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Are Epidermal Barrier Defects Responsible for the Underlying Pathology of Atopic Dermatitis?

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Abstract

Atopic dermatitis, often referred to as eczema, is a chronic inflammatory skin condition frequently seen in young children. It is a complex disease involving environmental factors, genetics and immune dysregulation. There is currently no cure with conflicting opinions from physicians regarding treatment and management. A clearer understanding of pathogenesis of atopic dermatitis can hopefully lead to new and improved treatment options for patients. Current evidence seems to support epidermal skin barrier defects as the cause of this disease. This paper seeks to investigate if this out-in hypothesis can be responsible as the sole pathogenesis of atopic dermatitis. To write this paper a systematic search of online databases was conducted to find relevant studies. Through analysis of the research it can be concluded that although epidermal skin barrier defects definitely play an important role in the pathogenesis of atopic dermatitis, further research will most likely blend existing theories.

Introduction

Atopic dermatitis (AD) is the most common childhood skin disorder in the United States and developed countries. The pathogenesis of atopic dermatitis is complex and not fully understood. Until recently, researchers believed in underlying immune system abnormalities. Current evidence seems to support the hypothesis that epidermal barrier defects may be responsible for the underlying pathology.

According to the American Academy of Family Physicians, the diagnosis of atopic dermatitis is dependent on the presence of three essential features; pruritus, eczema, and chronic or relapsing history. Eczema can be acute, chronic, or subacute with typical morphology and age-specific patterns. Examples provided are facial, neck, and extensor involvement in children, flexural involvement in any age group, and sparing of groin and axillary region. In addition to these nonnegotiable aspects, there are important features and associated features. Important features that support the diagnosis are onset at early age, personal or family history of atopy or immunoglobulin E reactivity, and xerosis (dry skin). Associated features that can help suggest the diagnosis are atypical vascular responses such as facial pallor and delayed blanch response; keratosis pilaris, hyperlinear palms, and ichythosis; ocular or periorbital changes; other regional findings such as perioral changes; and perifollicular accentuation, lichenification, and prurigo lesions. (Buys, 2007)

An alternative definition of atopic dermatitis relies on the UK refinement of the Hanifin and Rajka Diagnostic Criteria. In order to be considered AD, the patient must have an itchy skin condition in the last twelve months plus three or more of the following: onset before two years of age (not applicable in child under four years), history of flexural involvement, history of generally dry skin, history of other atopic disease (or history in first degree relative if child is under 4 years), and visible flexural dermatitis (Brown & Reynolds, 2006).

The term atopic dermatitis is often used interchangeably for eczema. Eczema is a type of dermatitis that can be subdivided into atopic and non-atopic dermatitis (Brown & Reynolds, 2006). Atopy is associated with IgE antibody sensitization, with a prevalence of 80% for IgE sensitization in infants with AD (deBenedictis et al., 2009), although more recent finding show inconsistent results in up to two thirds of individuals with eczema (Flohr et al. 2010). The atopic triad consists of asthma, allergic rhinitis, and atopic dermatitis (Hall, 1999). Up to 70% of patients with AD have a family history of asthma, hay fever, or eczematous dermatitis. Individuals with non-atopic eczema exhibit the same cutaneous manifestations without atopic features. Response to treatment has not been shown to differ, but prognosis for atopic dermatitis is worse (Habif, 2005). Those with AD are more likely to suffer from asthma later in life and their skin condition has a higher likelihood of persisting into adulthood (Flohr et al., 2010). The atopic march refers to the tendency of individuals with atopic dermatitis to develop asthma and allergic rhinitis later in life (Elias, 2010).

In light of the current evidence, is it possible that a defective skin barrier is the number one culprit in the pathogenesis of atopic dermatitis? Many studies claim factors are multifactorial and too complex for simplification but some point to an underlying genetic basis that undermines the skin barrier and leads to the development of the atopic triad. The importance of understanding the pathology of this skin condition is in its implications for treatment guidelines and recommendations. During recent years parents have been receiving conflicting advice from physicians, including highly specialized allergists and dermatologists, due to the disparities in the literature. Obviously, there is a need to hone in on the evidence to enhance treatment based medicine.

