Clinical Insights About the Role of pH in Atopic Dermatitis

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a prevalence of up to 25% of children and ranging from 2.1% to 4.9% of adults worldwide.[1] AD has tripled since the 1950s, now affecting 3.5% of adults in Canada and the US.[1] The dramatic increase in prevalence has occurred mainly in countries that follow a western lifestyle, and may be due to factors enhancing skin surface pH.[1]

AD presents with relapsing and remitting cycles; many AD sufferers describe being worried about the next disease exacerbation.[2,3] In fact, adult patients with AD report feeling helpless (31%), anxious (40%), and irritable (31%) "quite a lot" when they think about a new disease exacerbation.[3] Moreover, patients with moderate AD report having 113 days of disease exacerbation per year, while those with severe AD note having disease exacerbation more than half of the year (192 days).[4]

The pathogenesis of AD is multifactorial and includes genetic and environmental factors. AD presents clinically as erythematous and pruritic patches of skin with varying severity. Inflammation is believed to occur when the skin barrier becomes dysfunctional and an immune response is stimulated.[5] Vice versa, the inflammatory response itself may impair the skin barrier function; once the barrier is disrupted, feedback loops are initiated.[5,6] Maintaining a physiologically low skin surface pH may help to keep the skin barrier intact, reducing the risk for AD development and exacerbation of flares.

SCOPE

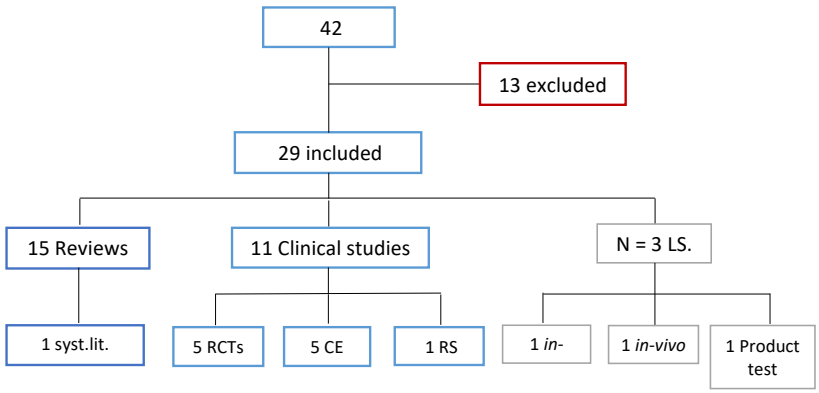
The current consensus paper explores the influence of genetic and environmental factors on the exacerbation of epidermal barrier breakdown in AD and to what extent these factors attribute to the elevation of stratum corneum (SC) pH. We further examine the effects of a sustained increase in skin surface pH in AD-affected skin, and explore clinical insights into the role of pH in AD. Furthermore, the influence of cleansing and moisturizer use as measure to sustain skin pH at physiological levels is also discussed.

The statements discussed in the consensus paper are intended for health care providers caring for patients with AD in pediatric and adult age groups, eg, dermatologists, pediatricians, nurses, and family physicians. Other conditions such as contact dermatitis are excluded because they have different pathogenic mechanisms.

METHODS

An expert panel of dermatologists convened for a one-day meeting (January 13, 2019; Toronto, ON) to evaluate the role of skin surface pH in pediatric and adult AD populations. Additionally, they discussed the influence of cleansing and moisturizer use in these AD populations. For this purpose, evidence coupled with the expert opinion and experience of the panel was used to adopt the proposed statements and/or to add any further information or make changes. The consensus process consisted of a nominal group technique.[7] Statements were developed based on the literature selected prior to the meeting; the panel then voted on the inclusion of statements after nominal group discussion.[7] Consensus required a minimum of 80% agreement.

FIGURE 1. Literature review on the role of pH in AD.



