Topical agents include anything that touches the infant’s skin. The skin is crucial to the way the infant perceives and responds to the care environment and, therefore, in neurodevelopment. Psychological stress negatively affects the barrier. The full-term infant has well-developed epidermal barrier despite spending 9 months being submerged in water. Vernix caseosa is a natural topical agent that facilitates stratum corneum barrier development through protective and adaptive mechanisms. Its properties include hydration, wound healing, anti-infection, and acid mantle development. The ontogeny of neonatal skin development and vernix biology provide the basis for assisting barrier maturation in premature infants, treating compromised skin and selecting topical agents. The published research on the effects of topical products on premature and damaged neonatal skin is very limited, especially for adequately sized randomized controlled clinical trials. Health care providers have keen interest and the skills to identify improved treatments through outcomes-based research.

Keywords: Skin barrier; Neonate, Topical agent; Stratum corneum; Compromised skin

Overview and Perspective

The article will review topical products in infants. Conceptually, we define topical products in the broadest sense to include anything that touches or interacts with infant skin. The skin is a primary care interface vitally important in any patient-caregiver interaction. The most recent information about skin structure, development, and function will be discussed to generate the context of topical treatments and products.

Touch is the first sense to develop in the infant. As a result, the skin is an important element in the process of how the infant perceives and reacts to the environment of care and, therefore, in neonatal neurodevelopment. Examples of skin-based infant interactions include skin-to-skin contact (kangaroo care), infant massage, Newborn Individualized Developmental Care and Assessment (NIDCAP), and tactile stimulation. Skin-to-skin contact immediately after birth results in increased temperature and blood glucose levels compared with swaddling next to the mother. Skin-to-skin contact for 1 hour shortly after birth impacted state organization and the time spent sleeping. Premature infants cared for with NIDCAP methods had significantly better neurobehavioral function and more mature neuronal fiber structure. In a longer-term study, infants receiving NIDCAP had significantly better mother-child interaction (cluster communication), better hearing/speech, and lower behavior symptom scores. Tactile stimulation via repeated stroking increased circulating lactate levels by 200% in the neonatal rat model. These findings demonstrate the critical role of simple infant-caregiver skin-based interactions on the cognitive development of the infant.

Specific skin receptors are sensitive to mechanical stimuli and are critical for survival. The signaling proteins involved in this transduction are being identified. Psychological stress due to environmental overcrowding is associated with a delay in skin barrier recovery in mice, an effect attributed to increased production of glucocorticoids. Psychological stress decreased epidermal cell proliferation, adversely affected differentiation, and decreased the size and density of corneodesmosomes, all of which negatively impact skin barrier function. Stress decreased antimicrobial peptides in the epidermis (animal model), an effect that resulted in more severe skin infections.

Skin Structure and Function

Human skin serves multiple functions including barrier (to water loss, irritant exposure, light, etc), immunosurveillance, infection control, sensation, structural support, and thermal regulation (Table 1). The major skin layers are the epidermis, dermis, and hypodermis (subcutaneous). Fig 1 shows a cross-section and the structures responsible for the functions. Two layers comprise the dermis. The upper is the papillary layer, contains capillary loops, and is loosely organized. The lower is the reticular dermis composed of tightly packed collagen and elastin with glycosaminoglycans, which provide mechanical properties and elasticity. The epidermis includes the stratum corneum (SC, outer) and the viable epidermis (Fig 2). An understanding of SC structure and function is essential for being
able to select topical products. The SC is the main barrier to water loss and penetration by outside agents. The viable epidermis has four layers (top to bottom): clear (stratum lucidum), granular (stratum granulosum), spinous (stratum spinosum, nucleated cells), and basal (stratum basale, nucleated cells). Two specialized dendritic cells are housed in the viable epidermis. Langerhans cells (antigen-presenting cells) are part of the immune system and serve as the line of defense if the SC barrier is breached (Fig 2). The melanocytes (pigment cells) reside in the basal layer and produce melanin, the pigment responsible in part for inherent skin color. When the skin is exposed to UV radiation, melanocytes are activated and transport melanin to the nuclei of the epidermal cells to shield them and protect the DNA. Skin tanning is the result of this process. The pigmentary system is influenced by irritation and inflammation and may respond by producing more pigment (hyperpigmentation) or by deactivation (resulting in hypopigmentation).

