Skin Physiology of the Neonate and Infant: Clinical Implications

Teresa Oranges, Valentina Dini, and Marco Romanelli*

Wound Healing Research Unit, Department of Dermatology, University of Pisa, Pisa, Italy.

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.

Marco Romanelli, MD, PhD

Submitted for publication February 13, 2015. Accepted in revised form May 11, 2015.

*Correspondence: Wound Healing Research Unit, Department of Dermatology, University of Pisa, Via Roma, 67, Pisa 56126, Italy (e-mail: m.romanelli@med.unipi.it).

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,

DOI: 10.1089/wound.2015.0642

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 full-term newborns, this process begins immediately after birth, while in preterm newborns by 2–3 weeks after birth, the skin is comparable to a full-term newborn's skin.[1] 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 keratinocytes 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.[7] 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.[17] 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.[18]

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 μm of depth from the skin surface.[2] 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 corneocytes, and the intercellular and extracellular hygroscopic molecular complex known as the natural moisturizing factor (NMF).[26] During the corneocyte 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,[2] 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 phospholipids[36] and cis-urocanic generation by degradation of histidine[37] are two of the most important endogenous mechanisms involved. Exogenous mechanisms such as lactate production in sweat glands[38] and microbial hydrolysis of sebaceous triglycerides[39] 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.[4] 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, Corynebacterium 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.[2] 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 lower[59] 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.[4,61] 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.[62] 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 drug-metabolizing 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.[74] Bathing newborns in the first hour after birth increases the risk of hypothermia, despite the use of warm water.[75] Rubbing the skin with a sponge during the bath also increases heat loss and should be avoided.[76]

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
pH	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.

ABOUT THE AUTHORS

Teresa Oranges, MD, graduated from the University of Florence, Italy. She is currently a resident in the Department of Dermatology at the Santa Chiara Hospital of the University of Pisa. She is a member of the European Academy of Dermatology and Venereology (EADV) and the Italian Society of Dermatology (SIDeMaST). **Valentina Dini, MD, PhD,** is an Assistant Professor of Dermatology at the University of Pisa School of Medicine. She received her doctorate in Experimental Dermatology in 2009 from the University of Pisa and did her postdoctoral fellowship at the Wound Healing Research Unit of the Department of Dermatology and Cutaneous Surgery, University of Miami. Her research interests focus on noninvasive diagnostic assessment of skin diseases and use of biologics in autoimmune diseases. **Marco Romanelli, MD, PhD,** is an Associate Professor of Dermatology at the University of Pisa, School of Medicine. He is also the chief of the Wound Healing Research Unit at the Santa Chiara Hospital of the University of Pisa. He is currently the President elect of the World Union of Wound Healing Societies (WUWHS).

REFERENCES

1. Fluhr JW, Darlenski R, Taieb A, et al. Functional skin and adaptation in infancy–almost complete but not fully competent. Exp Dermatol 2010;19:483–492.
2. Nikolovski J, Stamatas GN, Kollias N, et al. Barrier function and water-holding and transport properties of infant stratum corneum are different from adult and continue to develop through the first year of life. J Invest Dermatol 2008;128:1728–1736.
3. Evans NJ, Rutter N. Development of the epidermis in the newborn. Biol Neonate 1986;49:74–80.
4. Visscher M, Narendran V. The ontogeny of skin. Adv Wound Care 2014;3:291–303.
5. Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. Exp Dermatol 2008;17:1063–1072.
6. Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. Nat Rev Mol Cell Biol 2005;6:328–340.
7. Vaigundan D, Kalmankar NV, Krishnappa J, et al. A novel mutation in the transglutaminase-1 gene in an autosomal recessive congenital ichthyosis patient. Biomed Res Int 2014;2014:706827.
8. Fairley JA, Rasmussen JE. Comparison of stratum corneum thickness in children and adults. J Am Acad Dermatol 1983;8:652–654.
9. Stamatas GN, Nikolovski J, Luedtke MA, et al. Infant skin microstructure assessed *in vivo* differs from adult skin in organization and at the cellular level. Pediatr Dermatol 2010;27:125–131.