Methods

Relevant research concerning epidermal barrier dysfunction in atopic dermatitis was identified by searching online databases. Databases were searched for publications from 1999 through 2013 and were limited to full text, peer reviewed articles. Preference was given to original articles published in the last two years. Key articles were obtained primarily from EBSCO, Proquest Central, PubMed and MEDLINE using search terms, "atopic dermatitis", "eczema", "skin barrier", "atopic march", "pathogenesis", "immunoregulation",

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filaggrin", and "epidermal barrier defects" and "treatment".

Discussion

A large number of children are affected by atopic dermatitis as reported in epidemiological surveys. Studies of epidemiological trends in AD demonstrate increasingly higher prevalence, especially in developed countries. The Diepgen, 2000 most recent study reported a national prevalence rate of 10.7% with a wide range of 8.7 to 18.1%. Highest prevalence was reported for the East Coast states as well as Nevada, Utah, and Idaho. Eczema prevalence in New York was calculated at 11.75% and 13.14% for New Jersey (Shaw et al., 2010). Other localized studies conducted in the state of Oregon and Italy report prevalence rates on the higher end of the spectrum, 17% in school aged children and 18.1% among three to five year olds, respectively (Laughter et al., 2000; Peroni et al., 2008).

The pathogenesis of atopic dermatitis is complex and not fully understood (Peroni et al., 2007). Until recently, researchers believed in underlying immune system abnormalities (Habif, 2005). Current evidence supports the hypothesis that epidermal barrier defects are responsible for the underlying pathology (Cork & Danby, 2009; Elias, 2010; Palmer et al., 2006). The most superficial layer of the skin, the epidermis, is mainly comprised of keratinocytes which migrate upwards and differentiate over time into a dead end-product, the stratum corneum (Saladin, 2012; Hall, 1999). The stratum corneum functions as a permeability barrier to decrease water loss and block entry of allergens and microbes (Hall, 1999). As the keratinocytes move upwards they flatten due to the production of keratin filaments. They also increase their production of keratin and lamellar granules or lipid-filled vesicles. At the level of the stratum granulosum, several developments contribute to the formation of the epidermal water barrier. The keratinocytes' keratohyalin granules release filaggrin, a protein that binds the keratin filaments into tough bundles. Envelope proteins produced by the cells create a strong protein sac around the keratin bundles. The lamellar granules release a lipid mixture that spreads out over the cell surface and waterproofs it. Above the layer of the water barrier, the keratinocytes die as they are cut off from their nutrient supply. The tough waterproof sac that is left behind along with the tight junctions between the keratinocytes together with the intercellular lamellar material form the epidermal water barrier that is crucial for retaining body water. (Saladin, 2012)

Primary defects in the stratum corneum may be due to decreased production of filaggrin, or filament aggregating protein (Cork et al., 2006; Elias, 2010; Proksch et al., 2006). This view is supported by studies that find filaggrin gene mutations to be positively correlated with skin barrier dysfunction (Palmer et al., 2006). The filaggrin gene is located in the epidermal differentiation complex located on chromosome 1q21 and mutations of the gene predispose to the development of atopic dermatitis (Howell et al, 2007; ibid; Weidinger et al., 2008). A large number of individuals with atopic dermatitis have a filaggrin gene mutation with a prevalence of up to 50% (Elias, 2010; Jungersted, 2010.) Filaggrin gene mutation appears to be the strongest known risk factor for AD (Rodriguez et al., 2009). Low levels of filaggrin are especially prevalent in eczematous skin with visible lesions (Cork et al., 2006; Proksch et al., 2006). Interestingly, a study of infants with and without filaggrin gene mutations found that infants with the gene mutation had impaired epidermal barrier function even in the absence of eczematous skin lesions compared to those without the genetic mutations (Flohr, et al., 2010). It seems that skin barrier dysfunction precedes the development of clinically evident eczema when associated with the filaggrin gene mutation, but it is not proof that epidermal barrier defects are the initiating factor in the development of atopic dermatitis.