The function of the viable epidermis is to continually build and replenish the SC. The cells “move up” from the basal layer and transition to SC cells through a programmed process. About 28 days is required for a cell to go from the basal layer and be lost from the outer SC. The SC is made up of about 16 layers of flattened cells (corneocytes) joined together by molecular “rivets” (aggregates of large molecules) called desmosomes (insert in Fig 2). The SC is about half of the thickness of a sheet of paper but incredibly strong. The process of going from nucleated cells to SC corneocytes begins in the upper spinous and granular cells with formation of the cross-linked cell envelope. Structures, called lamellar bodies, in the spinous layer store lipids. In the upper granular layer (below the SC), the lipids (cholesterol, fatty acids, ceramides) are secreted from the lamellar bodies into the intercellular spaces between the corneocytes to form a regular “brick (cells) and mortar (lipids)” structure. The lipids form a regular ordered bilayer structure, alternating with water, between the cells. By design, the SC structure is difficult to penetrate from the outside. It is the barrier to water loss but allows normal water vapor from respiration to be released. The integrity of the SC is measured in terms of the rate of transepidermal water loss (TEWL). Normal skin has TEWL values of approximately 6 to 8 grams per square meter per hour, and higher rates indicate a damaged barrier, poorly developed SC, or SC with fewer layers than normal. The important goal of topical skin treatments is to maintain or restore the SC barrier. A schematic of showing normal and compromised SC barriers is shown in Fig 3. Normal skin looses about one SC layer per day through the process of desquamation where the connections between SC cells degrade and release the cells to the environment. An appropriate level of hydration is required for proper desquamation. Stratum corneum that is too dry will not desquamate properly and results in large aggregates of cells, scales or dry skin flakes. The protein filaggrin in the SC corneocytes is converted to small water-binding amino acids called natural moisturizing factor (NMF). Natural moisturizing factor is in part responsible for maintaining the appropriate level of SC hydration, and loss of NMF or disruption of the NMF generation will result in low SC moisture. Excess hydration will also cause barrier damage as will be discussed later.

### Neonatal Skin Development

Birth marks are a significant environmental change for the infant from a warm, sterile, and safe womb to a dry high-oxygen environment with multiple organisms (bacteria) and demands for self-sufficiency such as air breathing, enteral nutrition, waste elimination, and maintenance of water balance. Neonatal skin serves many functions at birth, including a barrier to water loss and chemicals, temperature regulation, tactile discrimination,

<table>
<thead>
<tr>
<th>Table 1. Skin Functions</th>
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<tbody>
<tr>
<td>Function</td>
</tr>
<tr>
<td>Barrier</td>
</tr>
<tr>
<td>Physical (irritants)</td>
</tr>
<tr>
<td>Light</td>
</tr>
<tr>
<td>Immunologic</td>
</tr>
<tr>
<td>Resilient foundation</td>
</tr>
<tr>
<td>Sensation</td>
</tr>
<tr>
<td>Tactile discrimination</td>
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<tr>
<td>Thermal regulation</td>
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Fig 1. Skin structures. A cross-section of the skin shows the structures responsible for the functions. The major skin layers are the epidermis, dermis, and hypodermis (subcutaneous). The outermost layer, the SC, is directly exposed to the environment. The figure was provided by the National Institutes of Health for use by the public and can be found at [http://media.nih.gov/imagebank/display_search](http://media.nih.gov/imagebank/display_search).
infection control, immunosurveillance, antioxidation, and acid mantle formation.

The Full-Term Infant

The full-term infant has well-developed epidermal barrier at birth, despite spending 9 months being submerged in water. In most cases, overhydration of the skin has a damaging effect, that is, maceration, barrier disruption, and tissue injury. Transepidermal water loss (rate of respiratory water vapor loss, TEWL) is very low at birth for full-term infant, equal to or lower than adults, indicating a highly effective skin barrier. Within minutes to hours after birth, skin hydration (moisture) varies with body site (chest, back, forehead), time under the warmer, and retention or removal of vernix caseosa. Hydration decreases rapidly in the first day and then increases during the first 2 weeks compared with constant values in the mother. This change indicates that significant adaptive changes occur in the upper SC. Newborn skin was significantly drier than the skin of older infants (1, 2, and 6 months) and the mothers. Water-binding ability increased during the first 14 days, denoting changes in the water-handling processes within the SC. To identify possible causes of low hydration, we measured the NMF levels at birth and found it to be extremely low. They were higher at 1 month but lower than levels in adults. Natural moisturizing factor is water soluble and may be extracted from the SC into the amniotic fluid. Alternatively, NMF generation from filaggrin may be activated as part of the adaptation to dry conditions. At birth, the full-term skin pH is relatively neutral, decreases significantly during the first 1 to 4 days, and continues to drop during the first 3 months. The antimicrobial protein lysozyme was found in newborn SC at levels five times higher than adults. Lysozyme activity was not altered with routine bathing.