10. Villone D, Fritsch A, Koch M, et al. Supramolecular interactions in the dermo-epidermal junction zone: anchoring fibril-collagen VII tightly binds tobanded collagen fibrils. J Biol Chem 2008;283: 24506–24513.

11. Ellison J, Garrod DR. Anchoring filaments of the amphibian epidermal-dermal junction traverse the basal lamina entirely from the plasma membrane of hemidesmosomes to the dermis. J Cell Sci 1984;72:163–172.

12. Holbrook KA. A histologic comparison of infant and adult skin. In: Maibach HI, Boisits EK, eds. Neonatal Skin: Structure and Function. New York: Marcel Dekker, Inc., 1982:3–31.

13. Perera P, Kurban AK, Ryan TJ. The development of the cutaneous microvascular system in the newborn. Br J Dermatol 1970;82:86–91.

14. Agache P, Blanc D, Barrand C, Laurent R. Sebum levels during the first year of life. Br J Dermatol 1980;103:643–649.

15. Hoeger PH, Enzmann CC. Skin physiology of the neonate and young infant: a prospective study of functional skin parameters during early infancy. Pediatr Dermatol 2002;19:256–262.

16. Friedman Z. Essential fatty acids revisited. Am J Dis Child 1980;134:397–408.

17. Mack MC, Tierney NK, Ruvolo E Jr, et al. Development of solar UVR-related pigmentation begins as early as the first summer of life. J Invest Dermatol 2011;131:1388.

18. Kulichivá D, Dáňová J, Kunte C, et al. Risk factors for malignant melanoma and preventive methods. Cutis 2014;94:241–248.

19. Caspers PJ, Lucassen GW, Carter EA, et al. *In vivo* confocal Raman microspectroscopy of the skin: noninvasive determination of molecular concentration profiles. J Invest Dermatol 2001;116:434–442.

20. Green M. Comparison of adult and neonatal skin eccrine sweating. In: Maibach HI, Boisits EK, eds. Neonatal Skin. New York: Marcel Dekker, 1981:35.

21. Harpin VA, Rutter N. Sweating in preterm babies. J Pediatr 1982;100:614–619.

22. Harpin VA, Rutter N. Development of emotional sweating in the newborn infant. Arch Dis Child 1982;57:691–695.

23. Giusti F, Martella A, Bertoni L, Seidenari S. Skin barrier, hydration, and pH of the skin of infants under 2 years of age. Pediatr Dermatol 2001;18: 93–96.

24. Visscher MO, Chatterjee R, Munson KA, et al. Changes in diapered and non-diapered infant skin over the first month of life. Pediatr Dermatol 2000;17:45–51.

25. Saijo S, Tagami H. Dry skin of newborn infants: functional analysis of the stratum corneum. Pediatr Dermatol 1991;8:155–159.

26. Rawlings AV, Matt PJ. Stratum corneum moisturization at the molecular level: an update in relation to the dry skin cycle. J Invest Dermatol 2005;124:1099–1110.

27. Bouwstra JA, Groenink HW, Kempenaar JA, et al. Water distribution and natural moisturizer factor content in human skin equivalents are regulated by environmental relative humidity. J Invest Dermatol 2008;128:378–388.

28. Fluhr JW, Darlenski R, Lachmann N, et al. Infant epidermal skin physiology: adaptation after birth. Br J Dermatol 2012;166:483–490.

29. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. Skin Pharmacol Physiol 2006;19:296–302.

30. Yosipovitch G, Maayan-Metzger A, Merlob P, Sirota L. Skin barrier properties in different body areas in neonates. Pediatrics 2000;106(Pt 1):105–108.

31. Lund C, Kuller J, Lane A, et al. Neonatal skin care: the scientific basis for practice. Neonatal Netw 1999;18:15–27.

32. Jauniaux E, Gulbis B. Fluid compartments of the embryonic environment. Hum Reprod Update 2000;6:268–278.

33. Korting HC, Kober M, Mueller M, Braun-Falco O. Influence of repeated washings with soap and synthetic detergents on pH and resident flora of the skin of forehead and forearm. Acta Derm Venereol (Stockh) 1987;67:41–47.

34. Mauro T, Holleran WM, Grayson S, et al. Barrier recovery is impeded at neutral pH, independent of ionic effects: implications for extracellular lipid processing. Arch Dermatol Res 1998;290: 215–222.

