Health Economics and Nutrition: Atopic Dermatitis

Editors
Jörg Spieldenner, Lausanne
Sibylle Koletzko, Munich

Editorial Board
Jatinder Bhatia, Augusta, Ga.
Carlos Lifschitz, Buenos Aires
Maria Makrides, Adelaide
Etienne Nel, Cape Town
Frank M. Ruemmele, Paris
Hania Szajewska, Warsaw
Sponsor Note
This publication was supported by an unrestricted educational grant by the Nestlé Nutrition Institute. The institute is a not-for-profit association which was created to provide medical and scientific information to health professionals in the field of pediatric, adult and sports nutrition with latest information on nutrition and nutrition-related disorders (available at www.nestlenutrition-institute.org). Any liability of the sponsors for the content of the papers is hereby expressly excluded.

Disclosure Statement Guest Editors
Jörg Spieldenner is employed by Nestec SA in the Nestlé Research Center, Lausanne, Switzerland. Sybille Koletzko declares that she has no conflict of interest.
The above articles were originally published as a supplementary issue of *Annals of Nutrition and Metabolism* and are reprinted here with permission.
The Nestlé Nutrition Institute was created to provide health professionals with up-to-date information on nutrition and nutrition-related disorders in order to enable them to continuously improve patient care based on the latest medical and scientific developments.

One of the key pillars of the Nestlé Nutrition Institute is *Annales Nestlé*, a pediatric journal that has been published on a regular basis since 1942. It contains review articles on clinical practice and research in all fields of pediatrics with focus on nutrition.

*Annales Nestlé* comprises 3 issues each year and with around 50,000 copies per issue, it is one of the most widely read pediatric journals in the world.

*Annales Nestlé* is edited by an independent editorial board of opinion leaders in pediatric research, thus guaranteeing the medical and scientific impartiality of the journal, and hence the high level of respect and appreciation in medical and scientific circles. The editorial board sets the editorial policy, identifies topics to be addressed, selects authors and is in charge of the review process of each publication.

As of 2011, *Annales Nestlé* is published as a supplement of *Annals of Nutrition and Metabolism* and can be accessed online in PubMed.

We are pleased to offer you our innovative design, which results from a creative and effective cooperation with *Karger Publishers, Switzerland*.

*Policy Statement*

Natalia Wagemans, MD
Head of
Nestlé Nutrition Institute
Vevey (Switzerland)
The last few decades have witnessed a considerable increase in atopic diseases, including asthma, allergic rhinitis and atopic dermatitis or eczema according to the new nomenclature, which collectively affect an estimated 20% of the world’s population – particularly children [1–3]. This increase in atopic disorders is not confined to industrialized countries but also affects developing nations. At first glance, atopic diseases appear to be a group of heterogeneous, unrelated disorders that share some risk factors. Indeed, the complex nature and etiology of these diseases have made it difficult to develop a unifying hypothesis to explain their steeply increasing prevalence worldwide. If two or more allergic diseases (asthma, eczema and allergic rhinitis) occur within one child, the question is whether this occurs purely by chance due to the high prevalence of these disorders or whether there are other factors at play. Furthermore, can the presence of atopy (defined as being positive for a specific IgE) contribute to the excess comorbidity frequently seen with these conditions? Pooled data from different European birth cohort studies including data from more than 10,000 children with information on underlying diseases and sensitization at 4 and 8 years of age showed that IgE sensitization is associated with the presence of excess comorbidity, irrespective of preexisting diseases [4]. However, the level of comorbidity is even higher in children with no sensitization. The authors concluded that the presence of sensitization accounted for <40% of comorbidity, suggesting that IgE sensitization can no longer be considered the dominating causal mechanism of allergic comorbidity.

Atopic dermatitis or eczema is a chronic pruritic skin disorder whose appearance signals the first step of the atopic march (a term that refers to the progression of atopic diseases). It is the most common skin disorder in preschool children, with a prevalence of up to 20%, and affects up to 3% of adults [5]. Around half of the patients suffer from moderate to severe disease symptoms [6]. The disease course differs greatly from patient to patient and is characterized by flares of varying severity and duration [7]. The most debilitating feature, however, is the recurrent pruritus, which can lead to infection and cause great emotional stress for the patient and the family. In the first article, Sophie Nutten [5] covers the global epidemiology and risk factors that affect the function of the skin barrier and how these modulate the immune response. By linking the environmental, genetic and physiological players, Nutten outlines the pathogenesis of the disease and applies this knowledge to possible preventive actions.

How does atopic dermatitis affect the developing world and emerging economies, which are already burdened with urgent health-care issues? In the second article, Bee Wah Lee and Patrick R. Detzel [8] examine the management and cost burden of childhood atopic dermatitis in the Asia Pacific region. The treatment practices in this region are not only influenced by the different healthcare systems, but also by cultural and environmental factors, such as climate and access to medical care. Not surprisingly, atopic dermatitis presents a significant economic burden in this part of the world. Using an extensive literature search, Lee and Detzel provide several estimates of the direct and indirect costs of the disease in several
countries in the Asia Pacific region. These findings shed new light on a previously obscure aspect of the disease and provide an economic vantage point from which to gauge the effectiveness of different treatment options.

How can we implement a cost-effective measure for preventing atopic dermatitis in infants? In the third article in this series, Marc Botteman and Patrick Detzel [9] explore the cost-effectiveness of using partially hydrolyzed whey formula instead of standard cow’s milk formula for the primary prevention of atopic dermatitis. High-risk infants (including those with a family history of atopy) who receive standard cow’s milk formula as a supplement or breast milk replacement may be at greater risk of developing atopic dermatitis. Botteman and Detzel examine the results of three national health economic studies performed in Malaysia, Singapore and the Philippines. Each of these studies evaluated the clinical and economic impact of feeding partially hydrolyzed whey formula in the first 17 weeks of life compared to cow’s milk formula. Botteman and Detzel designed a mathematical model that captures the reduction in the risk of atopic dermatitis and the estimated cost savings associated with the use of partially hydrolyzed whey formula.

The final article by Carlos Lifschitz [10] takes a look at how atopic dermatitis affects quality of life. Patients who suffer from skin disorders can experience a wide range of symptoms from minor irritation to major clinical manifestations that affect many aspects of their lives. Since atopic dermatitis often develops in the first year, the disease affects not only patients but also their families. Lifschitz explores the consequences of atopic dermatitis on the health-related quality of life in children and their families around the world. From the quality of life perspective, Lifschitz reveals that atopic dermatitis affects patients with the same magnitude as other chronic diseases and skin conditions, including hypertension, diabetes and psoriasis.

Clearly, we have a long road ahead before achieving optimal management and prevention of atopic dermatitis. Given the scope of the problem and its effects on health and the associated costs in both developing and industrialized countries, it makes sense to focus on cost-effective interventions that target infants and young children, particularly in developing countries where health resources are scarce. The medical community needs to work in partnership with policy makers and industry in order to implement effective strategies such as prevention to halt the inevitable progression of the atopic march.

References

Fifty percent of all those with atopic dermatitis develop other allergic symptoms within their first year of life and probably as many as 85% of patients experience an onset below 5 years of age

Key insights
Atopic dermatitis often begins in early childhood and is the first step in the so-called ‘atopic march’. This concept summarizes the natural history of atopic manifestations, which typically begin with atopic dermatitis in early childhood followed by the development of other allergic disorders in later life. The onset of atopic dermatitis in childhood often foreshadows the later development of asthma and/or allergic rhinitis (hay fever).

Current knowledge
Atopic dermatitis has a complex etiology, whereby genetic and immune mechanisms act in concert with environmental factors to influence the manifestations of the disease. Genetic mutations in epidermal barrier proteins (such as filaggrin) have recently been shown to affect skin barrier function. The presence of food sensitization and allergies is also predictive of severe atopic dermatitis. The inter-country variations and urban-rural gradient in disease prevalence suggest that environmental factors act in concert with intrinsic genetic factors to drive disease progression.

Practical implications
Breastfeeding is a protective factor; for infants who cannot be breastfed, the use of clinically proven partially or extensively hydrolyzed whey formulas is preferable to cow’s milk formulas. Encouraging results have been obtained with the use of prebiotics and probiotics to modulate the gut flora, although the data are still in the exploratory phase and need further study. Finally, protecting the skin barrier is an important strategy for prevention, particularly in children who have mutations in the skin barrier genes and in those who show early signs of skin barrier impairment.

Recommended reading
Atopic Dermatitis: Global Epidemiology and Risk Factors

Sophie Nutten
Nutrition and Health Department, Nestlé Research Center, Lausanne, Switzerland

Key Messages
- Atopic dermatitis (AD) is a common inflammatory skin disease posing a significant burden on health-care resources and patients’ quality of life.
- AD usually starts in early childhood and can be the initial step of the so-called ‘atopic march’.
- The prevalence of AD is as high as 20% in children in some countries and continues to increase, affecting not only developed countries but also low-income countries.
- AD is a complex disease, and the relationship between allergy and AD (allergy being a cause and/or an exacerbating factor of AD) is still debated.
- Genetics has recently been shown to be an important risk factor for AD, and the strongest association so far with the gene encoding filaggrin has raised the recent interest in the role of skin barrier impairment in the development of AD.
- Environmental factors and specifically exposure to microbes are also recognized to play a role in the development of the disease.
- AD is a multifactorial disease presenting with different endophenotypes.
- The prevention of AD should start as soon as possible (possibly even in utero), targeting both skin barrier, immune/allergy and environmental aspects.

Key Words
Atopic dermatitis · Atopic march · Skin barrier defect · Immune dysregulation · Genetics · Environment

Abstract
Atopic dermatitis (AD) is a chronic inflammatory skin disease posing a significant burden on health-care resources and patients’ quality of life. It is a complex disease with a wide spectrum of clinical presentations and combinations of symptoms. AD affects up to 20% of children and up to 3% of adults; recent data show that its prevalence is still increasing, especially in low-income countries. First manifestations of AD usually appear early in life and often precede other allergic diseases such as asthma or allergic rhinitis. Individuals affected by AD usually have genetically determined risk factors affecting the skin barrier function or the immune system. However, genetic mutations alone might not be enough to cause clinical manifestations of AD, and it is merely the interaction of a dysfunctional epidermal barrier in genetically predisposed individuals with harmful effects of environmental agents which leads to the development of the disease. AD has been described as an allergic skin disease, but today, the contribution of allergic reactions to the initiation of AD is challenged, and it is proposed that allergy is rather a consequence of AD in subjects with a concomitant underlying atopic constitution. Treatment at best achieves symptom control rather than cure; there is thus a strong need to identify alternatives for disease prevention.
Introduction
Atopic dermatitis (AD), also called atopic eczema, is a common chronic or recurrent inflammatory skin disease and affects 15–20% of children [1] and 1–3% of adults worldwide. It is characterized by acute flare-ups of eczematous pruritic lesions over dry skin.

AD usually starts in early childhood and may represent the initial step of the so-called ‘atopic march’ (fig. 1) which represents the natural history of atopic manifestations, characterized by a typical sequence of atopic diseases in childhood preceding the development of other allergic disorders later in life [2–4]. Fifty percent of all those with AD develop other allergic symptoms within their first year of life and probably as many as 85% of the patients experience an onset below 5 years of age. Patients usually outgrow the disease in late childhood as around 70% of the patients with a disease onset during childhood have a spontaneous remission before adolescence. However, early childhood AD is often the initial indication that a child may later develop asthma and/or allergic rhinitis (hay fever) [5].

