

Skin Physiology of the Neonate and Infant: Clinical Implications

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Significance: The skin is a complex and dynamic organ that performs several vital functions. The maturation process of the skin starts at birth with the adaption of the skin to the comparatively dry environment compared to the in utero milieu. This adaptive flexibility results in the unique properties of infant skin. To deliver appropriate care to infant skin, it is necessary to understand that it is evolving with unique characteristics.

Recent Advances: The role of biophysical noninvasive techniques in the assessment of skin development underlines the importance of an objective evaluation of skin physiology parameters. Skin hydration, transepidermal water loss, and pH values are measurable with specific instruments that give us an accurate and reproducible assessment during infant skin maturation. The recording of these values, following standard measurement procedures, allows us to evaluate the integrity of the skin barrier and to monitor the functionality of the maturing skin over time.

Critical Issues: During the barrier development, impaired skin function makes the skin vulnerable to chemical damage, microbial infections, and skin diseases, possibly compromising the general health of the infant. Preterm newborns, during the first weeks of life, have an even less developed skin barrier and, therefore, are even more at risk. Thus, it is extremely important to evaluate the risk of infection, skin breakdown, topical agent absorption, and the risk of thermoregulation failure.

Future Directions: Detailed and objective evaluations of infant skin maturation are necessary to improve infant skin care. The results of these evaluations should be formed into general protocols that will allow doctors and caregivers to give more personalized care to full-term newborns, preterm newborns, and infants.

SCOPE AND SIGNIFICANCE

THE SKIN OF PRETERM newborns, full-term newborns, and infants undergoes a characteristic process of maturation, and therefore, skin care delivered to this spectrum of patients needs to be tailored to the individual patient. The principal aims of safe and effective skin care are to identify the agents that can influence the skin barrier or those that can induce systemic toxicity and avoid their utilization, thereby minimizing the risk

of thermoregulation failure, which will protect newborns against potential skin breakdown and loss of its barrier function.

TRANSLATIONAL RELEVANCE

Many studies have correlated functional infant skin parameters according to age, anatomical site, and the presence of skin or systemic disease. It would be useful to study how these functional parameters change in newborns after the onset of skin infection,



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*Correspondence: Wound Healing Research Unit, Department of Dermatology, University of Pisa, Via Roma, 67, Pisa 56126, Italy (e-mail: m.romanelli@med.unipi.it). skin breakdown, or the application of topical agents. The results of these evaluations could be formed into general protocols, which will allow doctors and wound care providers the ability to give more personalized care to full-term newborns, preterm newborns, and infants.

CLINICAL RELEVANCE

Understanding the characteristics of newborn and infant skin will permit the delivery of appropriate skin care with the main goal of avoiding skin damage and inducing dermatological pathology and systemic consequences that can affect the overall well-being of the pediatric patient.

INTRODUCTION

Skin is a dynamic complex organ, which performs several vital functions; in particular, it forms a physical barrier between the organism and the environment. It provides UV protection, prevents invasion of pathogens, and regulates body temperature and sensory perception.

Functional and structural skin maturation is a dynamic process, which starts at the moment of delivery and ends in the first year of life. In fullterm newborns, this process begins immediately after birth, while in preterm newborns by 2-3 weeks after birth, the skin is comparable to a fullterm newborn's skin. Skin growth in infants is higher than in adults and is characterized by a higher ability to restore itself as a barrier. This adaptive flexibility of skin maturation results in the unique properties of infant skin.² Regulatory mechanisms control epidermal and dermal development, eccrine sweating, sebum secretion, skin surface acidity, transepidermal water loss (TEWL), capacitance, and natural moisturizing factors (NMF), which develop during the physiologic maturation process.