35. Hachem JP, Man MQ, Crumrine D, et al. Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity. J Invest Dermatol 2005;125:510–520.

36. Fluhr JW, Behne MJ, Brown BE. Stratum corneum acidification in neonatal skin: secretory phospholipase A2 and the sodium/hydrogen antiporter-1 acidify neonatal rat stratum corneum. J Invest Dermatol 2004;122:320–329.

37. Krien PM, Kermici M. Evidence for the existence of a self-regulated enzymatic process within the human stratum corneum -an unexpected role for urocanic acid. J Invest Dermatol 2000;115:414–420.

38. Ament W, Huizenga JR, Mook GA, et al. Lactate and ammonia concentration in blood and sweat during incremental cycle ergometer exercise. Int J Sports Med 1997;18:35–39.

39. Puhvel SM, Reisner RM, Sakamoto M. Analysis of lipid composition of isolated human sebaceous gland homogenates after incubation with cutaneous bacteria. Thin-layer chromatography. J Invest Dermatol 1975;64:406–411.

40. Rissman R, Groenink HW, Weerheim AM, et al. New insights into ultrastructure, lipid composition and organization of vernix caseosa. J Invest Dermatol 2006;126:1823–1833.

41. Pickens WL, Warner RR, Boissy YL, et al. Characterization of vernix caseosa: water content, morphology, and elemental analysis. J Invest Dermatol 2000;115:875–881.

42. Kaerkkaeinen J, Nikkari T, Ruponen S, Haahti E. Lipids of vernix caseosa. J Invest Dermatol 1965; 44:333–338.

43. Visscher MO, Narendran V, Pickens WL, et al. Vernix caseosa in neonatal adaptation. J Perinatol 2005;25:440–446.

44. Tay SS, Roediger B, Tong PL, et al. The skin-resident immune network. Curr Dermatol Rep 2013;3:13–22.

45. Gallo RL, Nakatsujj T. Microbial symbiosis with the innate immune defense system of the skin. J Invest Dermatol 2011;131:1974–1980.

46. Drake DR, Brogden KA, Dawson DV, Wertz PW. Thematic review series: skin lipids. Antimicrobial lipids at the skin surface. J Lipid Res 2008;49:4–11.

47. Schittek B, Hipfel R, Sauer B, Bauer J, Kalbacher H, Stevanovic S, et al. Dermcidin: a novel human antibiotic peptide secreted by sweat glands. Nat Immunol 2001;2:1133–1137.

48. Harder J, Schroder JM. RNase 7, a novel innate immune defense antimicrobial protein of healthy human skin. J Biol Chem 2002;277:46779–46784.

49. Elias PM. The skin barrier as an innate immune element. Semin Immunopathol 2007;29:2–14.

50. Walker VP, Akinbi HT, Meinzen-Derr J, et al. Host defense proteins on the surface of neonatal skin: implications for innate immunity. J Pediatr 2008; 152:777–781.

51. Rosenthal M, Goldberg D, Aiello A, et al. Skin microbiota: microbial community structure and its potential association with health and disease. Infect Genet Evol 2011;11:839–848.

52. Capone KA, Dowd SE, Stamatas GN, Nikolovski J. Diversity of the human skin microbiome early in life. J Invest Dermatol 2011;131:2026–2032.

53. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 2010;107:11971–11975.

54. Grice EA, Kong HH, Conlan S, et al. Topographical and temporal diversity of the human skin microbiome. Science 2009;324:1190–1192.

55. Dini V, Barbanera S, Romanelli M. Quantitative evaluation of maceration in venous leg ulcers by transepidermal water loss measurements. Int J Low Extrem Wounds 2014;13:116–119.

56. Alanen E, Wiesemann F, Nuutinen J, et al. Measurement of skin hydratation in the diapered area of infants with a closed chamber TEWL meter. Skin Res Technol 2003;9:199.

57. Pinnagoda J, Tupker RA, Agner T, et al. Guidelines for transepidermal water loss (TEWL) measurement. A report from the Standardization Group of the European Society of Contact Dermatitis. Contact Dermatitis 1990; 22:164–178.