An important clinical measurement used in the description of AD is transepidermal barrier water loss (TEWL). TEWL measurements differ significantly between AD and healthy skin (Agner, 1991; Holm et al., 2006) with higher TEWL values for AD. These studies show that even in the absence of skin lesions, barrier function is impaired in AD. Jungersted et al. (2010) reported highest TEWL values for those with filaggrin mutations opposed to AD without the mutations.

Natural moisturizing factor is generated from the breakdown of filaggrin. High levels of natural moisturizing factor are becoming increasingly recognized as a crucial component in the formation of a healthy skin barrier. As a humectant, natural moisturizing factor attracts water to itself causing the corneocytes to swell and form a resilient barrier. Urea is a substance found in natural moisturizing factor that may be responsible for its humectant properties due to its sponge-like characteristics. Urea may in fact be used as part of atopic dermatitis treatment based on this premise (Cork & Danby, 2009). In eczematous skin, natural moisturizing factor levels are decreased and corneocytes shrink as a result (Cork et al., 2009) Shrunken corneocytes release cytokines, pro-inflammatory markers that cause itching. In addition, the shrunken corneocytes develop cracks between themselves which allows for the penetration of irritants and allergens and a subsequent inflammatory response. (Cork & Danby, 2009)

Thickness of the stratum corneum is maintained by the balance between proteases and protease inhibitors. Proteases allow for desquamation and turnover of the stratum corneum by breaking down corneodesmosomes, the link between corneocytes. Protease action is balanced by protease inhibitors such as LEKT1 to ensure a constant thickness. If the stratum corneum becomes too thin it allows for the penetration of allergens and irritants. Protease activity is enhanced by increased pH, which explains the effect of irritants that raise the pH of the skin (Cork & Danby, 2009).

Another contributing factor may be due to impairment in tight junctions. Tight junctions proteins are situated below the stratum corneum in the stratum granulosum and function as an additional skin barrier by regulating the selective permeability of the paracellular pathway (DeBenedetto et al., 2010; Kubo et al., 2012).

Research published in the Journal of Allergy and Clinical Immunology in December 2010 suggests that reduction in

claudin-1, a tight junction protein, results in increased permeability of the barrier. The research findings also imply that variants in the tight junction gene, Claudin-1 is associated specifically with atopic dermatitis.

The lipid content of the stratum corneum appears to play a role in atopic dermatitis. It is known that altered ceramide levels are present in AD (Proksch et al., 2008; Jungersted et al., 2008). Authors Danby and Cork liken the lipid lamellae to mortar around a corneocyte brick wall. The barrier lipids help keep the water content high in the corneocytes. Defective lipid lamellae present in eczematous skin increases water loss and shrinkage of corneocytes (Cork & Danby, 2009). However, it has not been established whether altered lipid content is associated with filaggrin mutations. Research is lacking in this area, but a more recent study by Jungersted et al. (2010) detected no clear relationship. The authors discerned that ceramide 1 and 4 are decreased in AD, while ceramide 7 is increased, a confounding finding. More research is necessary to determine the role of filaggrin gene mutations in relation to characteristic skin findings of AD.

It seems to be a difficult proposition to blame the filaggrin gene mutations for the sole underlying pathology in AD if these mutations are not present in all individuals with AD and are not associated with important AD characteristics, although additional research will hopefully provide further elucidation. Perhaps skin findings in AD such as the altered ceramide profile are not inherent to the pathogenesis of the disorder.

It is important to distinguish the difference between a characteristic finding and underlying pathogenesis in regard to the skin disorder. It is widely known that barrier dysfunction is present in AD. To this end researchers use isolated measures of barrier function and dysfunction for classification of disease severity (Danby et al., 2011; Mochizuki et al., 2008). The question is whether to take an out-in or in-out approach to understanding the responsible pathology.