Systematic literature (syst.lit.); Retrospective study (RS); Randomized Controlled Trial (RCT); Clinical evaluation (CE); Laboratory studies (LS)

Literature Review

A literature review explored clinical insights into the role of pH in AD and into the influence of cleansing and moisturizers. For this purpose searches were performed on PubMed and Google Scholar of the English-language literature (2010–2018) using the terms: Atopic eczema; Atopic dermatitis; Skin pH; AD pathogenesis; Filaggrin; Inflammation in AD; Risk factors for AD; Acid mantle; Immune response and epidermal skin barrier function; Skin barrier; Skin barrier deficiency; Immunity; Stratum corneum hydration and skin surface pH in AD; Prevention; Emollients; Cleansers; and Moisturizers.

The selected publications were manually reviewed for additional resources by a dermatologist and a clinical scientist with experience in this field (AA). The searches yielded forty-two publications. After exclusion of duplicates and papers not relevant for skin surface pH in AD, twenty-nine publications were included (Figure 1). The two reviewers prepared statements using the results of the literature reviews for discussion by the expert panel. The panel discussed at length the consensus statements, revised them, and voted.

Statements Defined by the Panel

The defined statements were based on the expert panel's clinical experience and opinion coupled with support from the literature selected during the literature searches. The ten panel members reached consensus on eight statements on the role of pH in AD and the influence of cleansing and moisturizer use. Seven statements were accepted with a unanimous vote; statement number seven was passed with 8/10 panel members (80%) in agreement.

Statement 1: AD is a common chronic, relapsing skin disease, where there is interplay between the skin barrier, the immune system, and the skin microbiome.

The Skin Barrier

The epidermal barrier is composed of corneocytes, held together with corneodesmosomes.[8] Skin barrier function is dependent on the complex interplay of SC pH including filaggrin production into natural moisturizing factor (NMF) components pyrrolidone, carboxylic acid, and trans-urocanic acid, all of which acidify the SC.[6,8-11]

The Immune System

When there is protease hyperactivity within the epidermis and an overrepresentation of pathogens (eg, *Staphylococcus aureus* [*S. aureus*]), the cleavage of the corneodesmosome junctions is enhanced. This increase in cleavage leads to a defective skin barrier, which is open to water loss and to an invasion of irritants and allergens, leading to inflammation.[8] Skin lesions in AD affected skin are characterized by upregulations of T-helper cells (Th2), (Interleukin (IL) -4, IL-5, IL-13, IL-31), cytokines, and chemokines.[12,13] Th2 cytokines, IL-4, and IL-13, all play a major role in the disease pathogenesis leading to the dysfunctional epidermal barrier in AD.[13] Finally, IL-4 and IL-13 promote *S. aureus* binding and inhibit antimicrobial peptides, predisposing AD-affected skin to *S. aureus* colonization and infection.[13]

The Skin Microbiome

Antimicrobial peptides produced from keratinocytes, neutrophils, and mast cells are regulated by pH[6] while skin commensal organisms contribute to the skin's acidic pH. Moreover, pathogenic organisms *S. aureus* and *Streptococcus pyogenes (S. pyogenes)* are inhibited by acid skin surface pH.[6] When less filaggrin is produced in the skin, the surface pH increases, activating serine proteases, which, in turn, enhances cell degradation and decreases lipid synthesis.[6,11] Serine proteases are pH dependent and break down corneodesmosomes, leading to barrier disruption and an unbalanced microbiome.[6,8,13]

A physiological skin surface pH acts as an antimicrobial defense mechanism limiting bacterial colonization[6,11]; moreover, acidic filaggrin breakdown products decrease *S. aureus* growth rates.[6] If in healthy skin the surface pH increases, filaggrin proteolysis supports restoring the slightly acidic pH.[6,11]

Statement 2: Genetic and environmental factors can influence the pathogenesis of AD, including impaired skin barrier and lipid metabolism, activation of multiple immunologic and inflammatory pathways, skin microbial imbalance, and changes in the skin pH.