SKIN STRUCTURE DEVELOPMENT

Skin maturation starts during embryogenesis through intercellular and intracellular signals between different tissue layers. Barrier development increases with gestational age, and the epidermal maturation is complete by 34 weeks of age.³ The epidermis is composed of four major layers, which are the basal, spinous, granular, and stratum corneum.⁴ The physical barrier is mainly localized in the stratum corneum, involving corneocytes, corneodesmosomes, lipid-enriched intercellular domains, and nucleated epidermis cells.⁵ The cornified envelope is composed of several layers of dead kera-

tinocytes and consists of keratins that are enclosed within cross-linked proteins and surrounded by a lipid matrix. Transglutaminases are the enzymes responsible for cross-linking between proteins and have a central role in the cornified envelope formation.⁶ Pathological defects during the cornified envelope formation are associated with permeability barrier abnormalities. Mutations in the gene that encodes transglutaminase I are linked to autosomal recessive congenital ichthyosis development, in particular, lamellar ichthyosis. The preterm neonate has decreased epidermal and stratum corneum thicknesses compared to those of an adult. Although this is a point of some discussion as a number of authors have observed that full-term neonates have a well-developed epidermis with epidermal and stratum corneum thickness similar to adult skin,8 others have observed that the infant epidermis is thinner compared with an adult.9

Skin homeostasis depends on the stable cohesion between the epidermis and the dermis, which are tightly interconnected through the dermoepidermal junction. The anchoring complex within the dermoepidermal junction zone is responsible for the stability of the dermal-epidermal cohesion and consists of the hemidesmosomes of basal keratinocytes, the anchoring filaments linking the hemidesmosomes to the basement membrane, and the anchoring fibrils connecting the basement membrane with the underlying dermis. 10,11 During skin maturation, cell attachments and epidermal cellularity increase and the dermoepidermal junction becomes undulated.³ In preterm neonates, the papillary dermis underlying the dermoepidermal junction is edematous, collagen fibrils are smaller than those of the term newborn or adult, and the anchoring structures are decreased, with wide spaces between connecting points.¹²

The microvasculature in the skin of newborns presents a horizontal plexus with a capillary network that is not yet organized. Immediately after birth, capillary loops are observable only on the nail beds, palms, and soles and are evident in all anatomical sites at 14–17 weeks of age. ¹³

Sebum levels in the first week of life are high, due to a strong androgenic stimulation of sebum secretion before birth; such levels subsequently decrease. Infant skin contains less total lipids compared to adults and this correlates with low sebum levels measured at 6 months of life. ¹⁴ Epidermal desquamation reflects epidermal turnover and is inversely correlated to the sebum levels of the skin surface. During the first 3 months of life, desquamation increases above all on the facial areas due to increased epidermal

turnover, but not in the diaper region due to the occlusive effect of the diaper. The lower desquamation on the cheeks compared to the forehead may be related to the higher density of sebaceous glands in the cheeks. ¹⁵ Malnutrition is linked with changes in surface lipids. In neonates who received incomplete parenteral nutrition, an alteration in skin lipids has been observed due to essential fatty acid deficiency. ¹⁶

Melanin creates a density filter and protects the epidermal cells from UV light damage. The melanin concentration is correlated to the reduction of the UV light penetration through the epidermis. Infants have a lower concentration of melanin compared to adults in sun-exposed skin. The adaptive response of the skin to UV lights begins as early as the first summer of life. The Frequent sunburns and exposure to sunlight in childhood are strongly related to melanoma development; therefore, appropriate measures of photoprotection have been considered to decrease the risk of melanoma and nonmelanoma skin cancer. Is

SKIN PHYSIOLOGY

Perspiration

In investigating human perspiration or sweating, we may measure the levels of lactate and urea, which are the principal sweat constituents. The concentration profiles of lactate and urea show higher amounts in the skin surface and drop rapidly below the surface. 19 In the premature neonate, the sweat glands have not completely formed and the secretory coils of the glandular segment and the sweating response to external stimuli are limited. The capacity to sweat is correlated with gestational age and there is a tendency to total anhidrosis in the preterm newborn in the first days after birth.²⁰ Eccrine sweating can be stimulated by an increase in ambient temperature, causing the activation of thermal sweating, or by emotions such as fear, pain, and anxiety, causing another type of sweating that is termed emotional or mental sweating. Thermal sweating, involving first the forehead, and emotional sweating, involving mainly palms and soles, have been reported in full-term newborns.^{21,22} Infants of less than 36 weeks of age start to sweat after thermal stimulation during the second week of life, but the intensity of the sweat response depends on gestational age and thermoregulation is initially low.²¹ In addition, emotional sweating can be observed only after 36 weeks of gestational age, with a clear relationship between arousal and palmar skin water loss.²²

