of the following: drop of blood pressure, collapse, loss of consciousness, incontinence (urine, stool), cyanosis

patients, 20%) than in wasp venom (3 patients, 8%) allergic subjects; this latter tendency however, was not statistically significant (OR 0.33, 95% Cl 0.07–1.25, $P = 0.0955$).

Overall, 29% of the girls, compared to only 12% of the boys, developed a systemic adverse event; this difference was statistically significant ($P = 0.034$, multivariant analysis). None of the patients in group A (4 to 8 years of age) showed systemic side effects compared to 18% in group B (8 to 12 years of age) and 19% in group C (12 to 15 years of age). All but one reaction occurred within 30 minutes after injection of venom. In one boy generalised urticaria developed 3 hours after injection.

4. Discussion

When starting specific immunotherapy, various protocols for increasing the dose of allergen up to the maintenance dose have been introduced in the past years, attempting to maximize protection, minimize side effects, and optimize patient convenience. It is difficult to compare the results because the regimens differ. Increasing data in adults demonstrate good tolerance and safety for the ultrarush induction in insect venom immunotherapy. For example, Birnbaum et al. found fewer systemic reactions with a 3.5-hour (210 min) protocol with a cumulative dose of 101.1 μg venom compared to 6-hour and to 4-day protocols, which attained cumulative doses of 226.6 μg and 527.6 μg, respectively [5, 7]. The nine years of experience with initiation of specific immunotherapy to insect venom by ultrarush protocol in paediatric subjects, which is summarized in this paper, demonstrates that ultrarush insect venom immunotherapy is a well-tolerated and safe induction regimen also in children. Few side effects were observed, no cardiac or circulatory side effects and no systemic allergic reactions in the youngest age group (4–8 years). Three subjects had unclassified reactions with prickle of the tongue and throat and dizziness. These reactions did not fit the usual categories of allergic reactions, and it was not clear whether they were related directly to the immunotherapy or whether they were caused by the circumstances of the treatment (hospitalization in the intensive/intermediate care unit, subcutaneous injections, monitoring, etc.). In order to assess this question a control group undergoing the same procedures but getting placebo injections would be needed. However, this was beyond the scope of this retrospective study.

Antihistamines are efficiently and widely used to suppress allergic symptoms. There are studies which support the strategy of premedication with antihistamines in order to

Table 3: Subjects with side effects.

Sex	Age (y)	Insect	Grade at sting	Side effects	Grade	At dose in μg	Therapy
F	8.1	Bee	II	*Generalized urticaria, cough* (no wheezing, no dyspnoea, no stridor)	II	50	Antihistamines, Corticosteroids i.v.
M	9.5	Bee	Sensit. (IV)	*Dizziness*	other	30	None
M	9.5	Bee	II-III	*Generalyzed urticaria*	I	30	Antihistamines i.v.
M	10.9	Bee	III	*Urticaria, dyspnoea, wheezing*	III	30	Antihistamines, Corticosteroids i.v., Salbutamol-inhalation
M	14.7	Bee	III	*Generalized urticaria; dyspnoea, constriction in chest*	IIII	2050	Antihistamines, Corticosteroids i.v.dito + inhal. of Adrenalin/Salbutamol
F	10.3	Bee	II-III	*Urticaria* about 3 h after last injection (50 μg)	I	50	Antihistamines, Corticosteroids i.v.
F	10.4	Bee	II	Slight *dyspnoea*; fast, spontaneous normalization	III	1	None
M	12.1	Bee	III-IV	*Generalized urticaria*, itching in the throat	I	30	Antihistamines, Corticosteroids i.v
M	10.5	Bee	II-III	*Itching in the throat*	other	50	Cetirizin per os
F	8.7	Bee	III	*Chest pain, inspiratory stridor, chest pain, in-and expiratory stridor*	IIIIII	1050	Antihistamines, Corticosteroids i.v., Adrenalin-inhalation dito + Salbutamol-inhalation, Corticosteroids i.v. (before going home)
F	14.1	Bee	III	*Slight periorbital swelling*	II	1, 30 and 50	Antihistamines i.v. after 1ug
M	15.1	Bee	II	Itching in meatus acusticus, *rash* chest, *several urticarial lesions* on the left arm	I	50	None
F	15.0	Wasp	III	*Dysphagia, passing dyspnea*	III	0.1	Antihistamines and Corticosteroids i.v, and again before going home
F	11.3	Wasp	III	*Slight prickle of the tongue*	other	10	None
M	10.3	Bee	IV	Redness and *one urticarial lesion on the left cheek*	I	50	none, 1 Levocetirizine per os before going home
M	10.7	Wasp	III	*Generalyzed urticaria*	I	50	Levocetirizin per os
All children				Local redness and swelling, sometimes overheating and itching at the injection site. Therapy if needed: Coldpack and/or Antihistamin gel			

reduce allergic side effects and enhance the safety and efficacy of allergen-specific immunotherapy [12, 13]. However, there is also data which suggests that medication with antihistamines may impair allergen-specific immunotherapy [14]. The patients in this retrospective study did not receive treatment with antihistamines prior to immunotherapy.