The out-in or outside-inside hypothesis relies on the epidermal barrier dysfunction as the cause for the disease. (Cork & Danby, 2009; Elias & Wakefield, 2011; Elias et al., 2008; Palmer et al., 2006). It implies that skin barrier damage precedes immune dysregulation. Elias and others have been proposing this hypothesis since 1999 (Elias et al., 1999; Taieb, 1999), although it has only been gaining wider recognition in recent years. Authors Cork and Danby propose that skin barrier breakdown is the first event in the development of AD. The breakdown of the epidermal barrier is a result of interaction of environmental agents with several genetic mutations (Cork & Danby, 2009).

The most recent developments in the field provide supporting evidence for the epidermal barrier hypothesis. A study in mice discovered that a certain missing protein may be responsible for the development of AD. The COUP-TF interacting protein 2 (Ctip2) is important for maintaining the skin barrier and normal lipid metabolism. When functioning, it appears to suppress the skin inflammatory response. Ctip2 deficiency, studied by removing the protein from the epidermal layer of mice skin, caused atopic dermatitis lesions as well as a systemic inflammatory response. The absence of Ctip2 appears to increase expression of the thymic stromal lymphopoietin (TSLP) gene. The TSLP gene has been linked to asthma and a food allergy related disorder and is elevated in mice with atopic dermatitis. (Wang et al., 2012) These findings build on the premise of the epidermal barrier hypothesis where breakdown of the barrier is a trigger for AD and for wreaking havoc with the systemic immune system.

It is possible that the epidermal barrier dysfunction hypothesis can explain the pathogenesis of the AD triad, which consists of asthma, allergic rhinitis, and atopic dermatitis. Genetic research by Palmer et al., (2006) demonstrates evidence for a genetic defect that is common to atopic dermatitis and associated asthma. Two independent mutations of the filaggrin gene, 228del4 and R501X, appear to be the major variants in people of European origin, according to their study. These mutations were found to be a major risk factor for AD and due to their presence in people who subsequently develop asthma, a molecular mechanism can be provided for the asthma subtype that is associated with AD. Although these mutations are the most common and result in complete loss of function, there are likely mutations associated with reduced filaggrin expression, as well as different profiles for other populations.

The in-out or inside-outside hypothesis assumes that the barrier dysfunction is driven by immunologic abnormalities. Barrier dysfunction is due to the inflammatory response to irritants and allergen. Characteristics of the impaired immune response are both systemic and cutaneous and include excessive T-helper type 2 (Th2) cell signaling leading to increased interleukin-4 production, which promotes IgE production (Boguniewicz & Leung, 2011; Nicol, 2010). Although a debatable finding, studies have found increased serum IgE levels in up to 80% of patients with AD (Leung et al., 2004; Flohr et al., 2004). A proteomic study by Howell et al. found that an important protein, S100/A11, is downregulated in AD. This protein has an immunomodulatory effect on the filaggrin gene (Howell et al., 2008). Authors Boguniewicz and Leung interpret these findings to mean that there is immune dysregulation that affects the integrity of the skin barrier as well as the body's innate immune response (Boguniewicz & Leung, 2011).

More recent literature (Wolf & Wolf, 2012; Boguniewicz & Leung, 2011) remains inconclusive. The authors continue to support the existing immune theory although they show evidence to support the defective barrier theory.

Genetic studies provide support for both skin barrier defects and immunologic abnormalities in AD. Authors Boguniewicz and Leung suggest that immune and skin barrier genetic variations may work together to increase risk for AD (Boguniewicz & Leung, 2011). There may be a unique type of AD that is associated specifically with the filaggrin gene mutation. This phenotype of AD predisposes to early onset AD that persists into adulthood (Barker, 2007). Adults with AD are more

likely to have the filaggrin gene mutation although not all individuals with AD have the filaggrin gene mutation (O'Regan et al., 2008).

