DERLEME / *REVİEW*

Atopic Dermatitis and New Approaches for Treatment: Review

ATOPİK DERMATİT VE TEDAVİDE YENİ YAKLAŞIMLAR

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Abstract

Atopic dermatitis is a hereditary, chronic inflammatory skin disease of which the etiology is yet unknown. Although its prevalence is rising in the industrialized countries, the risk factors are also not well described. Food allergy and some diets are still controversial risk factors in the etiology and are believed to play a role especially in children until the age of 5 years. Although most cases of atopic dermatitis are mild, the disease may be severe and widespread with a prominent impact on morbidity including the psycho-social life of child. The clinical features seem to be age-related. Atopic dermatitis is known as a chronic-relapsing disease that often requires an individualized therapeutic approach. Various treatment options that address known pathogenetic pathways when used in combination are often very successful. Financial costs of taking care of atopic dermatitis may be very high, stressing the importance of the health care system.

Key Words: Atopic dermatitis, eczema, childhood, immunomodulators, tacrolimus, pimecrolimus

Özet

Atopik dermatit sebebi bilinmeyen, kronik, inflamatuvar ve genetik faktörlerin rol oynadığı bir hastalıktır. Gelişmiş ülkelerde prevalansı giderek artmaktadır. Gıda allerjileri, ve diyetin rolü tartışmalıdır. Ancak özellikle 5 yaşına kadar çocuklarda önemli olduğu düşünülmektedir. Çoğunluğu hafif seyretmekle beraber ağır ve yaygın tutulumlu olguların psikososyal hayatı ve morbidite önemli ölçüde etkilenir. Klinik özellikler yaş ile de ilgilidir. Kişiselleştirilmiş tedavi yaklaşımları gerektirir ve kronik relapslarla gider. Bilinen patolojik yollara yönelik çok sayıda tedavi yaklaşımı vardır. Genelde kombine tedaviler daha başarılı olmaktadır. Atopik dermatitlinin tedavi maliyeti yüksek olup, sağlık sisteminin önemini bir kez daha ortaya koymaktadır.

Anahtar Kelimeler: Atopik dermatit, egzema, çocukluk dönemi, immunomodulatörler, takrolimus, pimekrolimus

Turkiye Klinikleri J Pediatr 2007, 16:38-49

Atopic dermatitis (AD) is primarily a childhood disease. Since the main and most bothering symptom is itch, it is sometimes even referred as ``itch that rashes``. It is also called eczema and it may ooze, or at times may look very dry. The red, scaly, itchy rash is characteristic of the disease and may cause intense scratching. Scratching may be intermittent during the day but it is generally worse in the early evening and at night. Nocturnal pruritus is a common symptom of AD. Disruption of normal sleep pattern is also common.

The typical rash appears mostly on the face, trunk and extensor surfaces. In adults the flexural lichenification and linearity is common, but in infants and children facial and extensor involvement are more frequent (Figs.1a-c). The infantile form of AD is characterized with rashes consisting of papules and vesicles on cheeks. It can spread symmetrically to neck, elbows, forearms, wrists, ankles, the antecubital/popliteal cavities and buttocks. However, the diaper area is generally not involved. Papulation mostly apparent on the extensor surfaces is quite common whereas exudation is less frequent between ages 2 and 12.

Geliş Tarihi/*Received:* 20.12.2005 **Kabul Tarihi/*Accepted:*** 18.09.2006

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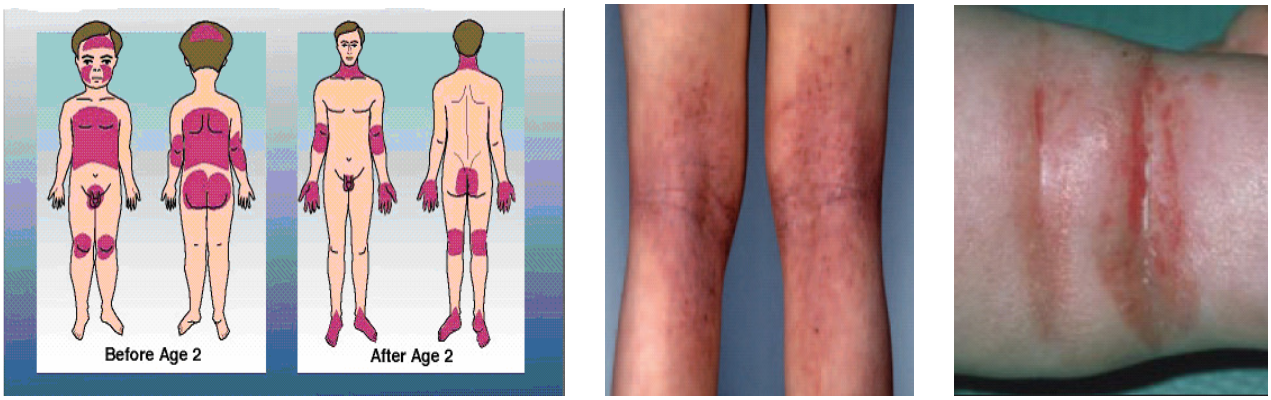

Figure 1a, b and c. Distribution pattern of eczema and flexural (popliteal) involvements in children.

In older children, AD does not occur on axillary and gluteal areas.