Skin hydration

Capacitance values correspond to stratum corneum hydration, which influences barrier mechanical properties and percutaneous absorption.²³ At birth, the skin surface is rougher and dryer compared with older children. During the first 30 days of life, skin smoothing is correlated to an increase in skin hydration. During the next 3 months, the hydration of the stratum corneum increases and exceeds the hydration level found in adults. 15,24 The functional maturation of sweat glands may be the principal mechanism related to the increase in skin hydration after birth.²⁵ The stratum corneum of infants between the ages of 3 and 12 months is significantly more hydrated compared with adult skin. The difference between infant and adult skin hydration is more evident on the skin surface, specifically between 10 and $14 \mu m$ of depth from the skin surface. The deficiency of the stratum corneum function results in reduced water-holding capacity of newborn skin compared with adult skin.²⁵ Infant skin has a higher rate of water absorption and desorption compared with adults.²

The main mechanisms used by the stratum corneum to preserve skin hydration are the intercellular lamellar lipids, the corneodesmosome-bound, the ceramide hydrophobed cornecytes, and the intercellular and extracellular hygroscopic molecular complex known as the natural moisturizing factor (NMF).²⁶ During the cornecyte maturation process, a profilaggrin protein is dephosphorylated to filaggrin, which is proteolyzed to amino acids and derivatives. These amino acids, ions, organic acids, and sugar combine to make the NMF. The major constituents of NMF are as follows: serine, glycine, pyrrolidone-5-carboxylic acid, arginine, ornithine, citrulline, alanine, histidine, and urocanic acid. The filaggrin breakdown enzymes increase the activity when moisture is low. 19,27 The concentration of NMF is lower in infants than in adults, but in the first 2 weeks of life, an analysis of the amount of NMF has been reported to have higher levels. The high level of NMFs in the first days of life may be a compensatory mechanism to rebalance alkaline pH and skin hydration during the postnatal period.²⁸

Skin pH

pH is defined as the negative logarithm of the activity of hydrogen ions in an aqueous solution, used to express acidity and alkalinity on a scale of 0–14. Normal values of pH in intact adult skin are acidic due to the presence of the acid mantle, while the interstitial fluid is characterized by neutral values.

Infant skin pH levels are higher than those of adult skin, which is usually characterized by a pH

value between 5 and 5.5.29 Newborns have alkaline skin surfaces, ranging from 6.34 to 7.5, depending on the anatomical site. 30,31 Several mechanisms may play a role in alkaline skin pH at birth, the most relevant could be the exposure to the alkaline amniotic fluid during the preborn life.³² The acid mantle is considered a mechanism for skin defense against infection, influencing the composition of cutaneous bacterial flora. 33 Skin acidification plays an important role in barrier maturation and in the activation of enzymes involved in the extracellular processing of stratum corneum lipids.³⁴ Alkaline pH amplifies the activity of serine proteases (kallikrein 5 and 7), resulting in a degradation of corneodesmosomes and of lipid-processing enzymes,³⁵ leading to desquamation. Exogenous and endogenous mechanisms are involved in the acidification of skin surfaces. Enzymatic generation of free fatty acids from phospholipids³⁶ and cis-urocanic generation by degradation of histidine³⁷ are two of the most important endogenous mechanisms involved. Exogenous mechanisms such as lactate production in sweat glands³⁸ and microbial hydrolysis of sebaceous triglycerides³⁹ also may play a role in skin surface acidification.

The vernix caseosa is a protective coating of the skin, which develops during the last trimester of gestation, when terminal differentiation of the epidermis and formation of the stratum corneum develop. It is composed of water (80.5%), proteins, sebum lipids, and antimicrobial peptides (AMPs) with biomechanical and water-binding properties. 40,41 Corneocytes are embedded in a hydrophobic lipid matrix, consisting of wax, sterol esters, squalene, cholesterol, triglycerides, and free sterol. The abundance of water-filled fetal corneocytes makes the vernix a highly viscous material, despite the high amount of water in its composition. 41,42 The retention of vernix on the skin surface contributes to a higher skin hydration, a lower skin pH, and relates to a reduced heat loss after birth. Neonates less than 28 weeks of gestational age and those that have a low birthweight have an immature epidermal barrier and also lack the protective coating of vernix caseosa; therefore, they have a greater risk of having a lower temperature.⁴³