Symptoms of AD include patches of skin that are red or brownish, dry, cracked or scaly skin and itchy skin, especially at night. In infants, eczema usually appears as tiny bumps on the cheeks, while older children and adults often experience rashes on the knees or elbows (often in the folds of the joints), on the backs of the hands or on the scalp.

AD poses a significant burden on health-care resources [6–8] and patients’ quality of life (mainly because of sleep deprivation due to itchiness, employment loss, time to care and financial costs) [9–12]. As a consequence, there has been a heightened interest in the identification of environmental risks and protective factors.

Epidemiology
The prevalence of AD is estimated to be 15–20% in children and 1–3% in adults, and the incidence has increased by 2- to 3-fold during the past decades in industrialized countries.

Some of the most valuable AD prevalence and trend data have come from the International Study of Asthma and Allergies in Childhood (ISAAC). This is the biggest (close to 2 million children in 100 countries) and only allergy study that has taken a truly global approach. The strength of the study is the use of a uniformly validated methodology allowing a direct comparison of results between pediatric populations all over the world (http://isaac.auckland.ac.nz/index.html).

The study revealed that over 20% of children are affected by AD in some countries, but that the prevalence varies greatly throughout the world. For the age group 6–7 years, data showed that the prevalence of AD ranged from 0.9% in India to 22.5% in Ecuador, with new data showing high values in Asia and Latin America. For the age group 13–14 years, data showed prevalence values ranging from 0.2% in China to 24.6% in Columbia. A prevalence over 15% was found in 4 of 9 regions studied including Africa, Latin America, Europe (1 center in Finland) and Oceania [13].

Over 20% of children are affected by AD in some countries, but the prevalence varies greatly throughout the world.

Importantly, the latest available data (Phase Three of the ISAAC study) [14] showed that while AD seems to have reached a plateau in the countries with the highest prevalence such as the UK and New Zealand, AD continues to increase in prevalence, specifically in young children (age 6–7 as compared to age 13–14 years) and in low-income countries, such as Latin America or South East Asia which have emerged as regions of a relatively high prevalence in the follow-up data [15] (fig. 2).

Immune Mechanisms
The immune response observed during the course of AD is characterized by a biphasic inflammation. A Th2-biased immune response (IL-4, IL-13, TSLP and eosinophils) is predominant in the initial and acute phase of AD, while in chronic AD skin lesions, a Th1/Th0 dominance has been described (IFN-γ, IL-12, IL-5 and GM-CSF) [16].

In addition, regulatory T cells and the innate immune system in the skin are altered [17]. The innate immune system represents the first line of defense against infections. In AD, a decrease in the antimicrobial peptides (one component of the skin innate immune system) has been observed and may explain the susceptibility to infections in AD patients [18]. Specifically, lesional and healthy skin of AD patients is frequently colonized with *Staphylococcus aureus* which exacerbates or aggravates skin lesions [19].
Allergy and AD

Presence of food sensitization and allergy earlier in life predicts a prognosis of severe AD. Around 50–70% of children with an early onset of AD are sensitized to one or more allergens. These are mainly food allergens (cow’s milk, hen’s egg and peanuts being the foods most frequently involved) [20] but also house dust mite, pollen and pets. Food allergy is actually much more common in children with AD with an association that ranges from 20 to 80% but is more accepted around 30%.

The relationship between food allergy and AD is complex and can be viewed from different perspectives. It has been proposed recently that food allergy may not have such an important impact on the initiation of AD. In most cases, rather than being a cause of AD (‘inside-out hypothesis’: the skin lesions of AD are a consequence of the inflammatory response to allergens), food allergy would be co-associated with AD or would be an exacerbating factor for AD [21]. Food allergies have indeed clinical manifestations on the skin and in the gastrointestinal and respiratory systems. Cutaneous reactions can be diverse, but only some of them will exacerbate AD, and they usually manifest as a late event. Skin reactions can anyway lead to excessive scratching and indirect exacerbation of preexisting eczema.

Genetic Factors

The role of genetics as an important risk factor for AD has first been found in observation studies, describing a positive parental history in AD patients, and in twin studies, showing a higher concordance rate in monozygotic twins compared to dizygotic twins [22]. Then, genetic linkage analysis as well as association studies identified several genes linked to either epidermal function or the immune system.

The recent discovery of the common loss-of-function variants in the FLG gene (encoding the epidermal barrier protein filaggrin) and their strong association with AD [23] has led to a heightened interest in the role of skin barrier impairment in the development of AD, allergic sensitization and also food and respiratory allergies. Filaggrin has a crucial role in skin barrier integrity. It is an important epidermal protein that is needed for the formation of the corneocytes as well as the generation of intracellular metabolites which contribute to stratum corneum hydration and pH of the skin. Ten percent of the westernized population and 50% of AD patients carry mutations in the FLG gene, and 20 mutations in the FLG gene have been described so far.

Impaired Skin Barrier Function

An intact epidermal barrier is a prerequisite for the skin to function as a physical and chemical barrier. Genetically determined alterations of the epidermis or lipid composition contribute to skin barrier dysfunction leading to inflammation. Moreover, the defective epidermal barrier allows easier and enhanced environmental allergen penetration through the skin, facilitating the interaction of the allergens with the local antigen-presenting cells and immune effector cells. This may lead to systemic IgE sensitization and transition from the non-atopic state to the atopic state of the disease (fig. 3). This is called the ‘outside-in hypothesis’, explaining the association between AD and an increased risk of developing food allergy, asthma and allergic rhinitis (atopic march). Allergic sensitization would be mainly a secondary phenomenon in AD and an important trigger of disease flares and driver of disease chronicity. Patients carrying variations for filaggrin and other genes and suf-
Atopic Dermatitis: Global Epidemiology and Risk Factors

Atopic Dermatitis: Global Epidemiology and Risk Factors

Reprinted with permission from:
Ann Nutr Metab 2015;66(suppl 1):8–16
DOI: 10.1159/000370220

ferred from an early onset and rather severe form of AD have the highest risk to develop allergic diseases and specifically asthma.

The skin barrier defect in AD also predisposes to colonization or infection by pathogenic microbes (e.g. *S. aureus*) whose exogenous proteases can also further damage the skin barrier.

Causes of this abnormal skin barrier are complex and driven by a combination of genetic and immunological factors (see above) but also environmental factors (fig. 3). Typically, addition of environmental interactions such as washing with soap and detergents can further impair the barrier function.

**Environmental Factors and Microbial Exposure**

Significant variations in the prevalence between and within countries (e.g. urban-rural gradient of disease) suggest environmental factors in addition to genetic factors as the main drivers of change in disease burden. En-

Fig. 2. World maps showing changes in the prevalence of AD symptoms for 13- to 14-year-olds (a) and 6- to 7-year-olds (b) in consecutive prevalence surveys conducted 5–10 years apart (between ISAAC Phases One and Three). SE = Standard error of the change. Reproduced from Williams et al. [15] with permission from Elsevier.
Environmental risk factors such as climate, urban versus rural setting, diet, breastfeeding and time of weaning, obesity and physical exercise or tobacco smoke and pollution have been proposed (table 1).

Also, studies have suggested that microbial exposure could influence the development of AD (table 2) [28]. The 'revised' hygiene hypothesis states that the decrease in early childhood exposure to prototypical infections (e.g. hepatitis and tuberculosis) and, by extension, in any microbial exposure [29] has increased the susceptibility to allergic disease. For AD, this hypothesis has been supported by some observations such as that the youngest among siblings has the lowest risk of AD or that AD risk is decreased in infants attending day care during their first year of life. The influence of a farm environment (and exposure to a variety of microfloras) has also been extensively studied within cohorts [30–35]. The results showed that rather than living on a farm, it is the consumption of unpasteurized farm milk during the first 2 years of life and the direct contact of pregnant mothers with farm animals which appeared to be protective [32, 35].

Studies on pets also proposed dog exposure as a protective factor [36], while for cat exposure, the situation is less clear with much more heterogeneous results [37].
The risk of developing AD is increased in infants who have been exposed to a cat during their first year of life only if they carry filaggrin mutations. This example underlines the complex interplay between genetics and the environment.

Antibiotics (rather than the infection itself which is treated with the antibiotics) seemed to be linked to an increased risk of AD [38, 39]. The explanation may be linked to the microbiota changes related to antibiotic use, knowing that the microbiota influences the immune response. There is actually evidence showing that the early gut microbiota of children who develop AD later in life is different from that of children who do not develop AD, both in terms of composition [40–43] and diversity [44]. More recently, the skin microbiota has been suggested to be involved in the homeostasis of the immune system of the skin and may also have an impact on AD [45].

**Prevention of AD**

Taking into account the burden on health-care resources, the impact on the quality of life of patients and their caregivers, together with increasing evidence that AD may progress to other allergic phenotypes, there is a clear need to improve disease prevention [46]. The still growing understanding of the pathoetiology and of environmental risk factors for AD contributes to this goal [47].

Due to the childhood prevalence of the disease, prevention is focused on the perinatal period. It is recognized that prevention should start as soon as possible (even possibly in utero), targeting the skin barrier, immune/allergy and environmental aspects.

**Infant Feeding**

Breastfeeding is a protective factor even though little evidence shows that exclusive breastfeeding beyond 3 months of age is protective [48]. While food avoidance was proposed earlier, the results of recent observational studies have shown that delaying the introduction of solids is a risk factor for AD [49–53], and today, methods favoring tolerance induction are used. For infants who cannot be breastfed, infant formulas have been developed. Specifically, partially hydrolyzed or extensively hydrolyzed formulas are proposed to fit infants at risk of allergy and infants already having symptoms of cow’s milk allergy. Intervention studies have shown that prolonged feeding with a partially hydrolyzed whey formula, compared to a cow’s milk formula, may result in an around 45% reduction in infantile AD in at-risk infants [54, 55]. The German Infant Nutritional Intervention (GINI) study even reported a significant risk reduction in AD up to 10 years of age for infants who received a whey-based partially hydrolyzed formula and those who received an extensively hydrolyzed casein formula [56–58]. One of the plausible mechanisms behind this observation is that a low exposure to protein or peptides (such as hydrolyzed proteins) could educate the immune system to develop tolerance.

**Modulating the Gut Flora**

Pre- and probiotics have also been used during the prenatal and/or postnatal period in an attempt to modify the gut microbiota towards more diversity and a ‘healthier’ composition. Different probiotics (mainly Lactobacilli and Bifidobacteria), used individually or in combination and administered at different periods (prenatally and/or postnatally), have been used in clinical trials. A recent meta-analysis associated the consumption of probiotics during pregnancy and early life with a relative risk reduction for AD of 21% [59]. Encouraging results have also been obtained with prebiotics (substrates inducing growth and activity of probiotics). A Cochrane review and a meta-analysis recently showed that using prebiotics in the postnatal period could reduce AD by 30% at 2 years of age [60]. However, due to heterogeneity in studies, further research is still needed before pre- and/or probiotics can be routinely recommended as an effective means to prevent AD [61].