A family history of atopy, early-age onset, chronic relapsing dermatitis with a typical morphology/distribution as well as pruritus are typical characteristics of AD. Although less common, some minor symptoms such as increased serum IgE, dry skin (xerosis), ichthyosis, intolerance to wool, itch when sweating, palmar hyperlinearity, keratosis pilaris, pityriasis alba, hand/ foot dermatitis, cheilitis, susceptibility to cutaneous infections, perifollicular accentuation, postauricular cracks, wrinkles on the skin under eyes (Dennie-Morgan folds), orbital darkening, recurring atopic keratoconjunctivitis, keratoconus and anterior subcapsular cataract are also described. Nipple dermatitis is rare among young women, but it still is a specific sign of AD. A white dermatographism or delayed blanch also exists and may contribute to the assessment of AD in infancy. Three major and three minor findings are required for a definitive diagnosis.[1] The major diagnostic criteria proposed by Hanifin and Raika are I-) visible flexural dermatitis, II-) family or personal history of atopy, III-) itching, and 4-) intermittent course of disease.[2]

The prevalance is increasing and ≈ 10-15% of the population is predicted to be affected by AD during childhood. According to the International Study of Asthma and Allergies in Childhood, the prevalence of symptoms of AD in children 6 or 7 years of age within a one-year period varied from less than 2% in Iran and China to approximately 20% in Australia, England, and Scandinavia.[3] A high prevalence was detected in the United States also. In the United Kingdom, a population survey of 1760 affected children from one to five years of age revealed that 84% of cases were mild, 14% were moderate, and 2% were severe.[4] The onset of AD is generally during the first years of life. Approximately 65% of AD cases develop before the age of one and 90% occur before the age of five. None of the signs is present during or before birth. The disease very rarely starts during the first 6-7 weeks of life.

Genetic and environmental factors are believed to play important roles in the onset of the disease. Hereditary factors are suggested to be responsible for most of the cases. An exact gene locus of AD is not yet defined although some genes were suggested. SPINK5 gene polymorphism and GM-CSF genes are associated with disease severity and food allergy in children with AD.[5,6] Reports suggest that genes cause AD by affecting the immune system leading to skin symptoms. Although termed atopic, it is known that up to 60% of children with the clinical phenotype do not have demonstrable IgE-mediated sensitivity to allergens. There is a subgroup of AD patients with normal total and specific IgE levels and negative skin tests for common allergens; this group is referred to as the **'intrinsic'** form of AD. Although previous studies demonstrated differences in the cytokine profile between the **`extrinsic`** and intrinsic subtypes, the overall inflammatory microenvironment in the two subtypes appears to be similar. However; strikingly, AD may be the initial clinical

manifestation of an allergic predisposition, usually preceding allergic rhinitis and asthma. This is called as `**atopic march**`. More than 50% of AD patients develop asthma. Approximately 75% of AD patients develop allergic rhinitis.[7,8]

AD develops from a complex interplay of environmental, genetic, immunologic and biochemical factors. The pathogenesis of AD is a complex inflammatory process involving resident/infiltrating cells of the skin, including keratinocytes, Langerhans' cells, lymphocytes, mast cells, eosinophiles, and cytokines, chemokines, and other mediators. However, T cell-mediated responses against environmental allergens appear to be a central pathogenetic event in many AD patients, with IgE-mediated uptake of allergens by skin dendritic cells playing an important role in eliciting and maintaining T cell activation in the skin. The skin lesions are mediated by a combined response of an IgE-dependent mast cell degranulation and the responses mediated by Th2 lymphocytes.[8](Bu cümlenin fiili yok) As with other allergic diseases, the inflammatory infiltration reflects a predominant Th2 cytokine profile, but unlike in other allergic diseases, Th1 cytokines also have a role in the chronicity of disease.[9,10] Therapies for AD must target this complex inflammatory process.

Differential Diagnosis

Skin biopsy has little value in the diagnosis of AD. Diagnosis is based on clinical features. A physician rarely has difficulty in the diagnosis of AD. The diagnosis is based on three factors: an 1) itchy, 2) "eczematous" or bubbly rash in an 3) atopic individual. If one of these three features is missing, the physician should reconsider the diagnosis.

The most common skin problem is **seborrheic dermatitis of infancy**. The distinctive characteristic of this type of dermatitis is its appearance right after birth. The rash may be minimally itchy or not. Red, shiny, relatively well-demarcated eruptions typically involving the diaper area are also present on the lower abdomen and armpits. Thick, yellow, greasy scales develop on the scalp (scalp scaling, cradle cap), face and the extensor surfaces. The skin behind the ears appears dried and cracked.

Patients with **scabies** generally suffer from the dermatitis seen on the scalp, axilla, genital areas, hands (palms) and feet (soles). The most important indication of scabies is the eczema that affects other family members also. Scabies presents with linear papulovesicules, burrows and pustules, and its typical appearance between the fingers of babies help to establish diagnosis.

Idiopathic **(discoid) nummular dermatitis** typically develops during late childhood and adulthood. Round, coin-shaped cracked" areas of erythema with a 1-5 cm diameter may be present on the gluteal and extensor surfaces but lacking on the face (Fig. 2a, b). In children, discoid eczema is most commonly associated with AD and is often confused with tinea infection (ringworm).

When some substances contact the skin, they may cause a rash called contact dermatitis. Some of these reactions are the result of an allergic reaction that involves the immune system, but many are the result of a non-allergic, or irritant reaction. Often, it is difficult to tell the difference between these 2 types of reactions. The hallmark of **allergic contact dermatitis** is that it occurs almost exclusively, where the offending agent-such as a plant or chemical-comes in contact with the skin. Allergic contact dermatitis is best exemplified by the itchy, red, blistered reaction that almost everyone experiences after touching a plant in the "rhus" family-poison ivy, poison oak or poison sumac.[11] A reaction may also develop from touching other items with which the plant has come into contact, including yard tools or the family dog. However, once the skin is washed, the reaction does not recur due to touching the rash or blisters. Unlike irritant contact dermatitis, which occurs within minutes of coming into contact with an offending agent, allergic contact dermatitis reactions may occur within 24-48 hours after contact. Once a reaction starts, it takes 14-28 days to resolve, even with treatment. Other agents that frequently cause allergic contact dermatitis include nickel (Fig. 3), perfumes and fragrances, dyes, rubber (latex) products and cosmetics. Some ingredients in medications applied to the skin, most commonly neomycin, an ingredient in antibiotic creams, also may cause an allergic reaction. To