Skin immune system

The skin is considered the first defense of the innate immune system through pro- and anti-inflammatory cytokines and chemokines, lipid and protein constituents, antigen-presenting cells, and mechanical barrier function. The rich network of skin-associated immune cells governs the defense against pathogenic microorganisms, responds to

environmental changes, and performs several homeostatic functions. Macrophages, dendritic cells, Langerhan cells, dermal dendritic cells, mast cells, dendritic epidermal T cells, dermal $\gamma\delta$ T cells, and innate lymphoid cells are all involved in innate immunity. 44 AMPs are part of the innate immune response in human skin and are mainly generated by keratinocytes, mast cells, neutrophils, and sebocytes. 45 Human beta defensins and cathelicidins are two classes of AMPs made by keratinocytes; dermcidin is an AMP expressed in eccrine sweat glands and secreted into sweat after proteolytic activation of the precursor protein. 46,47 An antimicrobial ribonuclease, termed RNase 7, revealed large spectrum of antimicrobial activity against many microorganisms. 48 Sapienic and lauric fatty acids generated from hydrolysis of triglycerides and sphingosines also have antibacterial properties. 46,49 Skin integrity and antimicrobial function are both interdependent. AMP levels are indeed lower under basal conditions rather than after epidermal injury.⁴⁹ The newborn skin surface is replete with host defense proteins at levels that are lower than in adults. In contrast to total proteins, the antimicrobial proteins, lysozyme and lactoferrin, are present in the newborn skin surface at levels that are higher than in adults.⁵⁰ Furthermore, the commensal bacteria produce their own AMPs, which support the normal production of AMPs by keratinocytes and repress excessive cytokine release after minor external insult to the barrier.⁴⁵

Skin microbiome

The human skin is colonized by a variety of microorganisms, most of which are innocuous or offer a benefit to their host; the skin barrier serves to prevent the invasion of pathogenic microorganisms and supports the growth of commensal bacteria. Skin microbiota variability depends on endogenous host factors, the local skin environment, demographic and genetic characteristics of the host, and transmission events. Disruptions in the microbiota balance resulting in an alteration of the continuing inter- and intraspecies interactions of the microorganisms may lead to skin disorders or infections. ⁵¹

From the time of delivery, newborns are exposed for the first time to different types of bacteria from a variety of sources. Immediately after birth, the skin microbiome seems to be undifferentiated across body sites; afterward, the composition of infant skin microflora proves to be site specific, similar to that of adults. ^{52,53} Infants delivered by cesarean section acquire bacterial microbiota resembling their own mother's skin surface microbiota. Vaginal delivery is linked with infant skin

bacterial communities dominated by the Lactobacillus, Prevotella, and Sneathia species. This is in contrast with the skin microbiome of infants born by cesarean section, which is dominated by the Staphylococcus, Corynebacterium, and Propionibacterium species.⁵³

Such differences in the microbial community are related to the specific characteristics of the skin at various anatomical sites. In adults, Propionibacterium and Staphylococcus predominate in sebaceous sites, Corvnebacterium and Staphylococcus predominate in moist sites, while Proteobacteria and Flavobacteriales predominate in dry sites.⁵⁴ During the first days after birth, the function of the skin barrier changes and the evolving skin environment stimulates the growth of some bacteria and limits the growth of others. The amounts of Staphylococcus species are higher on neonatal skin compared with adult skin. Given that infant skin is more hydrated than adult skin, the skin microbiome of newborns resembles the microbiome of moist skin sites in adults. Moreover, in contrast to adults, firmicutes predominate on infant skin, followed by Actinobacteria, Proteobacteria, and Bacteroidetes. The composition of microflora residing on the skin surface continues to evolve over the first year of life.⁵²

Transepidermal water loss

TEWL forms part of insensible water loss and correlates significantly with absolute rates of water loss assessed gravimetrically. This indicates that the intention of quantifying the amount of evaporating water at the skin surface as a marker for barrier function was reached. Different approaches exist for assessing TEWL.55 The method most currently used is based on an estimation of the water gradient through an open chamber, providing continuous measurements in ambient air, with little alterations of the microclimate overlying the skin surface. As an example of an open-chamber system, the Tewameter® (Courage-Khazaka Electronic, Koln, Germany) is well known. It is based on Fick's law of diffusion and represents a standard instrument for the evaluation of TEWL. Criticisms of this traditional open system are related to the confounding effects of ambient and body-induced airflows near the probe, probe size, the limitation in measurement sites, and application/probe angles.⁵⁶ Other important factors to consider during TEWL measurement with an open-chamber method are air convection, room temperature, and ambient humidity.⁵⁷