58. Hammarlund K, Sedin G. Transepidermal water loss in newborn infants. III. Relation to gestational age. Acta Pediatr Scand 1979;68:759–801.

59. Shlivko IL, Petrova GA, Zor'kina MV, et al. Complex assessment of age-specific morphofunctional features of skin of different anatomic localizations. Skin Res Technol 2013;19: e85–e92.

60. Eichenfield LF, Hardaway CA. Neonatal dermatology. Curr Opin Pediatr 1999;11:471–474.

61. Oza S, Lawn JE, Hogan DR, et al. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013. Bull World Health Organ 2015;93:19–28.

62. Lund CH. Disruption of barrier function in neonatal skin associated with adhesive removal. J Pediatr 1997;131:367–372.

63. Baharestani MM. An overview of neonatal and pediatric wound care knowledge and considerations. Ostomy Wound Manage 2007;53:34–36, 38, 40, passim.

64. Mannan K, Chow P, Lissauer T, Godambe S. Mistaken identity of skin cleansing solution leading to extensive chemical burns in an extremely preterm infant. Acta Paediatr 2007;10:1536–1537.

65. Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. J Pediatr 1983;102:419–425.

66. Rutter N. Percutaneous drug absorption in the newborn: hazards and uses. Clin Perinatol 1987;14: 911–930.

67. Khashu M, Chessex P, Chanoine JP. Iodine overload and severe hypothyroidism in a premature neonate. J Pediatr Surg 2005;40:E1–E4.

68. Vivier PM, Lewander WJ, Martin HF, Linakis JG. Isopropyl alcohol intoxication in a neonate through chronic dermal exposure: a complication of a culturally-based umbilical care practice. Pediatr Emerg Care 1994;10:91–93.

69. Chapman AK, Aucott SW, Milstone AM. Safety of chlorhexidine gluconate used for skin antisepsis in the preterm infant. J Perinatol 2012; 32:4–9.

70. Rayner W. Cyanosis in newly born children caused by aniline marking ink. Br Med J 1886;I:294.

71. Oesch F, Fabian E, Oesch-Bartlomowicz B, et al. Drug-metabolizing enzymes in the skin of man, rat, and pig. Drug Metab Rev 2007;39:659–698.

72. Ramírez ME, Youseef WF, Romero RG, et al. Acute percutaneous lactic acid poisoning in a child. Pediatr Dermatol 2006;23:282–285.

73. Chiaretti A, Schembri Wismayer D, Tortorolo L, et al. Salicylate intoxication using a skin ointment. Acta Paediatr 1997;86:330–331.

74. Smales OR, Kime R. Thermoregulation in babies immediatly after birth. Arch Dis Child 1978;53: 58–61.

75. Bergström A, Byaruhanga R, Okong P. The impact of newborn bathing on the prevalence of neonatal hypothermia in Uganda: a randomized, controlled trial. Acta Paediatr 2005;94:1462–1467.

76. Bryanton J, Walsh D, Barrett M, Gaudet D. Tub bathing versus traditional sponge bathing for the newborn. J Obstet Gynecol Neonatal Nurs 2004; 33:704–712.

77. Blume-Peytavi U, Cork MJ, Faergemann J, et al. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. J Eur Acad Dermatol Venereol 2009;23:751–759.

78. Fernandes JD, Machado MC, Oliveira ZN. Children and newborn skin care and prevention. An Bras Dermatol 2011;86:102–110.

79. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol 2014;134:818–823.

80. Conner JM, Soll RF, Edwards WH. Topical ointment for preventing infection in preterm infants. Cochrane Database Syst Rev 2004;1:CD001150.

81. Darmstadt GL, Badrawi N, Law PA, et al. Topically applied sunflower seed oil prevents invasive bacterial infections in preterm infants in Egypt: a randomized, controlled clinical trial. Pediatr Infect Dis J 2004;23:719–725.

82. Danby SG, Alenezi T, Sultan A, et al. Effect of olive and sunflower seed oil on the adult skin barrier: implications for neonatal skin care. Pediatr Dermatol 2013;30:42–50.

Abbreviations and Acronyms

AMPs = antimicrobial peptides
NMF = natural moisturizing factor
TEWL = transepidermal water loss