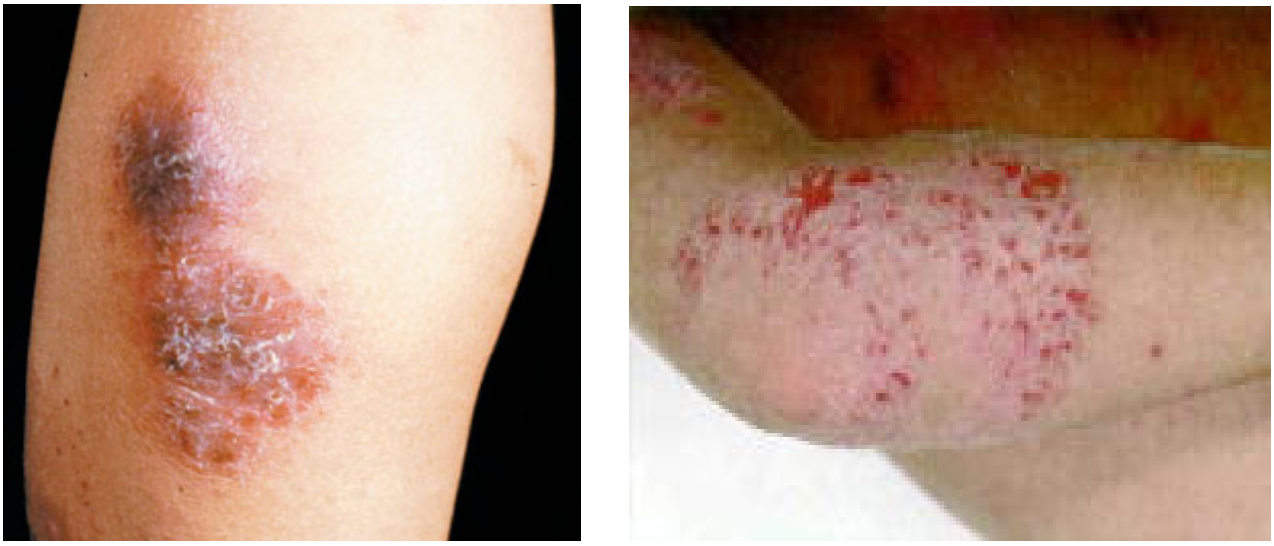

Figure 2a and b. Discoid (nummular) eczema in an infant. This pattern of eczema is frequently associated with AD and is often confused with ringworm infection.

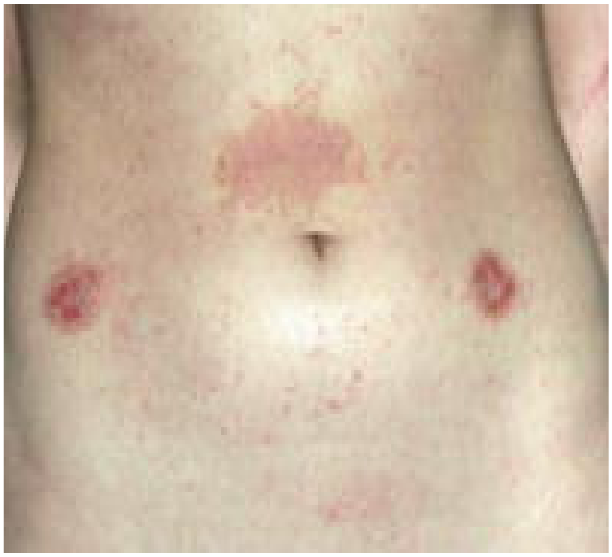

Figure 3. Allergic contact eczema due to nickel in studs and buttons on jeans in a child.

avoid reactions, any cream that ends in "caine" should never be applied to damaged skin.

Irritant contact dermatitis is often more painful than itchy, and is the result of an offending agent that actually damages the skin with which it contacts. The clinical appearance may be identical to that of AD, but location at sites of maximal exposure (e.g., fingers) may be helpful in making the diagnosis. The longer the skin is in contact-or the more concentrated the agent-the more severe the reaction. Water with added soaps and detergents is the most common cause. Thus, it is not surprising that these reactions appear most often on the hands, and are frequently work-related. Individuals with other skin diseases, especially eczema, are most susceptible. Some degree of irritant contact dermatitis is common in persons with AD (e.g., in babies, around the mouth, due to saliva and wet food, and in the diaper area, due to urine).

Special care should be taken to rule out the **congenital immunodeficiency** diseases often presenting with eczematous symptoms, which are usually seen in conjunction with recurrent infections and are generally resistant to traditional topical treatment. The most well known is the Wiskott Aldrich syndrome, but also others may be involved such as the hyper IgE/ Job's syndrome, combined variable immunodeficiency, Shwachman syndrome, and immunoglobulin deficiencies.[12] Moreover, diseases like chronic granulomatous disease and ataxia teleangiectasia may rarely manifest as eczematous reactions.

Some patients with AD have quite high IgE levels, generally when the AD is long-standing, with extensive skin involvement and often when complicated by a staphylococcal infection of involved skin areas. If the AD is relatively quiescent and localized to just a few skin areas, one must be sure that the

very high serum IgE levels are due to another condition. The first condition that comes to mind is the **hyper-IgE syndrome**. This is an unusual disorder characterized by a rash, which may resemble that of AD. However, there are generally recurrent folliculitidis/skin abscesses (hence the common name-Job/ Buckley syndrome), predisposition to certain other infections such as candidiasis and staphylococcal infections of the skin and the respiratory tract, and/ or a fine papular erythematous eruption with superficial vesicles and pustules on the face, scalp and body folds, especially on the axillae and groin areas. In addition, often skeletal/dental abnormalities are present in the autosomal/dominant form.[13] Eosinophilia is also common in the hyper-IgE syndrome (but may also be present in active AD). Some groups reported very high levels of serum IgE antibodies against S. aureus antigens in the hyper-IgE disorder. The patient should be questioned about the possible occurrence of a similar clinical picture in immediate family members. If the patient comes from a geographic area with heavy parasitism, this possibility should also be considered as a cause of very high serum IgE levels. Trichinosis is a consideration but its rash is usually urticarial. Onchocerciasis/filariasis may cause skin rashes as well as markedly increased IgE levels. The pruritic skin rash in schistosomiasis generally occurs only in those frequenting bodies of water in which the snail carriers of the parasite live.