Vernix Caseosa: Natural Topical Treatment

The question remains: How does the full-term infant develop an excellent barrier while in water? During the last trimester, vernix caseosa begins to coat the skin from head to toe and back to front and may facilitate SC barrier development. Vernix is a complex mixture of 80% water, 10% protein, and 10% lipids, with corneocytes embedded in a lipid matrix. Vernix formation is believed to be under hormonal control during gestation, with lipids generated by the sebaceous gland and cells from the hair follicle. It is "extruded" onto the interfollicular epidermis to cover the whole surface. Presumably, vernix forms a hydrophobic surface, thereby protecting the epidermis from exposure to water, and creates conditions under which the cornification and formation of the SC can occur. Vernix contains antimicrobials; for example, lysozyme, lactoferrin, and the antiinfective properties have been demonstrated by several researchers. Vernix treatment of adult volar skin increased the SC water-binding capacity. Native vernix treatment of SC wounds (tape stripped skin) assisted barrier repair relative to controls and

Fig 2. Structure of the epidermis. The SC is the main barrier to water loss and penetration by outside agents. The viable epidermis has four layers (top to bottom): clear, granular, spinous (nucleated cells), and basal (nucleated cells). Two specialized dendritic cells are housed in the viable epidermis. Langerhans cells (antigen-presenting cells) are part of the immune system and serve as the line of defense if the SC barrier is breached.
demonstrated wound healing properties. In some settings, vernix is removed immediately after birth. The role of vernix in neonatal skin adaptation was assessed by comparing the effects of vernix retention vs removal in parallel groups of full-term infants at delivery. Vernix retention resulted in significantly higher skin hydration 24 hours after birth. Skin pH values were lower in the vernix-retained group, suggesting that vernix facilitates the development of the acid mantle. Treatment of SC wounds (created by repeatedly tape stripping adult forearm skin to remove SC layers) with vernix assisted barrier repair relative to controls. In model systems, vernix enhanced SC formation without increasing epidermal thickness. Films of vernix impeded the penetration of the exogenous enzyme chymotrypsin (found in meconium, similar proteolytic enzymes present in feces) but maintained the activity of native enzymes (necessary for epidermal development) in vitro.

Overall, vernix facilitates SC barrier development in the normal full-term infant through a variety of protective and adaptive mechanisms. The findings provide support for the practice of vernix retention (rather than removal) at birth. The World Health Organization recommends waiting for at least 6 hours before bathing newborn infants in part to facilitate the positive effects of residual vernix.