The skin barrier function includes physical, chemical, and immunological aspects.[6] The acid mantle refers to the slightly acidic pH of the skin which affords protection against exogenous insults. The acid mantle contains amino acid, lactic acid, fatty acid, and other compounds (eg, ceramides), which play an important role in skin barrier homeostasis. Furthermore, the mantle provides a defense against pathogens and other factors such as frequent bathing, regular use of alkaline soaps increasing skin pH, dry air (eg, due to air conditioning), and physical stress.[6,14] Ceramides are synthesized from keratinocyte lamellar structures via pH-dependent enzymes (ie, sphingomyelinase, B-glucocerebrosidase), which require an acidic environment to function.[8] Lower levels of ceramides 1 and 3 as well as a lower ceramide/cholesterol ratio were noted in non-lesional AD-affected skin.[8]

The protective buffer capacity protects the skin against acid or alkaline assaults, and is influenced by keratinocyte-produced free fatty acids and components of NMF, including urocanic acid, carbonic acid, and keratins.[6,13] The buffer capacity is decreased in babies and elderly patients[15]; skin pH at birth is near neutral (6.5), and takes several weeks to reach the physiological

skin surface pH range, referred to as the "acidification of the mantle".[15,16]

Statement 3: The acidic pH of skin plays an important role in skin barrier homeostasis, which is a key factor in AD.

SC surface pH can be measured by documenting pH and buffer capacity of the skin; it is normally acidic (4.0–6.0).[17] The skin barrier protects against environmental stimuli by preventing their influx, including when failing inflammatory responses to the infiltrating stimuli follow.[11] Defects in this complex regulation system may lead to the loss of epithelial homeostasis, inflammation, and the development of AD. Elevated pH in the epidermis (pH around 6.5 in patients with AD compared to a pH of approximately 4.5 in those with healthy skin) leads to increased catalytic activity of proteases kallikrein 5 and 7 (KLK5 and KLK7).[11] Furthermore, a decrease in the basal expression rate of LEKTI, a KLK inhibitor, leads to compromised inhibition of KLK activity.[11]

Statement 4: Filaggrin and its degradation are essential for maintaining the acidic pH of the skin.

Skin barrier function is dependent on the complex interplay of filaggrin, pH-dependent lipid processing enzymes, serine proteases and the skin microbiome.[6,10,14-18] A further cohesive force holding corneocytes together is 'modified desmosomes', referred to as corneodesmosomes, which also provide tensile strength to skin barrier.[6,18,19] Corneocytes are held together by corneodesmosomes, and contain NMF derived from pro-filaggrin, which are a mix of hygroscopic compounds that help maintain skin hydration.[18] The balance between the expression and activity of proteases and protease inhibitors determines the rate of corneocytes shedding, which under normal conditions takes place in the upper skin layer. The production of filaggrin into NMF acidifies the SC, supporting the pH-dependent lipid processing enzymes that produce the mortar of the brick and walls of the SC.[6,10,14,19] Serine proteases, which are also pH dependent, break down corneodesmosomes in the SC[6,19] while a low pH acts as an antimicrobial defense mechanism limiting bacterial colonization. If the pH is increased in healthy skin, filaggrin proteolysis supports restoring the SC to a slightly acidic pH. When fewer filaggrin metabolites are produced and the skin pH increases, serine proteases are activated, triggering an enhanced breakdown of corneodesmosomes. This cascade leads to barrier disruption, thereby decreasing the thickness and function of the skin barrier (Figure 2).[6,18,19] Additionally, acidic filaggrin breakdown products decrease *S. aureus* growth rates.[6,19]

Statement 5: At an acidic pH, enzymes generate lipophilic components, which are essential to a physiologic skin barrier.

FIGURE 2. Increased skin surface pH leads to increased desquamation.

KLK5 and KLK7 are proteases
Adapted from Cork M et al[18]

The formation of the SC barrier, specifically the generation of its lipophilic components, involves several pH-dependent enzymes.[6,19] Two key lipid-processing enzymes, β-glucocerebrosidase and acidic sphingomyelinase, have pH optima of 5.6 and 4.5, respectively, and are both involved in the synthesis of ceramides. The processing of lipids secreted by lamellar bodies and formation of lamellar structures require an acidic environment; the activity of β-glucocerebrosidase is 10 times lower at pH 7.4 than at pH 5.5.[6,19] Additionally, free fatty acids in the extracellular space form lamellar liquid crystals at pH values of 4.5–6.0 through partial ionization.[19]

Statement 6: An alkaline skin surface pH decreases: stratum corneum cohesion; immune defenses; antimicrobial defense; All of which leads to increased water loss and inflammation.