Diagnostic Procedures

A diagnostic laboratory test of AD is not available. Skin biopsy is of little or no value in the diagnosis of AD. Radioallergosorbent test (RAST) is quite expensive and not reliable. There is a high frequency of elevated IgE levels but the exact role of IgE in the pathogenesis is not clear. Approximately 85% of AD patients may have elevated IgE with positive skin prick tests.[14] IgE may not be elevated in uncomplicated AD patients. IgE values of cord blood are not predictive for AD. Because of their high negative predictive value (>95%), negative skin prick or RAST tests for foods and environmental allergens may be useful for assessing the contribution of allergies to disease expression in children with severe disease.

Patch tests are useful for excluding a diagnosis of suspected superimposed allergic contact dermatitis. The clinical utility of patch testing with airborne allergens is still unclear. Defining IgE-mediated sensitivity (by skin or in vitro testing) and patch testing are useful in the differential diagnosis of atopic and contact dermatitis.[14]

Eosinophilia may be present and eosinophile counts starting to increase within 3 months after birth aids in the diagnosis of present or probable susceptibility to AD in the child. However, this is not specific for AD. Eosinophile cationic protein (ECP) is a type of protein that exists in eosonophile granules and it is elevated in serums of severe AD patients.[15] Increased number of eosonophils in blood is related to the severity of the disease. Leukocytosis may also be present. The number of IgE carrying cells tends to be increased. The level of monocytes is normal. A delay in neutrophil migration may be seen and this causes a susceptibility to staphyloccoccal infections. However, the number of basophiles and histamine contents are normal.

Soluble intercellular adhesion molecule, endothelial leukocyte adhesion molecule-1, E-/L- selectin, vascular cell adhesion molecule-1 were suggested as markers of disease activity in AD.[15,16] The importance of urinary eosinophile protein X and serum ECP were emphasized by some researchers. Furthermore, elevated serum levels of soluble CD30 was associated with AD.[17] The importance of checking leukotriene C4 and increased urinary leukotriene E4 excretion was also described.[18] Cutaneous lymphocyte antigen (CLA) expression and serum cytokine levels, especially interleukin-2 were also reported to be correlated with disease activity. Quantitative analysis of tryptase- and chymase-containing mast cells in AD was suggested as a marker for the disease.[19]

Complications

Cutaneous infections mostly caused by *Staphylococcus aureus* and *Herpes simplex* may develop. Molluscum contagiosum, verrucae, dermatophytosis may also be detected.

If the lesions are crusted and weeping pustules, then a bacterial infection caused by *S. aureus*

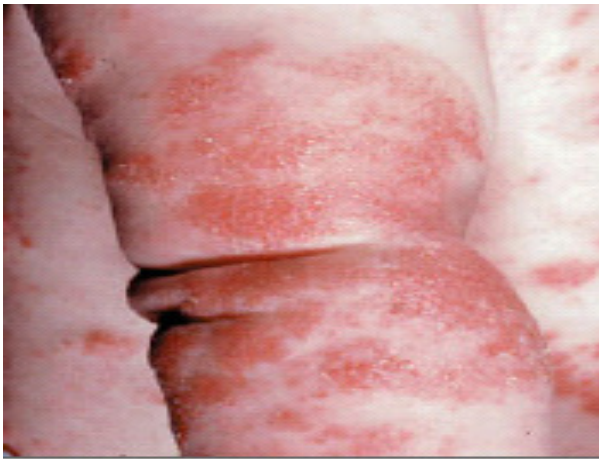

Figure 4. Acute, secondary infection in an infant with atopic dermatitis. Widespread moist, exudative lesions and crusting are present.

should be considered (Fig. 4). Ninety percent of staphylococci carried on the skin of patients with AD are resistant to penicillins.

Fungal infections mostly appear on the hands. There has been considerable interest in the role of *Malassezia furfur* (*Pityrosporum ovale*) in AD. *M. furfur* is a lipophilic yeast commonly present in the seborrheic areas of the skin such as the scalp, face, neck, and upper part of the chest. It is cultured with the same frequency from AD patients and from healthy age-matched controls, suggesting that colonization with *M. furfur* is not more common on atopic skin. However, IgE antibodies against *M. furfur* are more common in AD patients, and it is most frequently found in patients with head and neck dermatitis suggesting that the Th2 response in AD patients may predispose to IgE and hypersensitivity responses to *M. furfur*.[20]

Patients with AD have an increased propensity toward severe skin viral infections, especially *H. simplex*, which may result with Kaposi's varicelliform eruption (Fig. 5a, b). Kaposi's varicelliform eruption, or eczema herpeticum, is an acute, disseminated HSV infection with significant systemic symptoms, in patients affected by atopic dermatitis. The incubation period is a few days to 2 weeks. Dermatologic features are characterized by the eruption of multiple, pruritic vesicles and pustules in a disseminated pattern involving both eczematous and healthy skin. Systemic symptoms are fever, asthenia, and lymphoadenopathy. Viscera may be involved with subsequent mortality in 1% to 9%. An important diagnostic test is the Tzanck smear. The cytologic sample is obtained by scraping the base of a lesion to discover the presence of koilocytosis. Direct flurosecent staining of such specimens is a highly sensitive test.[20]

These patients are also prone to warts and mollusca contagiosa, a poxvirus infection. The viral manifestations of AD has recently attracted much worldwide attention because smallpox vaccination of such patients or even exposure to vaccinated individuals may cause a severe widespread skin rash called eczema vaccinatum, similar in