---

**Table 2. Individual factors linked to microbial exposure (nonexhaustive list)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on risk of AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day care</td>
<td>Day care attendance in the first 2 years of life is protective.</td>
</tr>
<tr>
<td>Farm environment and animals</td>
<td>Consumption of unpasteurized farm milk during the first 2 years of life is protective.</td>
</tr>
<tr>
<td>Pets</td>
<td>Dog exposure in early life is protective.</td>
</tr>
<tr>
<td>Endotoxin exposure</td>
<td>High endotoxin exposure levels and/or exposure during the first year of life are risk factors.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Postnatal antibiotic exposure is a risk factor.</td>
</tr>
<tr>
<td>Gut microbiome</td>
<td>Diversity and composition (Lactobacilli and Bifidobacteria) of the gut flora are protective factors.</td>
</tr>
</tbody>
</table>
Dietary Supplementation
Dietary supplementation (vitamins, zinc, selenium, oils, etc.) has also been tested prenatally or postnatally [62]. Due to its immune-modulatory effect, vitamin D has been studied in the AD prevention context; however, results are still conflicting. Numerous studies also suggested that a high consumption of fish during pregnancy decreased the risk of developing AD in the infant [63]. Similar results were obtained when fish was consumed during late infancy [64, 65].

The skin barrier may constitute a target of primary prevention of progression of eczema into allergic airway diseases.

Preventing a Skin Barrier Breakdown
Due to its major role in AD initiation, protecting the skin barrier should be a powerful measure for prevention, especially in children who carry skin barrier gene mutations and show early signs of skin barrier impairment. Moreover, the skin barrier may constitute a target of primary prevention of progression of eczema into allergic airway diseases. Encouraging results have been obtained with the application of emollients, combined with soap avoidance, and a large-scale randomized clinical trial is underway (Barrier Enhancement for Eczema Prevention study; http://www.beepstudy.org).

Conclusion
AD is a multifactorial, chronic inflammatory and heterogeneous skin disorder resulting from interactions between genetic, immune and environmental factors. It is common in most countries, although the prevalence varies greatly throughout the world. Recent data revealed that AD is a disease of developed as well as developing countries, and in poorer countries, AD will be competing for meager resources. AD has become a significant public health problem because of its presence in most countries and its increasing prevalence, together with increasing evidence that it may progress to other allergic phenotypes. The last few years have seen important improvement in the understanding of the interactions between the skin barrier, genetic and immunological factors. A better understanding of the key environmental risk factors that could be influenced, changed or modified is important for a better prevention of the disease.

Disclosure Statement
The author declares no conflicts of interest.
Atopic Dermatitis: Global Epidemiology and Risk Factors


18 Ong PY, Ohtake T, Brandt C, Strickland I, Bo-  

moffatt MF: SPINK5: a gene for atopic der-  


29 Flohr C, Yeo L: Atopic dermatitis and the hy-  

giene hypothesis revisited. Curr Probl Der-  

matol 2011;41:1–34.

30 Braback L, Hjern A, Rasmussen F: Trends in  

asthma, allergic rhinitis and eczema among Swedish conscripts from farming and non-  

farming environments. A nationwide study  

over three decades. Clin Exp Allergy 2004;34:  

38–43.

31 Braun-Fahrlander C, Gassner M, Grize L,  

Neu U, Sennhauser FH, Varonion HS, Vuille  

JC, Wüthrich B: Prevalence of hay fever and  

allergic sensitization in farmer’s children and  

their peers living in the same rural commu-  

nity. SCARPOI. team. Swiss Study on Child-  

hood Allergy and Respiratory Symptoms with  

Respect to Air Pollution. Clin Exp Allergy  


32 Douwes J, Cheng S, Traver N, Cohet C,  

Niezink A, McKenzi J, Cooperham C, Le  

Gros G, von Mutius E, Pearce N: Farm expo-  

sure in utero may protect against asthma, hay  


611.

33 Kilpelainen M, Terho EO, Helenius H, Ko-  

skenuvu M: Farm environment in childhood  

prevents the development of allergies. Clin  


34 Riedler J, Eder W, Obergfeld G, Schreuer M:  

Austrian children living on a farm have less  

atopic sensitization in children up to the age  


1387.

35 von Mutius E: Maternal farm exposure/inges-  

sure of unpasteurized cow’s milk and allergic  

disease. Curr Opin Gastroenterol 2012;28:  

570–576.

36 Langan SM, Flohr C, Williams HC: The role  

of furry pets in eczema: a systematic review.  


37 Pelucchi C, Galeone C, Bach JF, La Vecchia C,  

Chatenoud L: Pet exposure and risk of atopic  

dermatitis at the pediatric age: a meta-analysis  

of birth cohort studies. J Allergy Clin Immunol  


38 Dom S, Droste JH, Sariachvili MA, Hagendorens MM, Oostveen E, Bredts CH, Stevens WJ, Wieringa MH, Weyler J: Pre- and post-  

natal exposure to antibiotics and the develop-  

ment of eczema, recurrent wheezing and  

atopic sensitization in children up to the age  


1387.


40 Bjorksten B, Naaber P, Sepp E, Mikelsaar M, Hyvarinen A, Riedler J, Dalphin JC, Pe-  

kkonen J, von Mutius E, Braun-Fahrlander C,  

Launier R: Development of atopic dermatitis  

according to age of onset and association with  

early-life exposures. J Allergy Clin Immunol  

2012;130:130–136.


Atopic dermatitis not only negatively impacts the child’s quality of life but also that of the whole family and is associated with a burden on health-care costs and society

Reprinted with permission from: Ann Nutr Metab 2015;66(suppl 1):18–24

Treatment of Childhood Atopic Dermatitis and Economic Burden of Illness in Asia Pacific Countries
by B.W. Lee and P.R. Detzel

Key insights
Atopic dermatitis is the most commonly occurring inflammatory disease in childhood. Contrary to previous belief, this disease not only affects developed countries. In the Asia Pacific, the prevalence of atopic dermatitis is on the rise, affecting not only the patients but their entire families and generating a significant economic burden.

Current knowledge
The costs related to the disease may be classified according to direct costs (associated with the use of health-care resources) and indirect costs (the nonmedical costs such as missed work time and transportation). An infant suffering from atopic dermatitis generates estimated health-care costs between USD 199 and over USD 1,000 per year. In general, the costs are higher in developed countries (such as Australia, North Korea and Singapore) compared to less developed countries (such as the Philippines and Indonesia).

Practical implications
NICE guidelines recommend a stepped approach in the management of childhood atopic dermatitis, with treatment tailored to disease severity. This approach includes education, avoidance of triggering factors, use of emollients and topical corticosteroids, topical calcineurin inhibitors, bandages and systemic immunosuppressive therapy. In the Asia Pacific region, treatment of atopic dermatitis also depends on factors such as the country’s health-care system and the specific climate. Bathing followed by the application of a skin moisturizer are frequently used, but there is no consensus on the frequency or duration of bathing for atopic dermatitis. Bleach baths are useful for disinfecting skin lesions and provide a practical alternative to antibiotic treatment. Further data are needed to identify the most effective and cost-effective measures for treatment and prevention in different countries.

Recommended reading
Treatment of Childhood Atopic Dermatitis and Economic Burden of Illness in Asia Pacific Countries

Bee Wah Lee\textsuperscript{a}  Patrick R. Detzel\textsuperscript{b}
\textsuperscript{a}Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore;
\textsuperscript{b}Nestlé Research Center, Lausanne, Switzerland

Key Messages
\begin{itemize}
  \item Atopic dermatitis (AD) is the most common chronic inflammatory disease of childhood.
  \item Its prevalence in the Asia Pacific region is increasing.
  \item This condition impacts the quality of life not only of the patients but also of the whole family and carries a cost burden on society.
  \item Further evaluations of AD costs and the cost-effectiveness of pediatric AD prevention strategies in Asia Pacific countries are warranted.
\end{itemize}

Key Words
Atopic dermatitis · Treatment · Health economics · Infant · Children · Asia Pacific

Abstract
Atopic dermatitis (AD) is a common chronic inflammatory skin condition in children. In Asia, the prevalence of AD is increasing, which is largely attributed to environmental and socioeconomic factors including family income, parental education, lifestyle and metropolitan living. Current clinical guidelines recommend a stepped approach in the management of eczema in children, with treatment steps tailored to the severity of the eczema. To address the skin barrier dysfunction, skin hydration and the application of emollients is essential. There is evidence supporting the use of bleach baths as an antimicrobial therapy against \textit{Staphylococcus aureus}. In patients in whom topical treatment fails, wet wrap therapy may be considered as a treatment option before considering systemic therapies. In the second part of this article, the economic burden of AD is addressed. AD not only negatively impacts the child’s quality of life but also that of the whole family and is associated with a burden on healthcare costs and society. AD in an infant will lead to frequent additional visits to the pediatrician, to additional and partially expensive treatment costs and, in rare cases, to hospitalization. It is thus of utmost importance to define efficient strategies to not only treat AD but also to decrease the risk of developing the disease.

Introduction
Atopic dermatitis (AD) is a common chronic skin disorder and considered to be the earliest manifestation of the atopic march. It has a chronic relapsing and remitting course which deeply affects the child’s quality of life as...
well as that of the whole family and imposes a substantial medical burden on society. This paper reviews the current status with regard to the management and economic burden of AD in the Asia Pacific region.

**Prevalence of AD**

AD is one of the most common childhood skin conditions and is associated with a significant social and financial burden [1]. There is striking worldwide geographic variability in the prevalence of AD. The reasons for this variability are as yet unclear but have been attributed in part to many environmental factors, including urbanization, diet, climate, infections and aeroallergens [2].

The International Study of Asthma and Allergies in Childhood (ISAAC), an international multi-country cross-sectional survey of school children, was conducted to investigate the epidemiology and geographic variability and trends in prevalence of asthma, rhinitis and AD [3]. The ISAAC Phase One study was conducted in the early to mid-1990s. To monitor the evolution in the prevalence of these disorders, ISAAC Phase Three was carried out about 7 years later using the same methodology and survey questionnaire. This follow-up study involved 193,404 children aged 6–7 years from 66 centers in 37 countries and 304,679 children aged 13–14 years from 106 centers in 56 countries.

Data from the ISAAC Phase Three study revealed that the prevalence of AD symptoms in the 6- to 7-year and the 13- to 14-year age groups ranged from 1.8 to 23.4 and 0.9 to 21.1%, respectively [4]. In the Asia Pacific region, the 12-month prevalence of AD in children aged 13–14 years was reported to be as high as 9% in Malaysia and Singapore and as low as 0.9% in China. Notably, China had the lowest prevalence in the world. The reasons for these differences in AD prevalence are poorly understood, but industrialization and socioeconomic factors have been implicated [5–10].

Compared to the ISAAC Phase One results [11], 44 of the 52 centers recorded an increase in the prevalence of AD, whereas only 8 centers reported a decrease in ISAAC Phase Three. ISAAC Phase Three also highlighted the Asia Pacific as an area of increasing AD prevalence. Of the 44 centers with an increase in prevalence, 10 were from the Asia Pacific, hence putting this region second to Western Europe (17 centers) for centers with an increase in AD prevalence.

Data for Singapore, derived from the ISAAC surveys, indicated a modest increase in prevalence in both age groups, but an increased severity of symptoms in the 12- to 15-year age group [12]. The latter is in agreement with a cross-sectional epidemiological study involving 12,323 students in Singapore (7-, 12- and 16-year age groups) reporting a prevalence of AD of 20.8% [13], an incidence markedly higher than that reported in younger age groups [14, 15]. The increasing prevalence and severity of AD is concerning and further highlights the need for improved management of this condition.