It may be too early to tell, but implications for treatment are enormous. If the skin barrier theory holds true, it implies that first line therapy should focus on restoration of the skin barrier. As of December 2012, American Academy of Dermatology (AAD) revised their recommendations for the public based on this theory. Their clinical guidelines for AD are in the development process and are not yet available. Other dermatology educational websites have followed the lead of the AAD including National Institutes of Health (NIH). National Jewish Health is also a proponent of barrier restoration therapy due to underlying genetic filaggrin mutation theory.

The leaky skin barrier is the driving force for inflammation and dryness that characterize atopic dermatitis. Allergen sensitization occurs with increased penetration of environmental antigens to the body. Sensitization results in subsequent immune system hyperactivity associated with atopic diseases such as asthma and allergic rhinitis (Elias, 2010). Research demonstrates that the atopic march occurs early; over 50% of children will have allergies and/or asthma by their third birthday (Kapoor et al., 2008). An additional effect of the damaged skin barrier is the increased incidence of secondary infections. Skin infections are common in individuals with atopic dermatitis and may be due to the disturbed antimicrobial barrier (Elias, 2010).

There may be aggravating factors that affect relapses and severity of atopic dermatitis. The avoidance of environmental stimulants is important in management (Buys, 2007; Hanifin et al., 2003). Factors such as allergens, irritants, temperature fluctuations, low humidity, and stress may be triggers in certain individuals (Habif, 2005).

Allergens include contact, food, and inhalant allergens. The role of food and environmental allergens in eliciting or maintaining eczematous skin lesions is debatable (Leung et al., 2004). Food and inhalant allergens are associated with infantile atopic dermatitis. A study of risk factors showed that sensitizations to certain allergens were more common in children with AD compared to healthy children. The most common sensitizing allergens in the study were house dust mites and grass pollen. Dogs, cats, Parietaria, milk, and eggs allergens were more prevalent in those with AD (Peroni et al., 2008). The 2003 "Guidelines of care for atopic dermatitis" technical report determined the evidence on the effectiveness of allergen avoidance to be inconclusive. The 2006 Clinical Review of atopic and non-atopic eczema published in the British Medical Journal maintains that food allergens are responsible for relapse in a small number of individuals and this is usually obvious to the patient or caregiver. Some research suggests that reducing house dust mites improves severe AD, but a similar more recent study has not produced the same effect (Brown & Reynolds, 2006).

Other aggravating factors may be irritants. Soaps and detergents can irritate the skin and worsen symptoms (Brown & Reynolds, 2006). They insult the skin barrier by raising the pH in the stratum corneum. A higher pH inhibits lipid synthesis and increases protease activity, both of which increase the breakdown of the epidermal barrier in AD (Cork & Danby, 2009). Shampoos, bubble baths, shower gels, and dishwashing liquids can be potential triggers according to the UK National Institute for Health and Clinical Excellence (NICE) guidelines (Carr et al., 2007). Patients are recommended to use mild unscented non-soap cleansers (Siegfried, 2009). Individuals with atopic dermatitis may be sensitive to detergents and fabric softeners. Recommendations are to use fragrance and dye free detergents and/or to double rinse (Siegfried, 2009). The 2003 Technical Report's analysis of the peer reviewed literature found only one investigation that studied the effects of avoidance of enzyme enriched detergents on symptom relief and showed no difference between placebo and control (Hanifin et al., 2003). Irritants vary for each individual, therefore expert opinion recommends patients to identify and avoid known personal triggers (Carr et al., 2007). In concordance with the skin barrier theory, irritants may further destroy the epidermal skin barrier leading to the worsening of symptoms (Bieber, 2008; Jungersted et al., 2010;) It is important to note that although a study by Jungersted et al. showed that irritants serve as triggers in AD, their results were not statistically significant. In addition, their sample size was small with only 49 participants, but their findings can indicate avenues for further research.