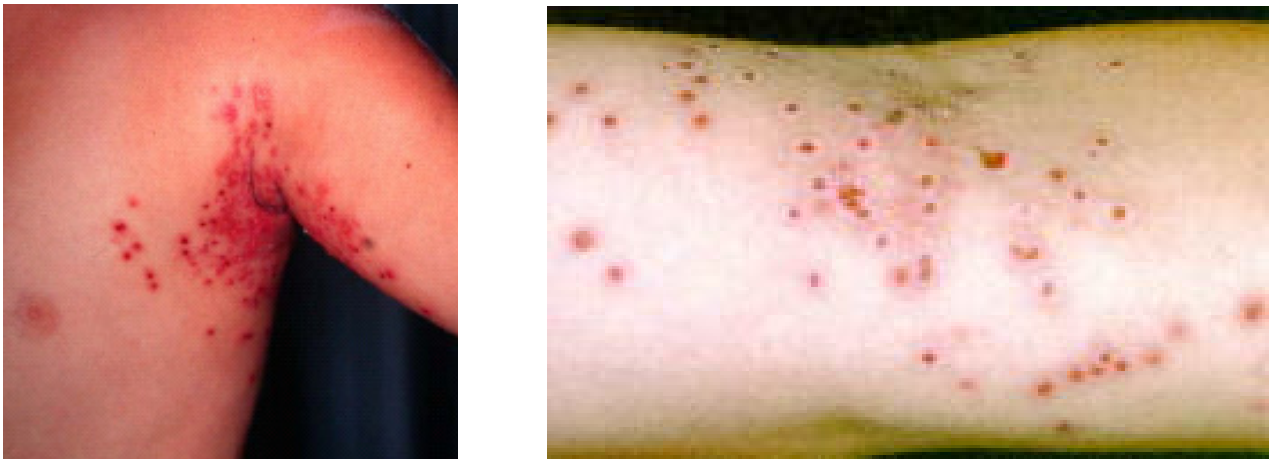

Figure 5 a and b. Herpetic vesicles, erosions, and crusts of the arm and popliteal area (**Kaposi Varicelliform Eruption**).

appearance to eczema herpeticum. The mechanisms underlying this propensity for viral infections in patients with AD likely relate to defects in innate and adaptive immune responses. Interestingly, LL-37, a skin cathelicidin recently found to be deficient in atopic skin, is a potent antimicrobial peptide with antiviral activity against vaccinia.[21]

Papular acrodermatitis (Gianotti-Crosti syndrome) is caused by hepatitis B and other viral infections. It may not need any treatment.[22]

In addition to atopic keratoconjunctivitis, retinal detachment is also rarely reported in AD patients even though the cause is not well-known.[23] A variant syndrome (Andogsky Syndrome variant) was also described as a combination of left retinal detachment with bilateral cataract and retinal degeneration.[24]

The risk of cancer/lymphoma development due to topical immunomodulators, especially tacrolimus was described recently.[25,26] Actinic reticuloid syndrome (chronic actinic dermatitis) is also known to be associated with the photosensitivity in such patients. Increase in melanocytic nevus development and/or association with the risk of skin cancers were reported too. However, this is still controversial and even some investigators reported fewer nevi development compared to the normal population.[27]

Infants affected by AD were found to have an impaired growth at 12 months of life.[28] Hypoproteinemia, hypoalbuminemia and Kwashiorkor in severe AD patients were reported.[29] Prevalence of hypertension among AD patients was also found to be higher than normal population.[30]

Treatment

Prevention is the main treatment for this allergic skin condition. By avoiding the trigger, the uncomfortable rash may be avoided all together. Preventing the eczema itch is the primary goal of treatment. Common triggers are overheating or sweating and contact with irritants such as wool, pets, soaps and food. However, long-standing lesions with thickened skin, particularly on the hands and feet, are more resistant and slower to respond to this therapy. Treatment will be described step by step in detail below:

1. Environmental Control of Allergens/ Irritants

The first step of the treatment of AD is eliminating and/or reducing contamination with allergenic foods and irritants such as avoiding from bubble bath, using too hot water, drying soaps, detergent solvents and frequent hand washing. Moreover, clothes including wool or nylon, thick-coarse fabrics, linens, and plastic beds should also be avoided. Fresh clothes should be washed to eliminate the chemical remnants of the production process and ought to be double rinsed. Staying away from dusty and dirty environment is also suggested. Patients with AD should be careful when choosing a job and working in very hot, dusty and damp workplaces e.g. food factory and bakery is not recommended. A job requiring frequent hand washing, use of detergents, solvents and caustic materials, contact with animals as well as vigorous effort is not advised. AD patients should prefer to work in offices dealing with computers, sales, banking/finance, teaching, broadcasting, etc. In addition, patients with AD should avoid from emotional or social stress and in this respect, staying away from the stressful environment is essential.[31]

Approximately 35% of young children with moderate to severe AD have food allergy; the association appears less common in adults, but is possible.[32] Allergic foods like eggs, milk, wheat, soy products, peanut and fish should be avoided. The role of early contact with allergen in the etiology of AD is debatable. Although various reports suggest that an application of allergen-free diet is not protective against AD, the studies claiming the opposite are in the majority.

The role of inhalant allergens is also disputable. Especially in hot weather, AD most likely exacerbates during the peak time of pollen season. The disease gets more severe in some patients when they lie or play on grass and when they avoid this they return to normal. Those patients develop reaction more frequently to direct contact with the grass rather than inhaling the grass pollens.

Although the effect of house dust mites is also controversial, mite allergy may trigger AD. In such patients, mite avoidance should be helpful. It is recommended to purify the living environment from the house dust mites. Woolly and furry bedding and furniture should be avoided. Carpets, curtains and other household fabrics should be washed once every 3 months and the temperature of the washing water should be no less than 55°C to be able to denature the antigens and kill the house dust mites.[33]

2. Hydration of the Skin

By bathing or soaking, the water content of the skin should be increased. Taking a shower is not effective and bathing for 20-30 minutes may be adequate. The water should be warm, but not too hot. Mild soaps or non-soap products should be used for cleansing. The skin should not be rubbed harshly. Adding sodium bicarbonate to the bathwater may alleviate the itching. The skin must be dried with a soft cotton towel patting gently. Three minutes after the bath, emollients or suitable creams should be applied. Lotions are not recommended, but water-in-oil moisturizers should be used frequently during the day.[34]