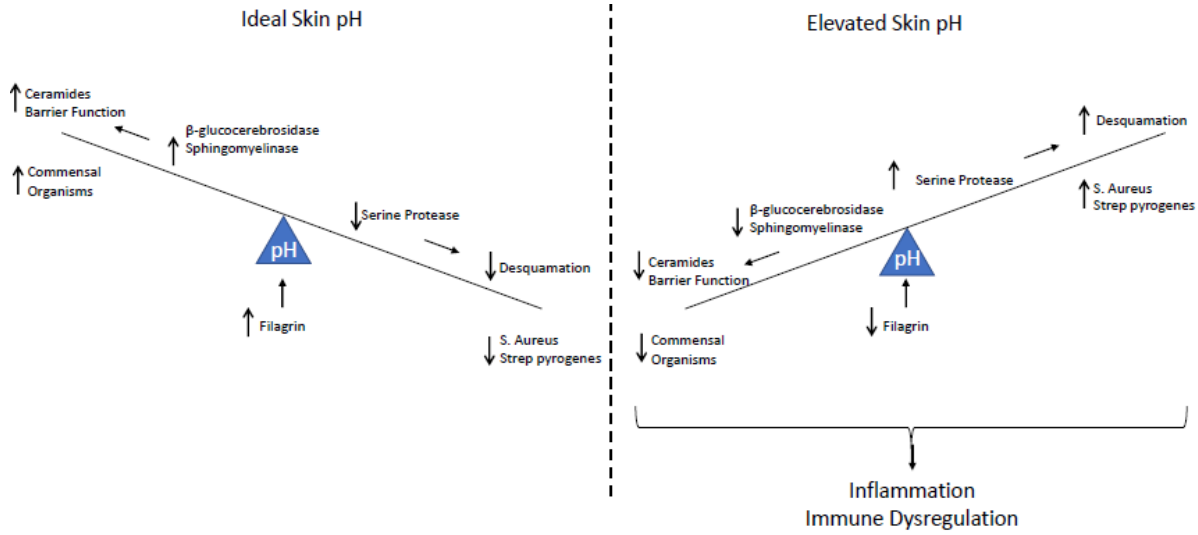
Stratum Corneum Cohesion

NMF contribute significantly to the acid mantle by decreasing skin colonization by pathogens.[18,19] Skin surface pH also plays a role in desquamation, permeability barrier homeostasis, and SC cohesion.[18] Furthermore, an increase in SC pH can cause disruption of keratinization, degradation of corneodesmosomal adhesion proteins, and creation of a ceramide, cholesterol, and fatty acids deficiency, all leading to decreased antimicrobial function.[6,10-13,18-23] The balance between the expression and activity of proteases and protease inhibitors, which is optimal at an acidic pH, influences the rate of desquamation[10,13,18] Hyperkeratosis and parakeratosis of the SC occur as a result of disruption to the cornification process, triggering hyperactivity of proteases, which facilitates cleavage of corneodesmosome junctions.[11,12,14] As a result, edema occurs due to damaged proteins involved in tight junctions, thereby triggering uncontrolled movement of fluids in the paracellular space.[12]

Immune Defenses

An elevated skin surface pH can disrupt the functioning of the epidermal barrier, which is based on 'crosstalk' between skin

FIGURE 3. pH AD exhibit.



barrier and immune systems.[10-12,18] Primary (eg, genetic) barrier defects are coupled with secondary defects due to inflammation affecting expression and activity of proteases, lipids, and structural proteins.[5,10-12,18] When comparing healthy skin to AD-affected skin, features such as hyperkeratosis, edema, and an increased number in and activity of immune cells are observed.[12] The immune response could be a primary feature of AD itself or a response to allergens penetrating the leaky skin barrier.[5,6,12,14,18] Also, skin pH values are higher in patients with active AD lesions than in asymptomatic individuals[18,19]; the elevated level of skin pH can be expected to delay barrier recovery and facilitate barrier breakdown.[18]