**Pathogenesis of AD**

AD is a chronic inflammatory disease often exhibiting marked xerosis, pruritus and skin lesions. Although it is incompletely understood, the pathogenesis of AD is thought to result from the complex interaction between defects in skin barrier function, immune abnormalities involving IgE-mediated and a non-IgE-mediated hypersensitivity and environmental as well as infectious agents [16, 17].

AD is mediated by Th1/Th2 immune responses. In the initial acute phase, AD skin lesions predominantly secrete the Th2 cytokines, whereas in the chronic phase, Th1 cells secrete IFN-γ [18]. The shift from Th2- to Th1-predominant immune responses plays an important role in the development of AD [19]. It has also been suggested that the hyperreactive immune response may be a consequence of defects in the epidermal barrier [20]. The defective epidermal barrier may allow the allergens to enter through the skin, facilitating the interaction of these allergens with the local antigen-presenting cells and immune effector cells. This may trigger the transition from a nonallergic to an allergic state associated with a rise in IgE [21–23].

Early sensitization has been shown to influence the onset, duration and severity of AD. In a population-based, noninterventional study of a cohort of 562 newborns conducted at the Danish Allergy Research Centre (DARC), early onset and persistence of allergen sensitization beyond the age of 2 years were associated with more persistent AD [24]. In contrast, children with early, non-IgE-mediated (intrinsic) AD were more likely to outgrow their eczema than sensitized children.
Management of AD

There are a number of evidence-based international guidelines on the management of AD. Of interest is ‘Management of Atopic Eczema in Children Aged up to 12 Years’ [25], published by the National Institute for Health and Clinical Excellence (NICE), which provides specific recommendations for children from birth to 12 years.

The NICE guidelines adopt a holistic approach in assessing AD, taking into account the physical severity of the atopic skin disorder and its impact on the quality of life. A grading system was outlined: clear = normal skin; mild = dry skin with infrequent scratching; moderate = areas of dry skin and frequent itching and redness; severe = widespread areas of dry skin, incessant scratching, redness, oozing and crusting, lichenification and pigment changes. Whereas scoring of AD severity is not required in clinical practice, documentation of symptoms, including descriptions of the extent and nature of lesions, skin dryness and intensity of itchiness, can help better manage the condition.

Patient education is paramount for successful therapy.

The NICE guidance recommends a stepped approach in the management of AD in children, with treatment steps tailored to the severity of the eczema [25]. In this regard, patient education is paramount for successful therapy. Mild AD should be managed with emollients, avoidance of triggering factors and mild-potency topical corticosteroids. Moderately severe AD should be managed with emollients, topical corticosteroids with mild potency, topical calcineurin inhibitors and bandages in a stepwise approach. In addition to emollients, moderate and severe AD requires a stepwise treatment which may include potent topical corticosteroids, topical calcineurin inhibitors, bandages and systemic immunosuppressive therapy. A recent review proposes an updated treatment algorithm for AD which includes recommendations for the treatment of refractory cases [18]. Treatment of complications such as skin infections, particularly due to *Staphylococcus aureus* and Herpes simplex virus, is also an important aspect of the management of eczema flares. In a small proportion of infants and young children with severe eczema, food allergy may also contribute to failure to respond to standard therapy [26].

Dermatologists in the Asia Pacific region have also published consensus guidelines of AD and highlighted the various treatment practices in this region, which are influenced by differences in health-care systems, access to medical care as well as by cultural and environmental factors including climate [27].

Bathing

Bathing, followed by moisturizer application, is thought to help hydrate the skin and reduce itchiness; however, there is little consensus regarding the frequency or duration of bathing appropriate for patients with AD. Of particular interest is bleach bathing to disinfect the skin lesions. During AD disease flares, the diversity of the skin microbiome is greatly reduced, *S. aureus* tends to predominate and AD symptoms tend to worsen [28].

Antibiotic therapy against *S. aureus* is an important component of AD management as it reduces both the severity of AD and the likelihood of secondary infections. However, with the growing concern regarding the emergence of antibiotic resistance, bleach baths are sometimes recommended for patients with AD to reduce *S. aureus* skin colonization or infection [29]. A randomized, placebo-controlled study has demonstrated that compared to placebo, coadministration of intranasal mupirocin ointment and bleach baths (0.005%) for 5–10 min twice weekly decreased the clinical severity of AD in patients with clinical signs of secondary bacterial infections [30].

Wet Wraps

In recent years, wet wrapping, i.e. the application of wet bandages wrapped over emollients and/or topical steroid creams, has been used as a treatment option for AD. A cohort study of 50 children (aged 4–27 months) with moderate to severe eczema was conducted to evaluate the effectiveness of wet wrap therapy to improve disease severity [31]. A comparison of disease severity at admission and at discharge showed an average of 70% reduction in SCORAD scores (49.68 ± 17.72 vs. 14.83 ± 7.45, respectively) in patients who received the in-patient wet wrap therapy [31]. The investigators suggest that wet wrap therapy may be considered as a treatment option before considering systemic therapies in patients for whom topical therapy has failed.

Economic Burden of Pediatric AD in the Asia Pacific Region

To estimate the economic burden of pediatric AD in the Asia Pacific region, an electronic literature search was conducted in PubMed, Google scholar and Asian elec-
tronic reference databases to identify studies reporting on pediatric AD cost estimates. These searches were complemented by manual reviews of bibliographies of the articles reporting cost estimates, discussions with AD experts and economic models (Singapore, Malaysia and Indonesia) presented at the International Conference of Health Economics – ISPOR 6th Asia-Pacific Conference (Beijing, China, 2014). All costs were inflated and converted to 2013 USD for comparison purposes.

A total of 5 published studies were identified (table 1): 2 for Australia [32, 33], 1 for South Korea [34], 1 for Thailand [35] and 1 for the Philippines [36], which required reanalyses to generate some of the outcomes presented herein. These studies were further complemented with unpublished analyses conducted by some of the coauthors in Indonesia, Malaysia and Singapore [37]. The analyses varied in terms of country considered, study design, target populations and setting of care, average age and range, sample size, the type of cost included and the case mix of AD severity (table 1).

Patients included in one of the Australian studies were attending a dermatology clinic [32], whereas patients in the South Korean study were recruited in an allergy department [34]. Patients from these 2 studies had the lowest proportion of mild cases. This led to a selection bias and to an overestimate of AD costs as mild cases were not well reflected in the estimates. Patients in the other studies were treated in a general/pediatric setting.

Most countries reported both direct and indirect costs (fig. 1), except for the study in Thailand, which assessed direct costs only. By direct costs, all costs are meant which are associated with the use of health-care resources. Indirect costs reflect nonmedical costs, such as time losses for parents, etc.

The direct costs of AD per patient per year ranged from USD 199 in Thailand to USD 4,842 in Australia. Discarding the Australian estimates (reflecting severe cases), a significant high economic burden of illness of AD in the region can still be observed (fig. 2). An infant suffering from AD will generate health-care costs between USD 199 and over USD 1,000 per year. This represents substantial medical costs for a disease characterized by a high and increasing prevalence.

The indirect costs of AD per patient per year ranged from USD 8 in the Philippines to USD 2,268 in South Korea. These costs will be covered exclusively by the parents/relatives of the infant suffering from AD as these costs are not related with the medical treatment of the child but are

Table 1. Studies regarding the economic burden of pediatric AD

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Population type/sample</th>
<th>Mean age (range), years</th>
<th>n</th>
<th>Year of cost data</th>
<th>Cost included</th>
<th>Case distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Su et al. [32], 1997</td>
<td>Australia</td>
<td>cross-sectional survey</td>
<td>presenting at dermatologic clinic</td>
<td>4.5 (0.3–15)</td>
<td>48</td>
<td>1997</td>
<td>yes yes</td>
<td>38 42 21</td>
</tr>
<tr>
<td>Su et al. [33], 2012</td>
<td>Australia</td>
<td>model and expert opinion</td>
<td>with atopic heredity</td>
<td>n.a. (0–1)</td>
<td>n.a.</td>
<td>2009</td>
<td>yes yes</td>
<td>60 35 5</td>
</tr>
<tr>
<td>Kang et al. [34], 2012</td>
<td>South Korea</td>
<td>cross-sectional survey</td>
<td>attending allergy clinic</td>
<td>5.49 (1–12)</td>
<td>n.r.</td>
<td>2009</td>
<td>yes yes</td>
<td>42 31 27</td>
</tr>
<tr>
<td>Ngamphaiboon et al. [35], 2012</td>
<td>Thailand</td>
<td>model and retrospective analysis</td>
<td>attending pediatric hospital department</td>
<td>n.a. (0–5)</td>
<td>n.a.</td>
<td>2010</td>
<td>yes no</td>
<td>79a 18a 3a</td>
</tr>
<tr>
<td>Bhanegaonkar et al. [37], 2014</td>
<td>Indonesia</td>
<td>model-based/expert opinion</td>
<td>urban, affluent, with atopic heredity</td>
<td>n.a. (1–6)</td>
<td>n.a.</td>
<td>2013</td>
<td>yes yes</td>
<td>50/60b 40/30b 10/10b</td>
</tr>
<tr>
<td>Bhanegaonkar et al. [37], 2014</td>
<td>Malaysia</td>
<td>model and expert opinion</td>
<td>urban, affluent, with atopic heredity</td>
<td>n.a. (1–6)</td>
<td>n.a.</td>
<td>2013</td>
<td>yes yes</td>
<td>43/50b 37/28b 20/22b</td>
</tr>
<tr>
<td>Bhanegaonkar et al. [37], 2014</td>
<td>Singapore</td>
<td>model and expert opinion</td>
<td>urban, affluent, with atopic heredity</td>
<td>n.a. (1–6)</td>
<td>n.a.</td>
<td>2013</td>
<td>yes yes</td>
<td>58/80b 38/17b 5/4b</td>
</tr>
<tr>
<td>Bhanegaonkar et al. [36], 2014</td>
<td>Philippines</td>
<td>model and expert opinion</td>
<td>urban, affluent, with atopic heredity</td>
<td>n.a. (1–6)</td>
<td>n.a.</td>
<td>2013</td>
<td>yes yes</td>
<td>60/85c 25/10c 15/5c</td>
</tr>
</tbody>
</table>

n.r. = Not reported; n.a. = not applicable. a Calculated based on the data in Matsuoka et al. [6]. b The first value is for age <1 year, the second value is for age >1 year. c The first value is for age <2 years, the second value is for age >2 years.
linked with the time losses and transportation costs of the parents.

The estimation of total AD costs varies significantly across countries and across severity levels (table 1). The lowest costs were observed in Thailand [35] (USD 199 across all severities, ranging from USD 124 among mild cases to USD 968 among severe cases), in part because only direct costs were reported.

Costs were higher in more developed countries (Australia, North Korea and Singapore), with overall costs ranging from approximately USD 1,000 to 6,000, than in less developed countries (Philippines, Indonesia and Malaysia), where costs ranged from USD 199 to 743.

The components of direct costs for AD are generally consistent across countries, with medical visits and creams, dressing, ointments and medications reported in all studies (fig. 3). This illustrates that infants suffering from AD are treated following consistent and coherent guidelines across the region.