3. Anti-Inflammatory Therapy

Topical corticosteriods

Topical steroid creams are the main treatment agents for AD. Corticosteroids should be applied straight after (within 3 minutes) baths or wet compresses. Application of 1% hydrocortisone on the infected area is reliable, but may be ineffective in severe conditions. Prolonged use of these agents may cause thinning and markings on the skin. In long-term treatments of AD, steroids should not be applied daily. Steroids should be used together with other softeners. On the face and groins, weak steroids like hydrocortisone or dexametasone are recommended. On the scalp, antecubital and popliteal fossae and extremities stronger preparations like betametasone, flunisolide or diflocortolon are prescribed. On such surfaces, triamsinolone, which is a moderately effective corticosteroid not too expensive and may be applied over wide areas, is also a good choice. On severely lichenified surfaces, stronger steroids should be preferred (e.g. betametasone). On acute relapses, a potent steroid should be applied for 7-10 days and afterwards continuing with a weaker preparation for 2-3 weeks or until the symptoms disappear, is recommended. A systemic steroid is not generally necessary. In more severe cases, a carefully instituted short course of oral steroid therapy may be given and is reported to be helpful. However, if the duration is too short, the disease may recur. If steroids are systemically used for more than 3-4 weeks, they may cause skin atrophy. Application of a topical steroid two times a week is adequate for chronic AD.[35] Furthermore, controlled studies report that just once a day steroid therapy is as helpful as three times a day.[36,37]

Nonsteroid anti-inflammatory agents

Leukotriene antagonists were tried in some AD cases and a significant decrease in severity of the disease was observed. Thus, leukotriene antagonists were suggested as another option for some AD patients.[38]

The effects of tar preparations are not as fast and dramatic as the effects of steroids. Tar preparations may be considered when a nonsteroid anti-inflammatory therapy is needed. They have both antipruritic and antiinflammatory effects on the skin.[39]

Immunopharmacological agents, immunomodulators, and IVIG

The effect of the thymic hormone, thymopoietin pentapeptide (TP-5, Thymopentin) was investigated in the past in resistant AD cases and was reported to be helpful. Thymopentin also greatly inhibited IgE synthesis from peripheral blood mononuclear leukocytes of AD patients in vitro although no significant effects on serum IgE were observed. A six-week double-blind clinical trial of TP-5 produced evidence of clinical improvement via either inducing suppressor T-cell activity or reducing helper T-cell activity.[40]

Tacrolimus (FK506, protopic) is a topical immunosuppressive agent improving the clinical scoring of AD for up to 65%. When applied topically, it is suggested to inhibit T cell activation in the skin,

an action thought to play a key role in the AD inflammatory reaction. There is no systemic immunosuppressive effect and only a slight transient burning sensation at the application site during the initial use of tacrolimus. Tacrolimus is a macrolide, proved to be safe in both children and adults, and it binds to the steroid receptors and prevents mediator release from mast cells. It does not cause any skin atrophy. Significant side effects were not reported even in long-term usage of twelve months. It is used topically as a 1% ointment.[41]

Pimecrolimus (Elidel) is also a macrolide derivative and shows similar effects to tacrolimus. Pimecrolimus inhibits T-cell and mast-cell activation by blocking synthesis and release of inflammatory cytokines. Like topical tacrolimus, it does not cause skin atrophy. It seems to exhibit a high skin-specific anti-inflammatory activity with low potential for affecting the systemic immune response. In contrast to cyclosporine and tacrolimus, pimecrolimus has low potential for systemic immunosuppression in animal models.[42]

Although a couple of years ago it was reported that topical application of the immunosuppressant tacrolimus accelerated carcinogenesis in mouse skin,[25,26] recently `Topical Calcineurin Inhibitor Task Force` of the ACAAI and AAAAI concluded that the actual rate of lymphoma formation reported to date for topical calcineurin inhibitors was lower than predicted in the general population.[43]

Topical cyclosporins may be useful in AD cases resistant to topical steroids.[44] However; due to its many side effects, they are not preferred. In severe and widespread forms of the disease, systemic immunosuppressive agents including methotrexate or azathioprine may be considered.

Interferon gamma (IFN-γ) is a Th1 cytokine that in vitro suppresses IL-4-mediated IgE production and is suggested to be beneficial in AD. In a number of studies, recombinant human IFN-γ 1b (rIFN-γ) therapy proved to be effective and safe in the treatment of moderate-to-severe AD.[45]

Intravenous immunoglobulin (IVIG) also was used in severe AD. IVIG has anti-inflammatory and immunomodulatory properties and was also investigated in steroid-resistant asthma cases. IVIG was demonstrated to reduce IL-4 secretion, ICAM-1/ELAM-1 expressions and ECP serum levels in AD. IVIG proved to be safe and effective in selected severe intractable AD cases. This is a very expensive therapy, however, and should be reserved for resistant cases.[46]

4. Antipruritics

Antihistamines are standard treating agents for AD. Although they are weak and similar in effect, hydroxizine is most frequently prescribed. Since local antihistamines sensitize the skin, they are not recommended. In severe cases, doxepin is helpful for persistent itching, but its strong sedative effect is a major disadvantage. It blocks H_1 and H_2 receptors and is a tricyclic antidepressant. Such drugs are commonly used for adults. Optimal results are obtained when they are used three times a day. Topical doxepin 5% is also effective when applied locally for a week without causing any sensitization.

Phosphodiesterase inhibitors including theophylline used systemically or topically may eliminate itching. Although oral theophylline also eliminates itching, it may lose its effect after prolonged use. Cyclosporine-A may also be administered orally to reduce itching. Rheumatological dose of acetyl-salisilic acid (aspirin) is another alternative to relive lichenification.