There is a large interindividual variability in TEWL values with higher values of variance in 3–

6-month-old children compared to older children and adults. There is an inverse linear relationship between TEWL and ambient relative humidity, and the susceptibility to changes in ambient humidity is higher at lower gestational ages. TEWL values are higher in preterm infants compared to full-term and there is an inverse correlation between TEWL and gestational age expressed with the equation: TEWL = 4.17 + 64.76e. (GA-24.99)/2.73 58 Most of the studies on TEWL show that full-term newborns and adults have similar TEWL values, 23,28 while others have reported a lower⁵⁹ or higher ² infant TEWL compared with that of adults. The high values of TEWL observed immediately after birth could be attributed to the skin's functional adaptation to the dry and gaseous extrauterine environment.²⁸ There is also an intersite variation in TEWL. Newborns have higher values in the forearm, palms, and inguinal region compared to other anatomical sites and this may be correlated with sweating and the predominant flexor pronation of the extremities in newborns. 30 After the first week of life, higher values of TEWL appear in the diaper region suggesting that the high humidity of diapering downregulates barrier competence. 1,23

CLINICAL IMPLICATIONS

Infant skin is functionally still developing, and the impaired barrier function of newborn skin makes it more susceptible to chemical irritation and local or systemic infections compared with adults.⁶⁰

In the late neonatal period, about 50% of all deaths are related to sepsis or other severe infections, and the incompetent epidermal barrier can be considered a major predisposing factor for neonatal sepsis development. The barrier permeability is correlated to the antimicrobial barriers, and most of the defensive skin functions are localized in the stratum corneum. Pathogen colonization is limited by the geometry of mature and intact skin layers, low skin water content, low skin pH, resident microflora, antimicrobial surface-deposited free fatty acids, and sphingosine. ⁴⁹

Fragility of the epidermis is marked in preterm infants due to incomplete maturation of the skin barrier. Therefore, use of adhesives on newborn skin and their removal necessitates particular care, especially in preterm newborns. After adhesive removal, TEWL is higher at the site of adhesive application than at other sites, correlating with damaged skin barrier function. Epidermal stripping caused by adhesive removal can be avoided with preventive liquid barrier films on the skin under adhesive dressings. Soft silicon and hydro-

colloid dressings are commonly used in neonatal and pediatric wound management, considering atraumatic removal of these dressings. ⁶³

Thermal and chemical burns can induce serious adverse effects, mostly in neonates who have a skin barrier function that is less effective compared with older children. Newborns sustain full-thickness burns from thermal insults, which may result in superficial thickness burns in older children, and preterm infants have major risks in term of morbidity and wound management. ⁶⁴

Neonatal skin has peculiar absorption characteristics, with high permeability to topical agents. In the early neonatal period, there is a marked topical drug absorption and high skin water loss because of incomplete development of the stratum corneum. There is a decrease in skin permeability with age, and infants of 37 weeks gestational age show no drug transcutaneous absorption and a good skin barrier function. 65 Topically applied agents that are absorbed may cause toxic systemic effects and may induce neurotoxicity, structural damage, and even death. 66 Newborns exposed to topical iodine solutions have an increased risk of developing transient hypothyroidism due to iodine overload. The use of iodine solutions should be avoided in neonates, especially in preterm newborns.⁶⁷ Although the skin of the newborn is relatively impervious to isopropyl alcohol, repeated use of this one can induce systemic intoxication by skin absorption and can cause severe hemorrhagic skin necrosis in preterm newborns. ⁶⁸ Chlorhexidine is a recommended topical antiseptic and can be considered as a safe alternative to alcohol in children >2 months of age because of limited safety data in younger babies.⁶⁹ Systemic toxicity with methemoglobinemia can be associated with skin absorption of aniline dye, which had been used to stamp the name of the institution on diapers. 70 In the process of detoxification, there are some drugmetabolizing enzymes in the skin, which play an important role. Epidermal cells can activate the enzyme system to detoxify or modify agents by oxidation, hydrolyzation, hydroxylation, deamination, or conjugation. Preterm neonates do not have a complete detoxification skin system; therefore, topical substances can be absorbed without chemical modifications. 71 Given the peculiarity of the skin barrier function in the newborn, topical agents should be used only if their systemic administration is not associated with toxicity. Newborns need particular attention in terms of topically applied agent selection, but the risk of intoxication has to be considered also in older children. The use of common topical keratolytic agents, such as lactic

acid or salicylic acid, can lead to systemic toxicity, especially in young patients affected by skin diseases with impaired barriers. 72,73