![Fig. 1. Annual total (direct and indirect) costs for AD in different countries.](image1)

![Fig. 2. Annual direct costs for AD in different countries.](image2)

![Fig. 3. Components of direct costs for AD in different countries. Data from South Korea [34] are not included as insufficient details were provided for analysis.](image3)
Conclusions

Allergic conditions are among the most common medical conditions affecting children, and the incidence of allergies, especially AD, is increasing. These conditions impact the quality of life not only of the patients but also of the whole family and carry a cost burden on society. Guidelines for treatment of AD are available; the NICE guidelines recommend a stepped approach in the management of AD in children, with treatment steps tailored to the severity of the eczema. The approach includes education, use of emollients, avoidance of triggering factors and topical corticosteroids, topical calcineurin inhibitors, bandages and systemic immunosuppressive therapy. Various bathing procedures and wet wraps have been reported to be effective.

The economics of pediatric AD in the Asia Pacific region have not been extensively studied. Based on available evidence, annual pediatric AD costs are generally high but vary widely across studies/countries. Variations in cost estimates make comparisons difficult and may be due to differences between studies in countries considered, population/sample studied, types of costs included, severity of AD and costing methodology.

Further evaluations of the AD costs and the cost-effectiveness of pediatric AD prevention strategies in Asia Pacific countries are warranted.

Disclosure Statement

B.W.L. received financial support to attend the ISPOR 6th Asia-Pacific Conference in September 2014. She has received honoraria for lectures supported by the Nestlé Nutrition Institute. P.R.D. is an employee of the Nestlé Research Center, Lausanne, Switzerland.

References

5 Bleiker TO, Shahidullah H, Dutton E, Grainger R: Various bathing procedures and wet wraps have been reported to be effective. J Invest Dermatol 2006;136:539–543.


High-risk infants fed with standard cow’s milk formula as a supplement or replacement of breast milk may be exposed to a higher likelihood of developing atopic dermatitis

Cost-Effectiveness of Partially Hydrolyzed Whey Protein Formula in the Primary Prevention of Atopic Dermatitis in High-Risk Urban Infants in Southeast Asia

by M. Botteman and P. Detzel

Key insights
Proteins found in standard cow’s milk formula have been associated with an increased risk of atopic dermatitis, especially in infants with a familial predisposition towards atopy. Compared to standard cow’s milk formula, partially or extensively hydrolyzed formulas are alternative protein sources that may reduce the risk of atopic dermatitis and other allergic disorders when used in high-risk infants. This study compared the long-term (i.e. 6 years) economic impact of using a partially hydrolyzed whey-based formula instead of a standard cow’s milk formula in the first 17 weeks of life in nonexclusively breastfed infants who are at high risk of developing atopic dermatitis in Malaysia, Singapore, and the Philippines. The analysis was based on the 6-year results of the German Infant Nutritional Intervention (GINI) study, a large randomized clinical trial comparing the risk of atopic dermatitis in following feeding with standard cow’s milk formula versus partially hydrolyzed whey-based formula.

Current knowledge
The development of childhood atopic dermatitis is associated with substantial costs, which vary depending on the country and disease severity. The main drivers of total costs are medical treatments, physician visits, and other indirect costs such as parental time lost to attend a child with atopic dermatitis. These costs are likely to be underestimated as they do not include the out-of-pocket expenses incurred by the patients’ families, since these are poorly documented.

Practical implications
The use of partially hydrolyzed whey-based formula as a replacement for cow’s milk formula in at-risk healthy infants reduces the clinical, economic, and quality of life burden due to atopic dermatitis. The 6-year net savings due to the risk reduction of atopic dermatitis per at-risk infant associated with the use of partially hydrolyzed whey-based formula were USD 237 in the Philippines, USD 372 in Malaysia, and USD 739 in Singapore. The higher initial cost of the formula itself was outweighed by the substantial decrease in costs due to the risk reduction of atopic dermatitis.

Recommended reading
Cost-Effectiveness of Partially Hydrolyzed Whey Protein Formula in the Primary Prevention of Atopic Dermatitis in High-Risk Urban Infants in Southeast Asia

Marc Botteman\textsuperscript{a}  Patrick Detzel\textsuperscript{b}

\textsuperscript{a}Pharmerit International, Bethesda, Md., USA; \textsuperscript{b}Nestlé Research Center, Lausanne, Switzerland

Key Words
Cost-effectiveness analysis · Prevention of atopic dermatitis · Partially hydrolyzed whey formula · Southeast Asia

Abstract

Background: Atopic dermatitis (AD) is one of the most common skin conditions among infants. Proteins found in cow’s milk formula (CMF) have been found to be attributable to heightened AD risk, particularly in infants with familial AD heredity. Previous studies have suggested that intervention with partially hydrolyzed formula in nonexclusively breastfed infants can have a protective effect against AD development. Objective: The aim of the present study was to compare the estimates of the economic impact of reducing the incidence of AD by feeding a partially hydrolyzed whey-based formula instead of a standard CMF to high-risk nonexclusively breastfed urban infants for the first 17 weeks of life in the Philippines, Malaysia, and Singapore. Methods: In each country, a mathematical model simulated AD incidence and burden from birth to 6 years of age of using partially hydrolyzed whey-based formula (PHF-W) instead of standard CMF to high-risk nonexclusively breastfed infants for the first 17 weeks of life in the Philippines, Malaysia, and Singapore. The models integrated literature, current cost and market data, and expert clinician opinion. Modeled outcomes included AD risk reduction, time spent after AD diagnosis, AD symptom-free days, quality-adjusted life years, and costs (direct and indirect). Results: Feeding high-risk urban infants partially hydrolyzed formulas instead of standard infant formula resulted in an estimated significant risk reduction of developing AD, a 0.69-year reduction in the time spent after AD diagnosis, and 16- 38-day reductions of flares, depending on the country. The per-child AD-related 6-year cost-saving estimates when feeding high-risk infants with partially hydrolyzed whey-based formula versus cow’s milk formula were USD 739 in Singapore, USD 372 in Malaysia, and USD 237 in the Philippines.

Key Messages
• The objective of the present study was to compare the estimates of the economic impact of reducing the incidence of AD by feeding a partially hydrolyzed whey-based formula instead of a standard cow’s milk formula to high-risk nonexclusively breastfed urban infants for the first 17 weeks of life in the Philippines, Malaysia, and Singapore.
• Mathematical models integrating literature, current costs, and expert clinician opinion were used. Modeled outcomes included AD risk reduction, time spent after AD diagnosis, AD symptom-free days, quality-adjusted life years, and costs (direct and indirect).
• Feeding high-risk urban infants partially hydrolyzed formulas instead of standard infant formula resulted in an estimated significant risk reduction of developing AD, a 0.69-year reduction in the time spent after AD diagnosis, and 16- 38-day reductions of flares, depending on the country.
• The per-child AD-related 6-year cost-saving estimates when feeding high-risk infants with partially hydrolyzed whey-based formula versus cow’s milk formula were USD 739 in Singapore, USD 372 in Malaysia, and USD 237 in the Philippines.
Introduction

Atopic dermatitis (AD) is a common inflammatory skin disorder affecting infants and young children [1, 2]. In Singapore, approximately 10–20% of children aged 6–7 years have atopic eczema [3–5]; secular trends suggest that this prevalence may be increasing [6]. AD is characterized by a chronic component which can lead to lifelong skin symptoms [7]. As such, AD imposes a substantial economic and quality of life (QOL) burden on patients, families, and societies [8–11]. Estimates of the annual direct cost of AD in Asia are limited but have ranged from USD 199 in Thailand [12] to USD 1,253 in South Korea [13].

A child’s risk of developing AD is affected by a combination of immunologic, environmental, and genetic factors [3, 14, 15]. In particular, if one parent has allergies, a child’s risk doubles; if both parents have allergies, the risk increases four-fold [15]. In Singapore, at least one first-degree family member with atopy was noted in 70% of children with AD [3]. Additionally, studies from various countries report that approximately one third of children with AD had a diagnosis of allergy or intolerance to cow’s milk and, conversely, up to 50% of infants with allergy or intolerance to cow’s milk had AD [16, 17]. Although the World Health Organization (WHO) recommends exclusive breastfeeding through the first 6 months of life [18, 19], this recommendation is not always followed. In such instances, high-risk infants fed with standard cow’s milk formula (CMF) as a supplement or replacement for breast milk may be exposed to a higher likelihood of developing AD.

Partially or extensively hydrolyzed formulas are two alternative protein sources that have been shown to reduce the risk of AD and other allergies compared to CMF in these high-risk infants [20–24]. In particular, the German Infant Nutritional Intervention (GINI), the largest comparative trial of infant formula in high-risk infants, found that nonexclusively breastfed infants with atopic heredity randomized to a partially hydrolyzed whey-based formula (PHF-W) versus CMF for the first 4 months of life experienced a lower cumulative incidence of AD 6 years following birth (27.4 vs. 39.1%; adjusted RR = 0.64; 95% CI 0.48–0.86) [23]. On the basis of such data, several national and international allergy organizations have suggested hydrolyzed formulas as an allergy risk reduction strategy for these high-risk infants [18, 25, 26].

As demonstrated in previous studies, the potentially higher costs of PHF-W relative to CMF during the 17-week interventional period should be partially offset by direct and indirect cost savings and QOL improvements associated with AD incidence reduction in this high-risk population [27–31].

The present study aggregated the modeling results of three national health-economic studies (the Philippines [31], Singapore [32], and Malaysia [33]). Using health-economic modeling techniques that combine data from the GINI study [23], expert opinions, and local cost data, these studies estimated the clinical and economic impact of PHF-W intervention for the first 17 weeks of life compared to CMF among high-risk urban infants in three Southeast Asian countries. A more detailed description of the methodology can be found in the publication on the Philippines [31].

Model Structure

Overview

Mathematical modeling (i.e. Markov cohort techniques, which are an extension of life table analysis) [34] was used to compare costs and outcomes associated with AD development over time among high-risk urban infants with first-degree atopic heredity partially or completely fed with PHF-W versus CMF in early infancy (from birth to week 17). Cohorts were followed from birth to 6 years of age. The target population, risk reduction, formula feeding and duration, and age-specific AD incidence were selected on the basis of the GINI study [23, 35].

The analysis adopted a societal perspective and included direct and indirect costs associated with formula and AD treatment. The
primary outcomes for each treatment arm included the proportion of patients developing AD, the number of days without AD symptoms, the time spent after AD diagnosis, quality-adjusted life years (QALYs), and overall costs.

Similar to previously published models [27–31], three treatment approaches were possible after initial AD development, as confirmed by pediatricians with AD treatment experience in these three countries. Depending on the country of analysis, AD patients could go through a series of dietary modifications (i.e. up to two formula types) and up to three different pharmacological treatments. Three country-specific mathematical models were developed to reflect the specificities of each country in AD management.