Pruritus induces scratching and perpetuates the itch-scratch-itch cycle by further damaging the skin barrier. Scratching also exposes the skin to secondary infection (Brown & Reynolds, 2006). Secondary infection in AD is common due to disturbance in the skin barrier (Elias, 2010). The majority of patients are colonized with Staphylococcus aureus infection. It is debatable whether there is a connection between S. Aureus infection and AD exacerbations (Buys, 2007). All of the above mentioned aggravating factors interact with the skin barrier and therefore can be used to demonstrate some support for the defective epidermal barrier theory in AD.

It is suggested that neuroimmunoregulation may be implicated in the effects of psychological stress on AD exacerbation (Brown & Reynolds, 2006). Several studies have investigated the effects of psychological treatment, including stress reduction techniques, on reducing symptoms (Hanifin, et al., 2003; Stabb et al., 2002; Stabb et al., 2006). Most found significant benefits for group therapy (Hanifin et al., 2003.). Neuorimmunoregulation directs support for the immune system theory, but there are insufficient studies to prove that reduced stress leads to the reduction of AD symptoms. A study that focused on the correlation between psychological stress levels and epidermal barrier dysfunction as measured by transepidermal water loss (TEWL) showed no significant correlation (Kepska et al., 2012). However a major study limitation was the small sample size. Although this study employed excellent design and had a superior idea to measure effects of psychological interventions on skin structure and function, if this was the best study on the topic there is clearly a need for more research in this area.

A cure is not possible for atopic dermatitis. It is a chronic skin condition with a fluctuating course that requires a multi-faceted treatment approach. Management focuses on preventing exacerbations and treating flare ups. A stepped approach is recommended by the National Institute for Health and Clinical Excellence (NICE) guidelines. The classification of AD used by the NICE guidelines is based on quality of life assessment including impact on everyday activities, sleep, and psychosocial wellbeing ranging from none to mild, moderate, and severe. The NICE recommendations are based on tailoring treatment according to severity and continual use of emollients even when skin is clear (Carr et al., 2007).

Emollients are considered the mainstay of treatment for prevention and maintenance (Brown & Reynolds 2006) to combat the almost universal feature of xerosis (Buys, 2007). Emollients soften and soothe dry, irritated skin. Emollients have been shown to reduce the requirement for topical corticosteroids by up to 50% (Lucky et al., 1997; Brown & Reynolds, 2006). Patients are recommended to apply emollients with or without moisturizer to the skin once or twice daily after showering or bathing when the skin is not fully dry, preferably within the first three minutes (Siegfried, 2009). Ointments are more efficacious than creams, but patients may find them too greasy. Lotions have a higher liquid content and are therefore not as superior as creams and ointments. Creams may be preferred for daytime use, while ointments may be better for nighttime (Buys, 2007). Emollient ingredients that include glycerol and urea combined in a complex emollient compound are useful for reducing the oil content while producing similar results to a greasier ointment product. Glycerol and urea are humectants that rehydrate the skin barrier, but are likely to be more cosmetically acceptable because they are less greasy (Cork & Danby, 2006). A placebo-controlled, double blind, randomized study of a glycerol-based emollient found it to have positive influence on AD skin with enhanced stratum corneum hydration (Breternitz et al., 2007).

The patient's prescribed topical medications are applied before moisturizing (Siegfried, 2009). Moisturizers may prevent penetration of medications into the skin (Nicol, 2010). In addition to moisturizing, adherence to an appropriate skin care regimen is important. Short daily baths or showers followed by the application of moisturizer are beneficial, contrary to previous beliefs that bathing should be kept to minimum. Warm water is preferred because hot water is drying to the skin (Siegfried, 2009).