The results presented in this paper compare favourably with the frequency of side effects reported in adults and with the incidence of severe adverse reactions in conventional and rush protocols [5, 7, 15–20]. The ultrarush induction protocol performed in a paediatric intensive or intermediate care unit allows for much better monitoring of the patients compared to the conventional desensitization protocol performed in an outpatient setting. Its short duration is much more convenient for the patients and their parents, and it has the additional advantages of achieving rapid protection as well as reduction in costs. Based on the results presented in this paper and due to these considerations, we suggest that the ultrarush induction regimen for desensitization, when performed in a suitable intensive care setting, will be

considered the treatment of choice in paediatric patients with hymenoptera venom allergy who qualify for immunotherapy.

References

[1] W. Strupler, B. Wuthrich, and C. Schindler, "Prevalence of insect venom allergy in Switzerland: a population study of the SAPALDIA sample," *Allergo Journal*, vol. 6, no. 1, pp. S7–S11, 1997.

[2] R. N. Ross, H. S. Nelson, and I. Finegold, "Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: a meta-analysis," *Clinical Therapeutics*, vol. 22, no. 3, pp. 351–358, 2000.

[3] D. B. K. Golden, "Insect sting allergy and venom immunotherapy," *Annals of Allergy, Asthma and Immunology*, vol. 96, supplement 2, pp. S16–S21, 2006.

[4] U. Müller and H. Mosbech, "Position paper—immunotherapy with hymenoptera venoms. EAACI subcommittee on insect venom allergy," *Allergy*, vol. 48, supplement 14, pp. 36–46, 1993.

[5] J. Birnbaum, D. Charpin, and D. Vervloet, "Rapid hymenoptera venom immunotherapy: comparative safety of three protocols," *Clinical and Experimental Allergy*, vol. 23, no. 3, pp. 226–230, 1993.

[6] F. Bonifazi, M. Jutel, B. M. Bilo, J. Birnbaum, U. Müller, and The EAACI Interest Group on Insect Venom Hypersensitivity, "Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice," *Allergy*, vol. 60, pp. 1459–1470, 2005.

[7] A. Roll, G. Hofbauer, B. K. Ballmer-Weber, and P. Schmid-Grendelmeier, "Safety of specific immunotherapy using a four-hour ultra-rush induction scheme in bee and wasp allergy," *Journal of Investigational Allergology and Clinical Immunology*, vol. 16, no. 2, pp. 79–85, 2006.

[8] J. C. Van der Zwan, J. Flinterman, I. G. Jankowski, and J. A. M. Kerckhaert, "Hyposensitisation to wasp venom in six hours," *British Medical Journal*, vol. 287, no. 6402, pp. 1329–1331, 1983.

[9] D. Schiavino, E. Nucera, E. Pollastrini et al., "Specific ultrarush desensitization in Hymenoptera venom-allergic patients," *Annals of Allergy, Asthma and Immunology*, vol. 92, no. 4, pp. 409–413, 2004.

[10] L. Cox, D. Larenas-Linnemann, R. F. Lockey, and G. Passalacqua, "Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System," *Journal of Allergy and Clinical Immunology*, vol. 125, no. 3, pp. 569–e7, 2010.

[11] H. L. Mueller, "Diagnosis and treatment of insect sensitivity," *The Journal of Asthma Research*, vol. 3, no. 4, pp. 331–333, 1966.

[12] A. Reimers, Y. Hari, and U. Müller, "Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial," *Allergy*, vol. 55, no. 5, pp. 484–488, 2000.

[13] U. Müller, Y. Hari, and E. Berchtold, "Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy," *Journal of Allergy and Clinical Immunology*, vol. 107, no. 1, pp. 81–86, 2001.

[14] P. Johansen, G. Senti, J. Maria Martínez Gómez, and T. M. Kündig, "Medication with antihistamines impairs allergen-specific immunotherapy in mice," *Clinical and Experimental Allergy*, vol. 38, no. 3, pp. 512–519, 2008.

[15] L. J. F. Youlten, B. A. Atkinson, and T. H. Lee, "The incidence and nature of adverse reactions to injection immunotherapy in bee and wasp venom allergy," *Clinical and Experimental Allergy*, vol. 25, no. 2, pp. 159–165, 1995.

[16] J. Birnbaum, M. Ramadour, A. Magnan, and D. Vervloet, "Hymenoptera ultra-rush venom immunotherapy (210 min): a safety study and risk factors," *Clinical and Experimental Allergy*, vol. 33, no. 1, pp. 58–64, 2003.

[17] H. Mosbech and U. Muller, "Side-effects of insect venom immunotherapy: results from an EAACI multicenter study," *Allergy*, vol. 55, no. 11, pp. 1005–1010, 2000.

[18] J. Wenzel, M. Meissner-Kraemer, R. Bauer, T. Bieber, and R. Gerdsen, "Safety of rush insect venom immunotherapy. The results of a retrospective study in 178 patients," *Allergy*, vol. 58, no. 11, pp. 1176–1179, 2003.

[19] R. Brehler, H. Wolf, B. Kütting, J. Schnitker, and T. Luger, "Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections," *Journal of Allergy and Clinical Immunology*, vol. 105, no. 6, pp. 1231–1235, 2000.

[20] J. Laurent, J. M. Smiejan, E. Bloch-Morot, and D. Herman, "Safety of Hymenoptera venom rush immunotherapy," *Allergy*, vol. 52, no. 1, pp. 94–96, 1997.