Premature Infant Skin Development

Unlike that of the full-term baby, the dermis of the premature infant is not fully formed and deficient of structural proteins. As a result, the mechanical properties are poor and the skin is easily torn. The preterm epidermis is markedly thinner, and the SC is poorly formed in contrast to the thick fully developed SC of the full-term neonate. The SC structural integrity is directly related to gestational age at birth, and rapid barrier development occurs from weeks 24 to 34. Very low-birth-weight infants are at greatest risk for skin damage during the early days of life. At 23 weeks, the SC is nearly absent with TEWL of 75 grams per square meter per hour (Fig 3). By week 26, a few cornified layers have formed (TEWL of approximately 45 grams per square meter per hour). The very premature infant has, essentially, a wounded skin surface. At 29 weeks, the TEWL is 17 grams per square meter per hour and markedly higher than the values of 5 to 6 grams per square meter per hour observed in the full-term infant. Around weeks 34 to 35, the barrier is relatively well formed. Infants born prematurely (ie, <28 weeks) do not have the covering of vernix. Poor SC integrity puts the premature infant at risk for high water loss, electrolyte imbalance, thermal instability and increased exposure to environmental irritants and infectious agents due to increased permeability. After birth, the barrier continues to develop, but even after 1 month, TEWL is significantly higher than in normal full-term infants. Further impairment of barrier function in premature infants was indicated by significantly higher values of skin hydration, and infants less than 30 weeks gestation have significantly higher values of skin hydration than those older than 30 weeks as a result of higher rates of water being lost through the skin. By day 5, the skin hydration was significantly lower for infants less than 27 weeks’ gestational age, indicating rapid barrier development. The humidity of the environment influences the rate and quality of SC barrier maturation. Exposure to low humidity (10% relative humidity [RH], animal model) resulted in a decrease in SC hydration and an increase in epidermal DNA synthesis. This observation suggests that low hydration triggers cell proliferation. Clinically, very premature infants frequently exhibit an abnormal pattern of desquamation several weeks after birth, indicative of a hyperproliferative SC. Humidity affects the degradation of epidermal filaggrin to NMF that binds water in the SC. Without NMF, the SC is dry, does not desquamate properly, and has poor water-holding capacity. At birth (animal model), filaggrin degradation occurred at 80% to 95% humidity but not at high (100% RH) or low humidities, suggesting that NMF generation depends upon ambient water activity. Natural moisturizing factor levels are likely to be very low under the conditions of rapid SC development such as for premature infants in low humidity.

Skin Occlusion

Appropriate SC hydration is necessary for effective skin function, for example, to allow sufficient plasticity and flexibility during movement, to prevent cracking, and for

Fig 3. The development of the SC occurs during the last trimester of gestation and is relatively well formed on average by week 34 to 35. At 23 weeks, the SC is nearly absent and TEWL values are 75 grams per square meter per hour. By week 26, a few cornified layers have formed (TEWL of approximately 45 grams per square meter per hour). At 29 weeks, the TEWL is 17 grams per square meter per hour and markedly higher than values of 5 to 6 grams per square meter per hour observed in the full-term infant.
However, prolonged exposure to water causes skin maceration, barrier breakdown, and dermatoses, including inflammation, irritation, and urticaria. Water exposure caused SC abnormalities, including disruption of the intercellular lipid bilayers, degradation of the desmosomes, and creation of amorphous regions within the lipids, as illustrated in Fig 3.

Hydration causes the SC corneocytes to swell, increases the fluidity of the lipids, and enhances molecular transport to increase permeability to exogenous materials. Occlusion of the skin surface can occur from any material that does not allow sufficient water to pass through it, including diapers, certain tapes, thick layers of topical products, and devices such as braces, casts, and splints. Water builds up under the material and causes SC hydration to increase and barrier damage to occur, as shown in Fig 4.

**Topical Treatments for Infants**

The biology of infant skin development and maturation provides the clues for identifying strategies for treating compromised skin. Vernix may be the “ideal” topical treatment, as some suggest, for infants and adults. Infants born prematurely (ie, <28 weeks) are missing protective covering of vernix. In the broadest sense of “topical treatments” as anything that interacts with the outer skin surface, specific strategies will be discussed.

**Treatments for Barrier Maturation**

*Environmental conditions* Humidified isoletes have been used to mitigate the high water loss in premature infants. Extremely low-birth-weight infants needed lower fluids and had improved electrolyte balance. Humidity is used routinely with levels adjusted to manage fluid loss, temperature, and so on to ensure that overhumidification does not cause bacterial contamination. A 2006 study among infants of 23 to 27 weeks’ gestational age showed that the SC barrier developed more rapidly for the neonates in isoletes at 50% RH compared with infants at 75% RH.

*Films* Transparent semipermeable dressings (eg, Tegaderm; 3M, St. Paul, MN) have been used to control water loss in premature infants. Tegaderm dressing was applied to large body surface areas on infants of 24 to 26 weeks’ gestational age, and daily fluid intake, serum sodium levels, and weight loss were significantly lower compared with infants who had not been treated. Transepidermal water loss was also reduced, indicating that the film had assisted in barrier maturation. In infants less than 32 weeks’ gestational age, TEWL decreased for a skin site treated with a semipermeable dressing relative to the untreated control, and counts of gram-negative bacilli were comparable. Application of nonadhesive semipermeable films to infants less than 32 weeks’ gestational age significantly reduced water loss and improved barrier maturation compared with the contralateral untreated control site. For infants of 770 to 1450 grams, those treated with a dressing required less current for thermal control and had lower TEWL than the untreated control group.