Topical corticosteroids have been considered the mainstay of treatment for exacerbations (Buys, 2007) and are the standard to which other treatments are compared (Hanifin, et al., 2003). Steroids are classified according to their potency, ranging from high potency (class one) to low (class seven). The NICE guidelines recommend tailoring corticosteroids according to severity of AD (Carr et al., 2007). Mild potency steroids are to be used for mild AD, moderate potency for moderate AD, and potent steroids for severe AD under specialist supervision if used for a length of time. Low potency steroids are preferred in infants due to their higher ratio of skin surface area to body mass index and increased potential for systemic absorption (Buys, 2007). The duration of therapy, frequency of application and quantity of application are uncertainties due to limited data. A large systematic review found that there was no added effectiveness to using steroids twice daily as opposed to once daily. Long term intermittent use of topical steroids appears to be safe and effective (Hanifin et al., 2003). Expert opinion recommends treating flare ups with the shortest course of steroids necessary to control the exacerbation for a maximum of four weeks. A study found that patients generally underestimate the quantity of steroids and emollients needed for long term therapy (Buys, 2007).

Local side effects limit long term use of topical steroids (Hanifin et al., 2003). Cutaneous complications include striae, telangiectasia, atrophy, and acne and are more common on the face, groin, and axillae. Systemic side effects include hypothalamic-pituitary-adrenal axis suppression, reduced linear growth in children, and bone density changes in adults (Buys, 2007). Evidence of significant systemic effect from proper use of topical steroids is inconclusive (Hanifin et al., 2003).

Second line agents are topical calcineurin inhibitors (TCI). Pimecrolimus (Elidel) and tacrolimus (protopic) are immunosuppressants that alter T cell function (Buys, 2007). A systematic review of TCI efficacy and safety in pediatric patients identified twenty randomized controlled trials (Chen et al., 2010). They found no significant difference between 0.01% and 0.03% tacrolimus. 1% pimecrolimus compared to corticosteroids showed possible superiority at six months, but not at 12 months. Tacrolimus was found to be superior to pimecrolimus. The authors concluded that TCI are safe and effective in pediatric patients for the treatment on AD, but they did not address their possible carcinogenicity. There is an FDA "black box" warning about the possible link to skin cancer and lymphoma, but at present it is still unclear whether long term topical calcineurin inhibitors are associated with malignancy (Williams & Shams, 2010).The most common adverse effects are local skin burning and irritation and users need to use proper sun protection. The FDA limits use to children over two years and recommends avoiding long term use (Buys, 2007.). In the stepped treatment approach, TCI are added for moderate atopic eczema (Carr et al., 2007).

Phototherapy is a second line treatment used in moderate to severe AD (Carr et al., 2007). Ultraviolet phototherapy options include UVB, narrow-band UVB, UVA, or psoralen plus UVA (Buys, 2007). UVB appears to be more effective than UVA which is found in conventional sunbeds. The potential increased risk of skin cancer must be explained to the patient and monitored long term (Brown & Reynolds, 2006).

Systemic therapy may be necessary in the treatment of severe atopic dermatitis (Carr et al., 2007; Brown & Reynolds, 2006). Immunomodulators are useful in refractory AD that does not respond to topical agents (Hanifin et al., 2003). Cyclosporine (Sandimmune) is a systemic immunosuppressant used for treatment of moderate to severe AD (Buys, 2007; Brown & Reynolds, 2006). Its efficacy is well established,

although careful monitoring is necessary. Side effects include immunosuppression, nephrotoxicity, and increased risk of cancer (Brown & Reynolds, 2006). Evidence shows that interferon gamma-1b (Actimmune) may be effective for severe AD (Buys, 2007; Hanifin et al., 2003).

Systemic corticosteroids are effective for gaining short termcontrol, but should be limited to sparing short term use in adults and rarely in children (Buys, 2007). Short term oral prednisone or intramuscular injections of triamcinolone acetonide are used for major exacerbations. Their use is limited due to rebound flare of symptoms and diminishing effects (Hanifin et al., 2003).

Evidence for mycophenolate mofetil (Cellcept), azathioprine (Imuran), and intravenous immune globulin (human; Baygam) is conflicting; no definitive conclusion has been reached (Buys, 2007). There is insufficient evidence to support the use of leukotriene inhibitors, methotrexate, desensitization injections, theophylline, or oral pimecrolimus (Buys, 2007; Hanifin et al., 2003).