Table 1. Epidemiologic inputs and clinical assumptions

<table>
<thead>
<tr>
<th></th>
<th>Malaysia &lt;1 year of age</th>
<th>Malaysia &gt;1 year of age</th>
<th>Philippines &lt;1 year of age</th>
<th>Philippines &gt;1 year of age</th>
<th>Singapore &lt;1 year of age</th>
<th>Singapore &gt;1 year of age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution of cases, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild AD</td>
<td>43.3</td>
<td>50.0</td>
<td>60.0</td>
<td>85.0</td>
<td>57.5</td>
<td>80.0</td>
</tr>
<tr>
<td>Moderate AD</td>
<td>36.7</td>
<td>28.3</td>
<td>25.0</td>
<td>10.0</td>
<td>37.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Severe AD</td>
<td>20.0</td>
<td>21.7</td>
<td>15.0</td>
<td>5.0</td>
<td>5.0</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Mild AD management, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch formula</td>
<td>3.3</td>
<td>0.0</td>
<td>5.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Combined</td>
<td>26.7</td>
<td>0.0</td>
<td>25.0</td>
<td>0.0</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical</td>
<td>70.0</td>
<td>100.0</td>
<td>70.0</td>
<td>100.0</td>
<td>95.0</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Moderate AD manage-ment, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch formula</td>
<td>3.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Combined</td>
<td>35.0</td>
<td>0.0</td>
<td>80.0</td>
<td>0.0</td>
<td>20.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical</td>
<td>61.7</td>
<td>100.0</td>
<td>20.0</td>
<td>100.0</td>
<td>80.0</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Severe AD manage-ment, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch formula</td>
<td>1.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Combined</td>
<td>45.0</td>
<td>0.0</td>
<td>90.0</td>
<td>0.0</td>
<td>20.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical</td>
<td>53.3</td>
<td>100.0</td>
<td>10.0</td>
<td>100.0</td>
<td>80.0</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Response rates, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All severities: for-mula switch</td>
<td>7.0</td>
<td>n.a.</td>
<td>5.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Mild AD, first-line PT</td>
<td>85.0</td>
<td>83.0</td>
<td>98.0</td>
<td>98.0</td>
<td>84.7</td>
<td>83.0</td>
</tr>
<tr>
<td>Moderate AD, first-line PT</td>
<td>67.0</td>
<td>67.0</td>
<td>65.0</td>
<td>75.0</td>
<td>66.7</td>
<td>63.3</td>
</tr>
<tr>
<td>Severe AD, first-line PT</td>
<td>53.0</td>
<td>52.0</td>
<td>30.0</td>
<td>50.0</td>
<td>55.0</td>
<td>48.3</td>
</tr>
<tr>
<td><strong>Response rates, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To second-line PT (all AD severity)</td>
<td>68.0</td>
<td>68.0</td>
<td>90.0</td>
<td>90.0</td>
<td>73.0</td>
<td>73.0</td>
</tr>
<tr>
<td>To third-line PT (all AD severity)</td>
<td>83.0</td>
<td>83.0</td>
<td>95.0</td>
<td>95.0</td>
<td>80.0</td>
<td>80.0</td>
</tr>
<tr>
<td>To fourth-line PT (all AD severity)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>13.0</td>
<td>13.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>To combination treatment (all AD severity)</td>
<td>77.0</td>
<td>n.a.</td>
<td>93.0</td>
<td>n.a.</td>
<td>70.0</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>12-week probability of flare-ups, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild AD</td>
<td>40.0</td>
<td>40.0</td>
<td>30.0</td>
<td>10.0</td>
<td>11.7</td>
<td>11.0</td>
</tr>
<tr>
<td>Moderate AD</td>
<td>50.5</td>
<td>53.0</td>
<td>50.0</td>
<td>30.0</td>
<td>36.7</td>
<td>35.0</td>
</tr>
<tr>
<td>Severe AD</td>
<td>58.0</td>
<td>60.0</td>
<td>70.0</td>
<td>50.0</td>
<td>60.0</td>
<td>63.3</td>
</tr>
</tbody>
</table>

PT = Pharmacotherapy; n.a. = not applicable.

Model Parameters

Epidemiologic inputs and clinical assumptions are provided in Table 1. Probability of AD and flares were stratified by severity (i.e. mild, moderate, and severe) and age (i.e. 0–1 year; >1–6 years). Based on the data from GINI, it was estimated that the 1-, 3-, and 6-year proportions of children initially fed with CMF who developed AD were 16.8, 33.5, and 39.1%, respectively. The corresponding figures for children initially fed PHF-W were 9.1, 19.4, and 25.0%, respectively.

Daily formula intake was age adjusted for nutrient needs from birth to 12 months by means of a previously reported method [31] that accounted for partial breastfeeding. Formula acquisition costs were based on market share in the three countries and end-consumer formula prices. The analysis took into account the addi-
 incremental costs that would be incurred as a result of feeding with alternative infant formula (such as PHF-W, soy-based formula, and extensively hydrolyzed formula).

Three groups of experts (3–4 per country) provided information on the type and amount of resources used with each treatment modality based on severity of AD, including the number of inpatient and outpatient visits (general practitioners or specialists) required for the management of AD by severity and therapy. For example, in Singapore, upon AD development, 50% of children saw a general practitioner and 36% saw a specialist. The number of general practitioner visits per child after initial AD development and for each flare was 0.20 for mild cases, 1.00 for moderate cases, and 0.70 for severe cases. The corresponding number of specialist visits was 0.38, 1.45, and 3.17 per child for mild, moderate, and severe cases, respectively.

Inpatient stays were assumed to occur once upon initial AD development in 2–24% of cases, depending on severity at presentation, age, and country. Specific IgE and skin prick tests were assumed to be performed in all children upon initial AD development.

Costs of inpatient/outpatient visits and diagnostic tests were based on average fees charged in the hospitals or laboratories of the three countries where information was available.

Emollients and/or moisturizer creams were assumed to be used by nearly all AD patients. Medicine acquisition costs were obtained from an online drug information tool commonly used in these countries. Reduced productivity (i.e. indirect costs) included lost work days to care for children with AD following the initial physician visit.

Based on previously published data, young children who did not have AD were assumed to experience a utility of 1.000, while those in controlled AD state after an episode had a utility of 0.980; thus, it is recognized that mild, subclinical episodes could permanently reduce QOL [36, 37]. The utilities associated with mild, moderate, and severe AD episodes were 0.863, 0.690, and 0.450, respectively.

Outcome Measures and Analyses
Using the data on AD incidence, flares, and episode duration, it was possible to estimate the per-child 6-year AD risk and the expected number of days with AD symptoms. Several incremental cost-effectiveness ratios (ICERs) were computed to estimate the relative economic value of PHF-W versus CMF, including the incremental cost per AD case avoided, incremental cost per AD-free day gained, and incremental cost per QALY gained.

In addition to the base case analysis, various sensitivity analyses were carried out to evaluate the robustness of the results. First, deterministic univariate sensitivity analyses were conducted on individual model parameters while keeping the base case values for other parameters in the model unchanged. Scenario analyses were conducted to test the impact of changing key model assumptions either alone or in combination. These included omitting any flares from the analysis and restricting the analysis to 1 year (as opposed to the 6-year time frame). Finally, multivariate, probabilistic sensitivity analyses were used.

All results were reported after applying a discount rate of 3% to all costs and effects beyond year 1. All costs reported in the study represent 2013 values, expressed in USD.

Results
Cost of the Treatment of AD
Figure 1 provides an overview of the annualized direct medical and other (indirect and nonmedical) costs by country and severity level. The overall costs for the treatment of a severe AD case (USD 2,538) are highest in Singapore, roughly twice that in the Philippines and Malaysia. These differences do not reflect the per capita wealth differences of these countries due to the focus on high-
risk urban infants. Whereas the costs in Singapore reflect the average costs per infant in that country, the treatment costs in the two other countries are representative only of the infants in the most affluent households.

The components of direct medical costs are generally consistent across countries, with pharmacological and physician’s visits accounting for the majority of costs (fig. 2). The relative homogeneity of the direct medical cost splits across countries is likely the consequence of consistent national treatment guidelines across the region but also linked to the recurrent nature of the disease and the rather symptomatic nature of AD treatment. Furthermore, traditional treatments were not taken into account. A study in South Korea showed that these costs were higher than direct medical costs [13].

The cost-effectiveness of reducing AD risk is driven by treatment costs but also by the efficacy and incremental costs of the nutritional intervention; partially hydrolyzed formulas are more expensive than intact protein formulas (i.e. CMF). The effectiveness of the intervention in terms of risk reduction (clinical effects) reflects the outcomes of the GINI study, whereas cost-effectiveness also takes specific treatment costs into account.

CMF was associated with a higher AD incidence (+14%) compared to PHF-W (CMF vs. PHF-W: 39 vs. 25%; 95% CI for the difference 1–24; table 2), while PHF-W was associated with less AD days (ranging from –16 to –38 days, depending on country) and fewer years (–0.69 years) in a post-AD diagnosis state (CMF vs. PHF-W: 1.69 vs. 1.00 years; 95% CI for the difference 0.25–1.13). Discounted QALYs were higher with PHF-W than with CMF, for a net difference varying from 0.02 to 0.04 QALYs, depending on country (table 2).

Primary drivers of total costs were associated with pharmacological treatments followed by indirect costs and physician visits. The resulting 6-year net savings due to risk reduction of AD per high-risk infant with PHF-W were USD –237 (95% CI –323 to –96) in the Philippines, USD –372 (95% CI –547 to –190) in Malay-
The comparison of PHF-W versus CMF using ICER values showed PHF-W to be a net cost saving strategy in all three countries and also resulted in reduction of AD cases and gains in AD-free days and QALYs. The higher formula costs for PHF-W in these countries were offset by reductions in AD-related costs.

Thus, PHF-W was the ‘dominant’ strategy (i.e. more effective and less expensive) relative to CMF in all three countries (fig. 3). Probabilistic statistical analysis also indicated that PHF-W was dominant in almost all 5,000 model runs in all three countries.

In univariate sensitivity analysis, the relative risk of cumulative AD incidence for PHF-W and CMF, and the probability of AD with CMF, had the largest influence on the difference in cost between PHF-W and CMF. Other variables with potentially minor effects on net cost savings were the costs of PHF-W, CMF, and emollients.

Discussion

In the review of these three different cost-effectiveness studies, early nutritional intervention with PHF-W as a replacement for CMF in healthy infants at risk was not only cost effective but cost saving compared to standard formula. It improves the QOL of infants by reducing the risk of developing AD and also leads to significant savings from a societal perspective.

Based on the present model, the development of AD in childhood is associated with significant costs, which vary across countries and by severity.

These costs are likely underestimated as they do not fully account for many of the out-of-pocket expenses and indirect costs incurred by families with children with AD, as these are poorly documented or measured and the expert panels could only provide limited information on some of these expenses. Another difficulty of using health-economic models developed in high-income countries is based on the assumption that all members of the society have equal access to universal health-care services. Health-care access is highly heterogeneous across Southeast Asia and dependent on household disposable income.

Conclusion

The present analysis compared the results of three cost-effectiveness studies using modeling techniques to assess the long-term cost-effectiveness of preventing AD via early nutritional intervention with PHF-W versus CMF in healthy infants with atopic heredity who are not exclusively breastfed. The analysis was conducted from a societal perspective, focusing on the urban population. The results suggest that across the region, the use of PHF-W in the defined patient population may be a dominant strategy relative to the use of CMF as it reduces the clinical and QOL burden of AD while decreasing overall costs, even after the inclusion of formula costs. While the analysis was conducted on the basis of limited evidence, various sensitivity and scenario analyses show that these conclusions may be robust. Nevertheless, additional research regarding the epidemiology, severity, treatment patterns, and resource use associated with the prevention and treatment of AD in these three countries are warranted.