5. Treatment of Superinfections

Macrolide antibiotics (such as erythromycin) are preferred for secondary bacterial infections of the skin. In such cases, topical antibiotics are less effective. For patients with macrolide-resistant *S. aureus*, a penicillinase-resistant penicilline (dicloxacillin, oxacillin, cloxacillin) may be preferred. First-generation cephalosporins (cephalexin, cefadroxil) are effective against both *staphylococci* and *streptococci. H. simplex* infection should be suspected when an optimum result is not achieved with oral antibiotics. In that case, a local povidone iodide therapy may be successful. In children or adults with immunodeficiency, iv acyclovir may be used 1-3 times a day with a favorable prognosis. An oral therapy of 10 days may be prescribed for

adult patients. Systemic acyclovir is also recommended for superinfection with *H. simplex* virus (eczema herpeticum) of which severe infection may be life-threatening.[47] Dermatophyte infections may be treated in one month with local imidazole or griseofulvine.[48]

6. Others

Ultraviolet (UV) radiation derived from daylight may be very useful for some patients with AD. Phototherapy with UV radiation of wavelengths between 280 and 320 nm (UV-B) is a safe and effective treatment for a variety of diseases. In addition to standard broadband UV-B, narrowband phototherapy with fluorescent bulbs emitting near monochromatic UV around 311 nm has become an important treatment for diseases such as psoriasis, AD and vitiligo.[49] However, it dries the skin and raises the temperature of the skin. As a result, the skin sweats and itches. Using sprays or swimming in a pool may eliminate the beneficial effects. In cases that cannot be treated with other therapeutic methods, UV lights may be used. However, this is not recommended for children and younsters.[50]

Allergen immunotherapy is not indicated for the treatment of AD. However, it may be considered for accompanying allergic rhinitis and asthma.[51]

Psychotherapy, hypnotherapy, special diets[52] which are rich in oleic acids are alternative therapies. Moreover, probiotics such as *Lactobacillus* GG is shown to reduce the AD symptoms.[53,54]

For the treatment of prolonged and/or severe symptoms, first, factors such as family, personal, compliance of the patient, and environmental factors should be explored in addition to threapeutic options mentioned above. Second, basic (<5 year-old children) and targeted elimination diet (consulting a specialist) should be advised when suggested by personal history. Third, a course of oral corticosteroids (0.5-1 mg/ kg/ day prednisone with tapering over 2-3 weeks) is administered to AD patients.

Prognosis

Prognosis of AD patients is quite good. AD may disappear spontaneously during adolescence or adulthood. Approximately 60% of patients with childhood AD are free of symptoms during early adolescence, although up to 50% may have recurrences in adulthood. However, early onset, severe early disease, concomitant asthma and hay fever, a family history of AD and a female gender may predict a more persistent course. One recent cohort study of 1314 German children also showed that the prognosis was related to disease severity and atopic sensitization, as evidenced by elevated serum levels of IgE antibodies to food and inhalant allergens at two years of age.[55]

Conclusion

In summary; new topical immunomodulator therapies (tacrolimus and pimecrolimus) are promising new therapies for AD. They are safe and efficacious and do not have either local or systemic side effects, which can occur with topical steroids. Other immunomodulatory therapies such as IVIG and IFN-γ may also be useful in some recalcitrant patients. Probiotics offer a potential new therapy for prevention and treatment of AD and food allergy. Although the etiology of AD remains unsolved, new therapeutic options are being developed targeting immunologic abnormalities in the pathogenesis of this disease.

REFERENCES

1. Beltrani VS. Clinical features of atopic dermatitis. Immunol Allergy Clin North Am 2002;22:25-42.
2. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatol Venereol 1980;92:44-7.
3. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998;351:1225-32.
4. Emerson RM, Williams HC, Allen BR. Severity distribution of AD in the community and its relationship to secondary referral. Br J Dermatol 1998;139:73-6.
5. Kusunoki T, Okafuji I, Yoshioka T, et al. SPINK5 polymorphism is associated with disease severity and food allergy in children with atopic dermatitis. J Allergy Clin Immunol 2005;115:636-8.
6. He JQ, Ruan J, Chan-Yeung M, et al. Polymorphisms of the GM-CSF Genes and the Development of Atopic Diseases in At Risk Children. Chest 2003;123(3 Suppl): 438S.
7. Spergel JM. Atopic march: link to upper airways. Curr Opin Allergy Clin Immunol 2005;5:17-21.