Newborns have a large surface area in relation to volume and a high thermal conductance with an increased risk of heat loss. Drying the neonate skin using an incubator at thermoneutral temperature can be useful in preventing a rapid decrease in body temperature after birth, especially for low-birth-weight babies who are particularly at risk of heat loss. Hathing newborns in the first hour after birth increases the risk of hypothermia, despite the use of warm water. Rubbing the skin with a sponge during the bath also increases heat loss and should be avoided.

Cleansing of newborns needs to be carried out with particular care to avoid skin or eye irritation and predisposition to skin infections and diseases. It is recommended that caregivers use liquid, pH-neutral, or mildly acidic cleansers for infant cleansing. Liquid cleansers are preferable to water alone, and liquid preparations are preferable to cleansing bars because the preparations often contain emollients. 77

The use of emollients can be helpful to restore skin elasticity, sustain skin homeostasis, and control TEWL, while regular emollient application from birth can be considered an effective approach for atopic dermatitis prevention in neonates at high risk of developing atopic dermatitis. ^{78,79} The application of emollient emulsions to the skin of premature newborns is controversial. Some authors have demonstrated that the application of topical ointments may increase the risk of infections in preterm newborns and therefore suggesting that

Table 1. Structural and functional differences between infant and adult skin

	Infant	Adult	Reference
Structural differences			
Epidermal thickness	Thinner	Thicker	9
	No significant differences		8
Cell attachments and epidermal cellularity	Less	More	3
Dermoepidermal junction	Flat	Undulating	3
Lipids	Less	More	14
Melanin	Less	More	17
Functional differences			
Sweat	Less	More	21,22
Water content	Higher	Lower	15,24
Natural moisturizing factor concentration	Lower	Higher	2
рН	Higher	Lower	29-31
TEWL	Lower	Higher	59
	Higher	Lower	2
	No significant differences		23,28

the prophylactic use of these should be avoided.⁸⁰ Others authors have described a highly significant reduction of nosocomial infections with the topical application of sunflower seed oil in preterm newborns, without side effects.⁸¹ Sunflower oil preserves stratum corneum integrity and improves hydration; it is superior to olive oil, which can promote the development of atopic dermatitis and exacerbate existing dermatitis.⁸²

Considering the susceptibility to irritation, infections, mechanical and thermal insults, and the high permeability to topical agents, especially in newborn skin, preventive care practices should be applied to preserve the integrity of neonatal and child skin and to avoid complications.

SUMMARY

The development of the skin barrier increases with gestational age, and the epidermal maturation is complete at 34 weeks of age. The skin of preterm newborns in the first 2-3 weeks of life is characterized by less functionality. The capacity of sweating is less developed in newborns than in adults and there is a tendency to total anhidrosis in the preterm newborns in the first days after birth. The hydration of stratum corneum is higher in newborns than in adults and their skin pH is alkaline. Most of the studies about TEWL show that full-term newborns and adults have similar TEWL values, but TEWL is higher immediately after birth (Table 1). Given the impaired function of newborn skin, suitable skin care is necessary.

AUTHOR DISCLOSURE AND GHOSTWRITING

The authors do not declare any conflicts of interest. The authors do not declare any ghostwriter contributions.

TAKE-HOME MESSAGE

- Infant skin is functionally still developing as indicated by TEWL values, high pH values, high desquamation, high skin hydration, and different skin microbiome.
- Newborn skin is more fragile, more susceptible to infections, has a high risk of heat loss for high thermal conductance, is more susceptible to chemical and thermal damage, and has high permeability to topical agents, which may induce toxicity.
- Special skin care in newborns, above all in preterm newborns, is necessary.

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Abbreviations and Acronyms

AMPs = antimicrobial peptides

NMF = natural moisturizing factor

TEWL = transepidermal water loss