Disclosure Statement

Partial research funding was received from the Nestlé Research Center, Lausanne, Switzerland, to conduct this study. M.B. is employee and owner of Pharmerit International which received partial research funding from the Nestlé Research Center to conduct this study. P.D. is an employee of Nestlé Research Center which funded this study. Nestlé Research Center is part of Nestlé, which manufactures and commercializes NAN-HA, one of the products evaluated in this study. Pharmerit International retained independent control of the methods used and result presentation of this study.

References


Botteman/Detzel
Patients with skin diseases experience a wide range of symptoms ranging from trivial problems to major handicaps which affect their lives

Reprinted with permission from: Ann Nutr Metab 2015;66(suppl 1):34–40

The Impact of Atopic Dermatitis on Quality of Life
by C. Lifschitz

Key insights
Since atopic dermatitis is one of the most common chronic relapsing childhood dermatoses, it has major social and financial implications for individuals, health-care providers, and society as a whole. Despite the prevalence of atopic dermatitis, relatively little attention has been given to the impact of treatment on quality of life. The assessment of disease-related quality of life is important because it complements the traditional clinical scoring systems and captures the effects of the disease on patients and their families.

Current knowledge
Atopic dermatitis has a large impact on quality of life, regardless of the age of the patient. Patients with the disease have inferior scores not only on symptoms, but also on social functioning and mental health. The severity of pediatric atopic dermatitis also has a significant negative impact on the physical and mental health of the families of these infants, particularly the mothers. If properly managed, the disease symptoms can be kept under control and patients are able to lead normal lives.

Practical implications
Health-related quality of life assessments not only evaluate qualities directly related to the disease, but also those that are indirectly related to the disease but that may be affected by it. The latter are often neglected by disease severity indexes. It is important to note that the instruments designed to measure quality of life usually assess patients’ current experiences and are not designed to assess the long-term impact of disease, which may change over time. Treating physicians should include a quality of life assessment as part of the treatment and follow-up for children with atopic dermatitis.

Recommended reading
Atopic Dermatitis

Carlos Lifschitz

Department of Pediatrics, Section of Gastroenterology, Hepatology and Transplantation, Hospital Italiano, Buenos Aires, Argentina

Key Messages

- Atopic dermatitis (AD) is a chronic disease. Because it affects the skin and produces itching, the quality of life (QoL) of the patient and family can be affected.
- AD has an impact on health-related QoL, particularly on social functioning and psychological well-being.
- Treating physicians should include QoL assessment when managing children affected by AD.

Key Words

Atopic dermatitis · Quality of life · Health-related quality of life

Abstract

Approximately 5–20% of children worldwide suffer from atopic dermatitis (AD), a kind of dermatitis characterized as an inflammatory, relapsing, noncontagious and itchy skin disorder. Children often develop AD during their first year of life. An increased rate of sensitization to both food and aeroallergens has been shown to coexist in patients with AD. Sensitization to well-known allergens such as cow’s milk protein can occur on average in 50% of children with AD. In general, quality of life (QoL) is perceived as the quality of an individual’s daily life, that is, an assessment of their well-being or lack thereof. QoL is a broad concept that includes such things as standard of living, community, and family life. Patients with skin diseases experience a wide range of symptoms ranging from trivial problems to major handicaps which affect their lives. The misery of living with AD cannot be overstated for it may have a profoundly negative effect on the health-related QoL of children and their families in many cases. Physicians taking care of children with AD should consult parents on how their child’s illness has impacted their lifestyle and recommend professional intervention if deemed necessary.

Introduction

Atopic dermatitis (AD), also known as atopic eczema or simply eczema, is a kind of dermatitis characterized as an inflammatory, relapsing, noncontagious and itchy skin disorder. Children often develop AD during their first year of life. The disease is characterized by the presence of dry and scaly patches on the skin of the scalp, forehead, and face, particularly the cheeks, flexor surfaces of arms, torso, etc. (table 1). AD is often very itchy. Infants...
Impact of AD on Quality of Life

**Table 1. Skin manifestations found in AD**

<table>
<thead>
<tr>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic pleat (Dennie-Morgan fold) – an extra fold of skin that occurs under the eye</td>
</tr>
<tr>
<td>Cheilitis – inflammation of the skin on and surrounding the lips</td>
</tr>
<tr>
<td>Hyperlinear palms – palms with an increased number of skin creases</td>
</tr>
<tr>
<td>Hyperpigmented eyelids</td>
</tr>
<tr>
<td>Ichthyosis – skin with dry, rectangular scales</td>
</tr>
<tr>
<td>Keratosis pilaris – small, rough bumps, present on the face, upper arms, and thighs</td>
</tr>
<tr>
<td>Lichenification – thick, leathery skin resulting from constant scratching and rubbing</td>
</tr>
<tr>
<td>Papules – small raised bumps that may open when scratched and become crusty and infected</td>
</tr>
<tr>
<td>Urticaria – hives (red, raised bumps) that may occur after exposure to an allergen, at the beginning of flares, or after exercise or a hot bath</td>
</tr>
</tbody>
</table>

may rub their skin against bedding or carpeting to relieve the itch. In children of all ages, the itch can be so intense that they cannot sleep. Scratching can lead to skin infection.

Approximately 5–20% of children worldwide suffer from AD [1]. The incidence of AD seems to be increasing. AD affects all races and geographic locations. However, the incidence seems to be higher in developed countries and mainly in urban areas, especially Western societies [2].

The cause of AD is not known. There is some evidence that genetic factors and probably growing up in a ‘sanitary’ environment (hygiene hypothesis) may predispose to the development of AD [3]. Regarding the genetic predisposition, many patients affected by AD have a family history of atopy, such as asthma, food allergies, AD, or hay fever. Approximately 80% of children with AD may also develop asthma and/or allergic rhinitis later in childhood [4]. An increased rate of sensitization to both food and aeroallergens has been shown to coexist in patients with AD. Sensitization to well-known allergens occurs on average in 50% of children and 35% of adults with AD [5]. At the skin level, food allergies are manifest mainly in two ways: urticaria/anaphylaxis and food-exacerbated AD. Only food-induced AD will be briefly discussed here. In food-exacerbated AD reactions, ingestion of the food, for example cow’s milk protein, can cause an exacerbation of the patient’s symptoms of AD such as erythema and pruritus of the skin lesions. If the reaction is mediated by immunoglobulin E (IgE), symptoms occur almost immediately and up to a few hours after exposure. However, symptoms may take hours to days to manifest if the reaction is non-IgE mediated. If the culprit food is eaten repeatedly, the subject may present chronic lesions.

Infants with AD may have cow’s milk protein allergy if they also have a history of vomiting, diarrhea, and/or failure to thrive [6]. Approximately 30% and up to 80% of patients with AD may be sensitized to one or more food items. However, the percentage of patients exhibiting symptoms is much lower (15%) [6]. Food-induced AD may be found in 1–3% of children who have mild disease, in 5–10% among those with moderate disease, and in up to 20–33% in those with severe AD [7]. Food-exacerbated AD is rare in adults.

AD coexists in one third of children with recurrent infections, and they present with recurrent rhinitis, cough, and even wheezing following common viral upper respiratory infections. It is important to note that primary immunodeficiencies and allergic disease can coexist [8]. Immunoglobulin A deficiency is a relatively common problem, which is usually asymptomatic and could be associated with celiac disease and atopic disorders. Other immunodeficiencies with associated atopy include common variable immunodeficiency, chronic granulomatous disease, and DiGeorge syndrome.

Quality of Life

In general, quality of life (QoL) is perceived as the quality of an individual’s daily life, that is, an assessment of their well-being or lack thereof. QoL is a broad concept that includes such things as standard of living, community, and family life [9]. Family functioning affects emotional and behavioral functioning of children, which may result in lower ratings on social functioning and well-being QoL domains. Parental and child depression has been linked to lower QoL ratings. Parental stress is also related to lower patient QoL scores. QoL may be affected by personality, education, employment, financial and social situation, as well as medical issues. Health-related QoL (HRQoL) assesses qualities directly related to the disease as well as those that are independent of the disease but may be affected by it. The latter are often neglected by disease severity indexes [10]. HRQoL gives a clearer picture of health than do disease parameters. The greatest difficulty in assessing HRQoL in an infant is that one needs to ask the parents to estimate the loss of quality in the life of their infants, as obviously infants cannot communicate their QoL loss. The literature on QoL has increased substantially over the past decade, whereas before, medical concerns were mainly centered on issues...
such as prevention, cure, and costs. Most of the literature focuses on reduction of cases, improvement of symptoms, or money saved by a particular vaccine or treatment. Impact on QoL includes all emotional, social, and physical aspects of an individual’s life which, in the case of pediatrics, affect not only the patient but also the family. Although chronic, debilitating illnesses are the ones that will affect patients’ QoL the most; even milder illnesses such as AD may affect QoL over time.

Even milder illnesses such as AD may affect QoL over time.

The interest in QoL has not only expanded recently, but it has also deepened concerning the assessment of QoL. The first attempts to measure HRQoL consisted of straightforward evaluations of physical abilities by an external observer, such as whether the patient was able to sit up, walk, take care unassisted of a basic need, or, for some illnesses, they quantitated certain aspects of the impairment, for example, the angle to which an arm or leg could be extended or flexed. In the past decade or so, the current concept of HRQoL has added, for older children and adults, the concept of how their actual situation differs from their own expectations. So, obviously, two individuals with almost exactly the same symptoms of a disease may have very different QoL assessments depending on their past medical and family history as well as family, friends, social support, well-being in other areas not related to their illness, etc. In addition, QoL may vary over time, reacting to changes in external situations. For example, an infant with AD with multiple skin lesions and itching might be handled with patience by the parents. Although afflicted, their life is not what they would have thought it would be, but they still can cope and handle it. Suddenly, the baby’s skin manifestations worsen, the skin is itchy, the baby cries all night, and the parents cannot sleep. The father or mother performs poorly at work because of their worries and lack of sleep. Mistakes are made at work, they get reprimanded or even fired, and their whole QoL is profoundly affected by just the worsening of the baby’s AD. Alternatively, a child’s AD might not worsen much, but a close relative may get ill and, all of a sudden, the problem of AD becomes overwhelming and QoL is affected. As with any situation that involves multiple perspectives, patients’, friends’, and physicians’ ratings of the very same situation may differ significantly. For this reason, the area of QoL has evolved into developing validated questionnaires directed to the patients and/or their families. In general, such questionnaires are directed towards evaluating multiple aspects of an individual’s life such as emotional, social, cognitive, work- or role-related, and even spiritual aspects as well as physical symptoms, treatments, and financial aspects [11].

One important aspect of certain chronic illnesses is the impact that they have on certain life decisions such as social or sport activities that are avoided, places not to go on vacation, jobs not accepted, etc. There are many published surveys assessing the impact of chronic diseases on patients’ QoL. However, these studies have not addressed the long-term impact of chronic diseases on critical life decisions taken by patients [12].