*Barrier creams* The effects of whole-body treatment topical petrolatum-based “skin barrier creams” in premature infants have been reported in various settings. Infants (n = 32, 29–36 weeks) received a cream (containing petrolatum, mineral oil,
mineral wax, wool wax alcohol, water) or no treatment twice a day for 12 days. Transepidermal water loss decreased for both groups, but skin condition was better for the treatment group vs the controls whose condition worsened. A second study among 60 babies (<33 weeks; mean, 29 weeks) who were treated with a similar formulation twice a day showed lower TEWL, less dermatitis, lower skin colonization, and fewer positive blood and cerebrospinal fluid cultures. A group of investigators from Association of Women’s Health Obstetric and Neonatal Nurses (AWHONN) and National Association of Neonatal Nurses (NANN) conducted a major research project to review the scientific literature and develop an evidence-based practice guideline for all aspects of skin care for neonates. Based on the available research, the guideline recommended twice-daily whole-body application of a barrier cream (eg, Aquaphor (Beiersdorf AG, Hamburg, Germany) containing petrolatum, mineral oil, mineral wax, wool wax alcohol, water). To test the effectiveness of the practices on outcome, that is, skin condition and compliance, they enrolled 51 units across the country to participate. The research plan involved education in the specific practices and evaluation methods. A total of 2820 infants (mean, 2100 grams; range, 500–5700 grams) were included. The skin condition score decreased, and the frequency of compliance with the guideline increased as a result (preguideline vs postguideline comparison). The skin scores reflected the combination of practices, and the effect of the topical treatment alone could not be determined. Infection rates were not formally evaluated.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Allowed Amounts (%)</th>
<th>Other Label Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allantoin</td>
<td>0.5–2</td>
<td>★, #</td>
</tr>
<tr>
<td>Aluminum hydroxide gel</td>
<td>0.15–5</td>
<td></td>
</tr>
<tr>
<td>Calamine</td>
<td>1–25</td>
<td></td>
</tr>
<tr>
<td>Cocoa butter</td>
<td>50–100</td>
<td>★, #</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>5–13.56 not to exceed 10 000 USP units of vitamin A, and 400 USP units cholecalciferol</td>
<td>★</td>
</tr>
<tr>
<td>Colloidal oatmeal</td>
<td>0.007 (minimum) or 0.003 (minimum) combined with mineral oil</td>
<td></td>
</tr>
<tr>
<td>Dimethicone</td>
<td>1–30</td>
<td></td>
</tr>
<tr>
<td>Glycerin</td>
<td>20–45</td>
<td>★</td>
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<tr>
<td>Hard fat</td>
<td>50–100</td>
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</tr>
<tr>
<td>Kaolin</td>
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</tr>
<tr>
<td>Lanolin</td>
<td>12.5–50</td>
<td>★, #</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>50–100 and 30–35 with colloidal oatmeal</td>
<td>★, #</td>
</tr>
<tr>
<td>Petrolatum</td>
<td>30–100</td>
<td>★, #</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Na</td>
<td></td>
</tr>
<tr>
<td>Topical starch</td>
<td>10–98</td>
<td></td>
</tr>
<tr>
<td>White petrolatum</td>
<td>30–100</td>
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</tr>
<tr>
<td>Zinc acetate</td>
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<tr>
<td>Zinc carbonate</td>
<td>0.2–2</td>
<td></td>
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<tr>
<td>Zinc oxide</td>
<td>1–25</td>
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Those with asterisk (★) may also claim “temporarily protects minor cuts, scrapes, and burns,” and those with pound sign (#) can state “helps prevent and temporarily protects and helps relieve chafed, chapped, or cracked skin. USP = United States Pharmacopeia.