Occlusive clothing is often used in management of AD, and recently silk clothing is being touted as being helpful in improving eczema. DermaSilk is made from woven silk and impregnated with an anti-bacterial agent. A systematic review of the literature reveals only two non-randomized trials and although they showed benefits for DermaSilk, the inadequacies of the trials make it too early to suggest firm clinical benefit (Williams & Shams, 2010).

Unproven treatment strategies include Chinese herbal therapies, homeopathy, massage therapy, dietary restrictions including exclusion of sugar, and salt baths (Buys, 2007). Patients need to be aware about the potential toxicities of Chinese herbal therapy. Unproven prevention techniques include delayed introduction of solid foods in infants and prolonged breastfeeding (Carr et al., 2007; Hanifin et al., 2003). Exclusive breastfeeding may postpone emergence of symptoms until the third year or later (Hanifin et al., 2003). The evidence is inconclusive regarding maternal dietary restriction in pregnancy (Brown & Reynolds, 2006). Probiotics during pregnancy may delay the onset of AD (Hanifin et al., 2003). The use of bath emollients is discussed on the uncertainties page of the British Medical Journal in November 2009 (BMJ, 2009). They are prescribed as part of complete emollient therapy, to avoid the use of bubble baths, and as an easy way to apply an emollient to a large body area. However, patients' attention may be diverted away from direct application of emollients and most of it is lost down the drain (Williams & Shams, 2010). Current evidence shows that bath emollients offer little or no benefit, but further research may focus on the development of bath bubbles that young children can enjoy without irritating their skin (BMJ, 2009).

Prognosis for AD is good; the majority of patients outgrow their condition by adulthood. Atopic dermatitis in children becomes less severe in the teenage years (Habif, 2005). Complications can arise due to the development of eczema herpeticum, or widespread herpes simplex virus. Immediate referral to a dermatologist is necessary if eczema herpeticum is suspected. Comorbidities may develop due to poor control, including sleep disturbance and limitation of psychosocial functioning (Carr et al., 2007). Partial sleep disturbance results in significant neurocognitive impairment (Brown & Reynolds, 2006). Emotional and behavior problems may be common in children with moderate to severe AD (Habif, 2005).

The above analysis of available treatment options for AD demonstrates the importance of emollient therapy in conjunction with occasional steroid application for exacerbations. Stronger therapies may have to be added for very severe cases, but complete emollient therapy should never be neglected. Additional therapies may be useful if caregivers and patients find them to be easy and helpful. Health care providers should stress the benefits of emollient therapy by recommending beneficial moisturizer products, writing down their names on paper, and demonstrating how much to apply. Educating patients requires some extra time, a precious commodity in a busy pediatric office, but it is likely to show results because many of the above mentioned treatments rely on lifestyle management changes and proper usage of creams. For example, it would be useless to recommend a greasy ointment based on its superior efficacy if it will not be tolerated by the patient. In this case, it is the job of the health care provider to find out if the child refuses to use thick creams. It would make sense to recommend a milder lotion even if not as efficacious because it will be used and therefore be effective. A discussion of irritants as possible triggers is relevant to every patient, although based on available evidence it does not seem to be worth the trouble to investigate every possible food allergen. More worthwhile is education regarding avoidance of harsh soaps and detergents that raise the pH and further damage the skin barrier.

Conclusion

Atopic dermatitis is a very common and distressing skin disorder that requires a multifaceted treatment approach. Therapeutic interventions in the field are continuously developing as current research deepens and changes our understanding of the underlying pathogenesis. Current research is emerging in favor of epidermal skin barrier defect theory although the evidence remains inconclusive and we may hold on to the immune system theory at least a little longer. Further research may ultimately blend existing theories. Additional peer reviewed studies facilitate guideline refinement in the pursuit of evidence based medicine. Evolving research theories are likely to be reflected by updated clinical guidelines in the near future.

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