Instruments to measure QoL usually assess patients’ current experiences and are not designed to assess the long-term impact of disease, which may change over time. Even follow-up studies, which might be expected to encompass more long-term issues, usually compare current impacts before and after a given intervention. In the study by Bhatti et al. [12], adult dermatology patients explained how their chronic disease had influenced major life-changing decisions. The authors evaluated 308 responses (mean age 51.8 years, mean disease duration 19 years). The most frequently reported major life-changing decisions in the dermatology interviews concerned career choice (66%), job (58%), choice of clothing (54%), relationships (52%), education (44%), stopping swimming (34%), moving abroad (32%), not socializing (34%), wearing make-up (22%), and having children (22%). It could be argued that this type of situations concerns more adults with chronic dermatological illnesses than children, but indirectly it may also concern children. For example, parents of an infant with eczema may opt not to go on vacation to the beach because the warm weather may worsen their child’s symptoms or a mother may decide not to go back to work after maternity leave in order to take care personally of her child affected by AD. Although the impact of disease on patients’ QoL is recognized as important in health care, the impact of illness on those living with the patient has largely been overlooked [13]. There are specialty and disease-specific studies related to the impact of illness on patients’ family members in dermatology (see Basra et al. [14], among others). These studies have shown that the impact of illness on families is widespread and severe and that few families are offered appropriate support. In a study exploring family QoL in dermatology, the emotional impact on the family was found to be the most commonly affected area, with 98% of family members interviewed...
reporting a degree of emotional distress as a result of the patient’s illness [15].

Another aspect that may have long-term consequences on the upbringing of a child is the parental perception of the child’s vulnerability. A recent study aimed to assess the prevalence of parental perception of a child’s vulnerability in a Dutch community-based sample and its relationship with children’s health and HRQoL [16]. In the study, parents of 520 Dutch children aged 5–18 years completed the Child Vulnerability Scale and a sociodemographic questionnaire. In all, 69 (13.3%) children had a chronic illness; 1.9% of children were perceived as being vulnerable, 3.0% in the group aged 5–7 years and 1.7% in the groups aged 8–12 and 13–18 years. Younger age of the child, presence of a chronic illness, and low QoL were associated with parental perception of the child’s vulnerability.

Anxiety and depression may also affect parents of a chronically ill child. Van Oers et al. [17] found that mothers of a chronically ill child (n = 566) scored significantly higher than the reference group (p < 0.001) on anxiety (mean 5.9 vs. 4.8) and depression (mean 4.5 vs. 3.1). Fathers (n = 123) had higher depression scores (mean 4.5 vs. 3.6; p < 0.05). Interestingly, illness-related characteristics of the child were not related. The authors concluded that parents of a chronically ill child, especially mothers, reported high levels of anxiety and depression.

Although not necessarily pertinent to the topic of AD in infants and young children, another issue that is important in determining QoL in pediatrics is the agreement between parents and their children in assessing the impact of the disease in question. For the impact of infantile asthma on QoL, for example, studies have shown that providers should ask both children and their caregivers about the effects of asthma on the child’s QoL, especially with regard to disease effect on activity limitation [18, 19]. These data further contribute to increasing evidence that caregiver reports cannot be used in place of a child’s report about disease-specific QoL [20]. Our own study in children with inflammatory bowel disease was aimed to evaluate the degree of concordance between parent and child ratings of HRQoL [21]. The IMPACT-III questionnaire was used to measure QoL in 27 patients (mean age 14.2 ± 3 years) and one of their parents [21]. Results indicated that parent proxy and patient ratings were similar on total IMPACT-III and its related domains (bowel symptoms, systemic symptoms, social functioning, body image, and treatment/interventions), except that significant differences on emotional functioning ratings were found (p = 0.003). In our study, parents served as a good proxy for QoL ratings in this population of pediatric patients with inflammatory bowel disease. The degree of concordance between parent and child scores, however, varied in that parents underreported their child’s HRQoL on the emotional functioning domain.

**AD and QoL**

Patients with skin diseases experience a wide range of symptoms ranging from trivial problems to major handicaps which affect their lives [22–25]. Lewis-Jones [26] stated that ‘the misery of living with AD cannot be overstated for it may have a profoundly negative effect on the HRQoL of children and their family unit in many cases’. As AD is one of the most common chronic relapsing childhood dermatoses (UK lifetime prevalence 16–20% by 20 years), with an increasing worldwide prevalence, this has major social and financial implications for individuals, health-care providers, and society as a whole.

The good news is that even if symptoms of AD can be uncomfortable and at times difficult to control, the disease in general can be successfully managed and in some cases even prevented [27]. Individuals affected by AD can lead almost normal lives. Having stated this, it needs to be kept in mind that children affected by AD can impact negatively on the entire family’s QoL. A child may be fussy and difficult to handle and parents may be unable to keep the child from scratching and rubbing the skin. Although distraction of the child and creating activities that keep hands occupied may be helpful, these require much effort and constant attention from the parents or caregivers. Another issue families face is the social and emotional stress associated with changes in appearance caused by AD. The child may experience difficulties in the nursery, day care, or school which they may be unable to understand. Older children may require additional support and encouragement from family members (table 2).

Quantification of QoL related to disease severity is important in patients with AD, because the assessment provides additional information to the traditional objective clinical scoring systems. McKenna and Doward [28] were surprised that, given the prevalence of pediatric AD and its impact on affected children and their families, so little attention had been devoted to the impact of treatment on
QoL. Six years have elapsed since that observation and, still, the literature is scarce on this topic. Whenever standardized measures are included in studies, they generally assess outcomes that are of greater interest to physicians than to patients and their caretakers. As stated above, measuring QoL associated with pediatric AD is particularly problematic due to the fact that a high proportion of study participants are too young to provide information about their own QoL. For this reason, McKenna et al. [29] developed the Parents’ Index of QoL in Pediatric AD (PIQoL-AD). This is a needs-based measure of QoL that assesses the impact of the child’s AD on their main caregiver. Example items from the PIQoL-AD are listed in table 3.

Holm et al. [30] measured HRQoL in patients with AD to analyze discriminant, divergent, and convergent validity by examining the association between various QoL methods and to examine the association between disease severity assessed by an objective Severity Scoring of Atopic Dermatitis (SCORAD) and QoL. HRQoL was assessed at two visits at a 6-monthly interval in 101 patients with AD and 30 controls with one dermatology-specific questionnaire [Dermatology Life Quality Index (DLQI) or Children’s DLQI (CDLQI)], one generic instrument (SF-36), and three visual analogue scales of severity and pruritus. Objective SCORAD was used to measure disease severity. Thirty-five children aged 3–14 years were included. Results showed that patients with AD had significantly lower QoL than healthy controls and the general population. DLQI/CDLQI, pruritus, and patient and investigator overall assessment of eczema severity were significantly (p < 0.0001) and positively correlated with SCORAD, while the generic questionnaire showed only poor correlation. The authors concluded that AD has an impact on HRQoL. Patients’ mental health, social functioning, and emotional role functioning seem to be more affected than physical functioning. Patients scored their disease as more severe compared with the investigator assessment. High correlations were found between patient and investigator assessments of severity, although patients scored their disease as more severe compared with the investigator. This difference was significant.

The impact of AD on the mother’s health was studied in Singapore [31]. The study examined maternal perceptions of pediatric AD and its impact on the family and determined risk factors including severity of AD, maternal physical and mental health, QoL of patients, and sociodemographics which predict a negative family impact. One hundred and four patients with AD and their mothers were studied. Their mean age (± SD) was 6.4 ± 4.3 and 37.2 ± 6.6 years, respectively. In multiple regression analysis, SCORAD appeared to be associated with a negative family impact and the association remained significant after adjustment for physical and mental health of the mothers. The authors concluded that the severity of pediatric AD leads to a negative family impact through reduction of physical and mental health of the mothers and is independent of patients’ HRQoL and sociodemographics. They recommended that the current approach for managing pediatric AD in Asian society should include early multidisciplinary intervention, aiming at enhancing physical and mental health of mothers, while minimizing the negative impact on the family and social isolation.

A study from Japan also looked at the impact of AD on QoL [32]. The authors used the Japanese version of Skin-dex-16 in a cross-sectional and longitudinal questionnaire study on 162 adult patients. Three to six months

<table>
<thead>
<tr>
<th>Table 2. Assessment of QoL (adapted from McKenna et al. [29])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Impairment (i.e. anxiety, depression, pain, itch, and problems with sleep): loss or abnormality of psychological, physiological, or anatomical structure or function; impairment is related to symptoms</td>
</tr>
<tr>
<td>2 Activity: ability of an individual to function (i.e. dressing, walking, personal care, or taking part in sports) as expected; activity includes physical, emotional, social, or other types of functioning</td>
</tr>
<tr>
<td>3 HRQoL relates to the effects of a combination of impairment and disability</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Integrated issues related to PIQoL-AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>- I have to be careful what she/he wears</td>
</tr>
<tr>
<td>- I never get a good night’s sleep</td>
</tr>
<tr>
<td>- I feel I have little freedom</td>
</tr>
<tr>
<td>- All my attention has to go to her/him</td>
</tr>
<tr>
<td>- I worry about the way she/he looks</td>
</tr>
<tr>
<td>- It is difficult to find time for shopping</td>
</tr>
<tr>
<td>- There is a lot of tension in the family</td>
</tr>
<tr>
<td>- She/he is very moody</td>
</tr>
<tr>
<td>- She/he cannot be comforted</td>
</tr>
<tr>
<td>- She/he is very demanding</td>
</tr>
<tr>
<td>- She/he misses out on a lot of childhood activities</td>
</tr>
<tr>
<td>- Other children don’t like holding her/his hand</td>
</tr>
</tbody>
</table>
after the initial testing and treatment, 135 (83.3%) of the patients again completed Skindex-16 and also answered a general question about whether their skin condition had improved, had remained the same, or had become worse. The scores of Skindex-16 of 162 patients with AD were significantly higher than those of patients with isolated lesions, particularly in the symptoms and emotions scales. Patients with severe AD showed significantly higher scores on the three scales (symptoms, emotions, and functioning), and there was a significant positive correlation between the severity and the three scale scores. Among the patients whose dermatitis had improved, the scores of Skindex-16 significantly decreased. On the other hand, patients who reported that their dermatitis had become worse showed an increase in the scores.

It is obvious that the impact of AD on QoL affects people of all ages. Another study that included 239 AD patients aged 4–70 years showed that patients with AD had inferior scores on vitality, social functioning, and mental health subscales compared with individuals in the general population [33]. Patients with AD had inferior mental health scores compared with those with diabetes or hypertension and inferior social functioning scores compared with patients with hypertension. When compared with a psoriasis cohort, patients with AD had inferior scores in the physical role, vitality, social functioning, emotional role, and mental health domains.

Finally, an international study performed in the Czech Republic, Singapore, Brazil, the Netherlands, and South Korea on QoL and family QoL in children with AD found a similar impact of the disease as rated by parents of 419 children under the age of 4 years in all countries [34].

**Patients with AD had inferior mental health scores compared with those with diabetes or hypertension and inferior social functioning scores compared with patients with hypertension.**

**Conclusion**

Results from multiple studies demonstrate that AD has an impact on HRQoL, particularly on social functioning and psychological well-being. Patient-assessed severity of AD correlates with HRQoL decrements, indicating a greater HRQoL impact with greater disease severity. AD has as large an impact on HRQoL as several chronic conditions and other dermatologic conditions.

**Disclosure Statement**

The author declares no conflicts of interest. The writing of this article was supported by Nestlé Nutrition Institute. The author has participated as a clinical investigator and/or is an advisory board member and/or consultant and/or speaker for Nestlé, Nestlé Nutrition Institute, Mead Johnson, Ipsen Pharma, and Seqouia.

**References**