Antimicrobial Defense

S. aureus microbial colonization and invasion are thought to play a critical role in the development of AD.[20-23] In a defective skin barrier, the reduced levels of NMF lead to a decreased ability of the corneocytes to hold water with a concomitantly elevated surface skin pH.[6]

The elevated pH favors serine protease activity and inhibits enzymes involved in the synthesis of lipid lamellae, weakening the skin's defense mechanism against pathogens.[6,20-23] Many microorganisms such as *S. aureus* and *Streptococcus pyogenes (S. pyogenes)* are inhibited by the skin's acid pH, which also regulates the activity of antimicrobial peptides.[20-23] The elevated level of skin pH can be expected to delay barrier recovery, further facilitating skin barrier breakdown.[18] Additionally, the skin cannot retain sufficient water, which leads to dry skin and the "itch, scratch, damaged skin, and inflammation cycle" (Figure 3).[4] Moreover, mechanical damage to the skin due to scratching enables pathogens to penetrate and to enhance inflammation.[4,22,23]

Statement 7: Many available soaps and cleansers have a high pH, which potentially disrupt the skin barrier.

A defective skin barrier can be triggered by genetic and environmental factors such as a 'western' lifestyle, frequent bathing,

TABLE 1.

Cleanser Categories		
Type of Cleanser	**pH**	**Example**
Soap: Contains fat and alkali-treated salts of fatty acids.	pH 9.0–12	Home-made soap
Syndet bar: Contains synthetic detergents and small amounts of soap-based detergents.	pH: 4.0–6.0	Ceramides-containing cleansing bar
Combar: Contains equal parts of soap-based detergent mixed with synthetic detergent.	pH: 10–12	Irish Spring combar
Liquid cleanser: Contains synthetic detergents, can be ionic or non-anionic in lotion, cream, oil or gel form.	pH: 6.0–7.0	Body wash, liquid hand cleanser
Lipid-free cleanser: Contains no soap or detergent and do not need water to cleanse.	pH: 5.0–7.0	Lipid-free ceramides-containing cleanser
Cleanser with polymer-surfactant complexes: Has a low concentration of free surfactant micelles as well as polymer-surfactant complexes.	pH: 4.0–5.8	Ceramides-containing cleanser

Adapted from Skotnicki S et al.[24]

especially with water with a high pH, and using regular soaps, all of which increase the skin surface pH.[5,24-27] Several studies have shown a significantly higher prevalence of AD in areas with the hardest water quality compared to those with softest water quality (classification based on calcium carbonate, soft- 0-60 mg/L, hard 121-180 mg/L, and very hard- 180 + mg/L).[24] As mineral content goes up, acid in the water is reduced by acting as a buffer, resulting in a higher pH.[24] Furthermore, increased mineral content interferes with the calcium gradient necessary for corneocyte development, thereby also increasing skin pH.[8,12]

Soaps, surfactants, and detergents, especially those products with a high pH, may excessively remove NMF and skin lipids, enhancing skin surface pH and triggering AD flares.[2,24] Filaggrin and its degradation products play a key role in the control of TEWL and skin pH.[6] Filaggrin undergoes proteolysis to release hygroscopic amino acids at the surface of the SC, when the outer skin starts to become dehydrated.[6] The acidic pH of skin acts as an antimicrobial defensive mechanism to limit bacterial colonization.[20-24] In healthy skin, even if the pH is increased, filaggrin proteolysis can contribute acidic amino acids to return the skin to the optimal slightly acidic pH.[6] However, in individuals at risk for developing AD, such as newborns and elderly individuals, skin surface pH may remain high.[15,16] Frequent washing with alkaline soap reduces buffer capacity by washing away inherent buffering components, enhancing the risk for irritation, thus triggering AD flares.[6,11,18,24-26]

Statement 8: The use of cleansers and moisturizers with a physiological skin surface pH (4.0–6.0) may allow for skin barrier repair, decreased inflammation, accelerated pH recovery, and increased antimicrobial defense.