8. Wahn U. Childhood risk factors for atopy and the importance of early intervention. J Allergy Clin Immunol 2001; 107:567-74.
9. Allam JP, Bieber T, Novak N. Recent highlights in the pathophysiology of atopic eczema. Int Arch Allergy Immunol 2005;136:191-7.
10. Leung DM. Immunopathogenesis of atopic dermatitis. Immunol Allergy Clin North Am 2002;22:73-80.
11. Lee NP, Arriola ER. Poison ivy, oak, and sumac dermatitis. West J Med 1999;171:354-5.
12. Bradley M, Soderhall C, Wahlgren CF, Luthman H, Nordenskjold M, Kockum I. The Wiskott-Aldrich syndrome gene as a candidate gene for atopic dermatitis. Acta Derm Venereol 2001;81:340-2.
13. Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. Immunol Rev 2005;203:244-50.
14. Darsow U, Laifaoui J, Kerschenlohr K, et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: A European multicenter study. Allergy 2004;59:1318-25.
15. Furue M, Koga T, Yamashita N. Soluble E-selectin and eosinophil cationic protein are distinct serum markers that differentially represent clinical features of atopic dermatitis. Br J Dermatol 1999;140:67-72.
16. Chun WH, Lee HJ, Lee KH. Soluble vascular cell adhesion molecule-1 (VCAM-1) in the serum of patients with atopic dermatitis. Br J Dermatology 1997;136:136.
17. Dummer W, Brocker E-B, Bastıan BC. Elevated serum levels of soluble CD30 are associated with atopic dermatitis, but not with respiratory atopic disorders and allergic contact dermatitis. Br J Dermatol 1997;137:185-7.
18. Oh J, Lee H. Study of urinary leukotriene E4 and serum eosinophil cationic protein in children with atopic dermatitis and their correlation with disease activity. J Allergy Clin Immunol 2004;113(2 Suppl):S56.
19. Jarvikallio A, Naukkarinen A, Harvima IT, Aalto ML, Horsmanheimo M. Quantitative analysis of tryptase- and chymase-containing mast cells in atopic dermatitis and nummular eczema. Br J Dermatol 1997;136:871-7.
20. Leung DY. Infection in atopic dermatitis. Curr Opin Pediatr 2003;15:399-404.
21. Howell, Jones JF, Kisich KO, Streib JE, Gallo RL, Leung DY. Selective killing of vaccinia virus by LL-37: implications for eczema vaccinatum. J Immunol 2004;172:1763-7.
22. Ricci G, Patrizi A, Neri I, Specchia F, Tosti G, Masi M. Gianotti-Crosti syndrome and allergic background. Acta Derm Venereol 2003; 83:202-5.
23. Choo V. Why retinas detach in atopic dermatitis. Lancet 1996;347:108.
24. Margolin L, Hershko K, Garcia-Rojas M, Ingber A. Andogsky syndrome variant: Atopic dermatitis associated with bilateral cataracts and retinal degeneration with left retinal detachment. Pediatr Dermatol 2003;20:419-20.
25. Wooltorton E. Eczema drugs tacrolimus (Protopic) and pimecrolimus (Elidel): Cancer concerns. CMAJ 2005;172: 1179-80.
26. Niwa Y, Terashima T, Sumi H. Topical application of the immunosuppressant tacrolimus accelerates carcinogenesis in mouse skin. Br J Dermatol 2003;149:960-7.
27. Synnerstad I, Nilsson L, Fredrikson M, Rosdahl I. Fewer melanocytic nevi found in children with active atopic dermatitis than in children without dermatitis. Arch Dermatol 2004;140:1471-5.
28. Agostoni C, Fiocchi A, Grandi F, Torcoletti M, Giovannini M, Riva E. Infants affected by atopıc dermatitis show an ımpaırment of growth at 12 months of life. J Ped Gastroenterol Nutrition 1999;28:586.
29. Baeck M, Buts JP, Lachapelle JM, Tennestedt D. Kwashiorkor and atopic dermatitis. Pediatr Dermatol 2004;21: 344.
30. Abramovits W, Stevenson l, Prendergast MM, Tong K. Prevalence of hypertension among patients with atopic dermatitis. Br J Dermatol 2003;148:380.
31. Tofte SJ. Current management and therapy of atopic dermatitis. J Am Acad Dermatol 2001;44(1 Suppl):S13-6.
32. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol 2000;105:582-6.
33. Huang JL, Chen CC, Kuo ML, et al. Exposure to a high concentration of mite allergen in early infancy is a risk factor for developing atopic dermatitis: a 3-year follow-up study. Pediatr Allergy Immunol 2001;12:11-6.
34. Bielory L. Complementary and alternative interventions in atopic dermatitis. Immunol Allergy Clin North Am 2002; 22:153-60.
35. Ellis CN. Cost-effectiveness analysis of tacrolimus ointment versus high-potency topical corticosteroids in adults with moderate to severe atopic dermatitis. J Am Acad Dermatol 2003;48:553-63.
36. Tharp MD. A comparison of twice-daily and once-daily administration of fluticasone propionate cream, 0.05%, in the treatment of eczema. Cutis 1996;57(2 Suppl):19-26.
37. Green C, Colquitt JL, Kirby J, Davidson P, Payne E. Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation. Health Technol Assess 2004;8:iii,iv,1-120.
38. Carucci J, Washenik K, Weinstein A, et al. The leukotriene antagonist zafirlukast as a therapeutic agent for atopic dermatitis. Arch Dermatol 1998;134:785-6.
39. Schmid MH, Korting HC. Coal tar, pine tar and sulfonated shale oil preparations: comparative activity, efficacy and safety. Dermatology 1996;193:1-5.
40. Cooper KD, Kang K, Hanifin JM. Effects of thymopoietin pentapeptide (TP-5) on in vitro and in vivo IgE production by atopic dermatitis cell subsets. Diagn Immunol 1983;1:211-5.
41. Rico MJ, Lawrence I.Tacrolimus ointment for the treatment of atopic dermatitis: Clinical and pharmacologic effects. Allergy Asthma Proc 2002;23:191-7.
42. Boguniewicz M, Leung D, Marshall K, et al. Treatment of children with atopic dermatitis with 1% SDZ ASM 981 cream. J Allergy Clin Immunol 2001;107:308-13.

43. Hultsch T, Kapp A, Spergel J. Immunomodulation and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. Dermatology 2005;211:174-87.
44. Berth-Jones J, Finlay A, Zaki I, et al. Cyclosporine in severe childhood atopic dermatitis. A multicenter study. J Am Acad Dermatol 1996;34:1016-21.
45. Boguniewicz M, Jaffe HS, Izu A, et al. Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. Am J Med 1990;88: 365-70.
46. Huang J, Lee W, Chen L, et al. Changes of serum levels of interleukin-2, intercellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1 and Th1 and Th2 cells in severe atopic dermatitis after intravenous immunoglobulin therapy. Ann Allergy Asthma Immunol 2000; 84:345-52.
47. Feye F, Halleux CD, Gillet J, Vanpee D. Exacerbation of atopic dermatitis in the emergency department. Eur J Emerg Med 2004;11:360-2.
48. Al Hasan M, Fitzgerald SM, Saoudian M, Krishnaswamy G. Dermatology for the practicing allergist: Tinea pedis and its complications. Clin Mol Allergy 2004;2:5.
49. Berneburg M, Rocken M, Benedix F. Phototherapy with narrowband vs broadband UVB. Acta Derm Venereol 2005;85:98-108.
50. Baron ED. Light treatment modalities for atopic dermatitis. Immunol Allergy Clin North Am 2002;22:125-40.
51. Grupta P, Saltoun C. Allergen immunotherapy: definition, indication, and reactions.Allergy Asthma Proc 2004;25(4 Suppl 1):S7-8.
52. Kobayashi H, Mizuno N, Teramae H, et al. Diet instruction for Japanese traditional food in therapy for atopic dermatitis. Adv Exp Med Biol 2004;546:281-96.
53. Gronlund M, Arvilommi H, Kero P, et al. Importance of intestinal colonisation in the maturation of humoral immunity in early infancy: A prospective follow up study of healthy infants aged 0-6 months. Arch Dis Child Fetal Neonatal Ed 2000;83:F186-F192.
54. Ogden NS, Bielory L. Probiotics: A complementary approach in the treatment and prevention of pediatric atopic disease. Curr Opin Allergy Clin Immunol 2005;5:179-84.
55. Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004;113:925-31.