Cleansers enable the removal of dirt and oil, and clears pores of debris to prevent dirt buildup, allowing sebum to reach the skin surface unimpeded.[27] Surfactants within skin cleansers solubilize and remove debris and oil; however, interaction of surfactants with the SC may cause erythema, dryness, skin barrier impairment, enhanced skin pH, and sensorial irritation (Table 1).[27-29] The use of gentle cleanser that employs advanced vehicles with a near-physiologic pH (4.0–6.0) and milder surfactants, and that rinses clean, leaving no residue, may help in maintaining skin barrier function.[27-29] Cleansing and moisturizing may help manage pH levels of the skin surface, enabling sufficient water retention and improving dry, flaky, and atopic skin.[28,29] A cleanser composed of a lower concentration of free surfactant micelles, as well as polymer-surfactant complexes, has been shown to be less aggressive than alkaline soaps.[25]

Although there are data[24] supporting enhancing skin pH can cause irritation when using cleansers with a high pH (9–10), conclusive evidence on lowering skin pH when using near physiological skin pH (5.0–7.0) products is lacking.[24]

Cork et al[18] plotted the skin barrier function with arbitrary units against the first 3 years after birth. At birth, in children with no genetic pre-disposition to AD, skin barrier function is insufficient while skin pH is high.[18] The skin barrier function gradually improves over a period of about 3 years, becoming more acidic.[18] However, depending on the degree of pre-disposition to AD and environmental factors such as the use of soap and detergents, which enhance skin pH, skin barrier defect may become exacerbated. On the other hand, effective treatment, including low pH moisturizer, can improve skin barrier function, thereby acidifying the SC pH.[18]

Improved knowledge about the central roles a defective skin barrier and dry skin may play in AD is increasingly recognizing the benefits of daily and ongoing use of moisturizers. Current treatments aim to reduce inflammation and to restore skin barrier function. Those moisturizers that contain humectants such as ceramides have shown benefits over standard emollients.[33]

DISCUSSION

Skin barrier function is dependent on the complex interplay of SC pH, filaggrin, pH-dependent lipid processing, and serine proteases, as well as the skin microbiome.[6,10-13,18-23]

In healthy skin, filaggrin proteolysis supports restoring the slightly acidic pH, whereas in skin affected by inflammatory skin conditions such as AD, the pH remains elevated.[6] Skin pH values are higher in patients with active AD lesions than in asymptomatic individuals.[18,19] Furthermore, the elevated level of skin pH can be expected to delay skin barrier recovery and facilitate barrier breakdown.[18] These mechanisms confirm that skin pH values are an important indicator for skin health, the severity of AD, as well as a predictor of AD flares.

The pH and hydrophilic index of a product may give important information to choose a suitable moisturizer for AD.[24,34] According to the panel, topical products with near-physiologic pH (4.0–6.0) are considered the best option for AD. Currently, pH values of moisturizers are frequently unknown to physicians and can range widely from 3.7–8.2, some of the frequently used moisturizers having a physiologic pH of 4.0–6.0.[34]

The choice of cleanser/moisturizer mostly depends on individual preference; to enable adherence to treatment, the cleanser/moisturizer should be found pleasant to use by the patient. However, according to the panel, the ideal agent should be safe, effective, inexpensive, and free from additives, fragrances, perfumes, and sensitizing agents.[35] Additionally, they stated, the cleanser and moisturizer should have a physiologic pH (4.0–6.0) or lower to support skin barrier repair.

CONCLUSIONS

An elevated skin pH weakens the immunological defense and

in AD can be expected to delay barrier recovery and to facilitate barrier breakdown. Several trigger factors may aggravate AD such as irritants (soap and detergents, occupational irritants, and disinfectants), microorganisms, aeroallergens, seasonal changes, and psychogenic factors. Over-bathing and use of cleansers that are not pH-adjusted may contribute to the incidence of AD. The use of a cleanser and moisturizer with a near-physiologic pH (4.0–6.0) may allow for acidification of the skin. Maintaining a physiologic skin surface pH to keep the skin barrier intact, which, in turn, may reduce the risk for AD development and for excerbation of AD flares, is of interest; however, conclusive evidence to support measures to maintain an acidic skin surface pH is lacking.

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