Fig 5. A, Normal and damaged SC. The SC cells are joined by molecular “rivets” called desmosomes. The lipid bilayer structure can be compromised, for example, from water exposure. Irritants can more easily penetrate a damaged barrier. Premature infant skin has fewer SC layers and, therefore, increased permeability. B, Effects of the diaper environment. The figure illustrates how factors of the “diaper environment” impact skin barrier structure, function, and response. The humid environment leads to overhydration of the SC causing disruption of the lipid bilayer structure. When the SC integrity is damaged, irritants and microorganisms can penetrate and reach the Langerhans cells and epidermis. Fecal enzymes disrupt the SC integrity by degrading proteins, providing another mechanism for barrier breach. Penetrants/irritants interact with keratinocytes, stimulating them to release cytokines. Cytokines act on the vasculature of the dermis, resulting in inflammation.
A Normal and Damaged Stratum Corneum

Disrupted lipid bilayer

Normal lipid bilayer

Normal SC Structure

Premature SC with fewer SC layers

Damaged SC with structural defects. SC penetration can occur more easily

B Effects of the Diaper Environment

Over-hydration

SC with structural defects. Penetration occurs more easily.

Enzyme damage

Penetrants interact with the keratinocytes and fibroblasts.

Microorganisms can enter to reach the Langerhans cells and epidermis.

Irritants stimulate cytokine release by keratinocytes.

Cytokines increases erythema via vasculature.
Another multicenter (n = 54 neonatal intensive care units) trial in 1191 younger premature infants (mean, 26.2 weeks) compared twice-daily treatment with an ointment (petrolatum, mineral oil, mineral wax, wool wax alcohol) with no treatment among parallel groups to isolate the effects of the ointment.\(^6\) The nosocomial infection rates were not different for the total group but were significantly higher for the treatment vs control among infants from 501 to 750 grams. The sepsis was caused by coagulase negative in more than 60% of the cases. This finding was not anticipated, given the favorable results of others. However, the infants from this multicenter trial had a mean estimated gestational age (EGA) of 26 weeks vs the mean of 29 weeks in previous reports. Transepidermal water loss was not measured, but TEWL for a 26-week infant would be about 45 grams per square meter per hour vs 15 to 17 grams per square meter per hour for a 29-week infant and represents a substantial difference in barrier maturation and integrity.\(^30,34\) Product doses may have differed between the trials. Levels of 0.5 to 2.0 grams per square centimeter can be quite occlusive.\(^6\) Normal adult volar forearm skin was occluded with plastic film for 5 days.\(^6\) Significant increases in total average microbial counts were seen on day 5, and coagulase-negative staphylococci (well tolerated in healthy adults) were present in the greatest amounts (63%). One possible explanation for the increased incidence of nosocomial infection in the extremely low-birth-weight infants is that the treatment was sufficiently occlusive to delay barrier maturation and to allow the growth of coagulase-negative Staphylococcus. In another report, an increase in systemic candidiasis was found in extremely low-birth-weight infants (n = 40) treated with topical petrolatum.\(^6\) Until the cause of the increased infection rates is understood, the use of petrolatum-based low-water ointments in very premature infants will remain controversial. A Cochrane review published in 2004 recommended that they not be used on premature infants because of the risk of infection.\(^6\) It is important to remember that a petroleum-based cream is a barrier to stool, but it does not allow the skin to breathe and remove toxins because it blocks the pores.

1. Monitor skin condition closely
   - Use the patient’s inherent color in a “normal”, non-damaged area as a reference
   - Note differences from normal, e.g., very faint redness

2. Assess patient for risk factors, including
   - Frequent stooling
   - Loose stools
   - Poor absorption of digestive enzymes or presence in stool
   - Conditions where bile salts are excreted
   - Drug withdrawal
   - Medications that change stool frequency or composition, including antibiotic therapy

3. Begin treatment at the first sign of dryness, erythema, rash
   - Check for candidiasis or bacterial infection

4. Reduce hydration
   - Use absorbent products to wick away moisture from the skin surface
   - Change frequently to minimize contact with irritants
   - Dry the skin after cleansing

5. Use gentle skin cleansing methods
   - Soft implements
   - Avoid products with known irritants, fragrance, alcohol
   - Minimize rubbing
   - If topical creams are in place, remove only the soiled portion to minimize rubbing

6. Use topicals to assist skin barrier recovery and prevent further damage
   - Treat with antifungal agent if candidiasis is present
   - Provide a semipermeable film/layer over damaged skin
   - Provide a physical shield between skin and irritants
   - Choose amount based on a balance of “semipermeability” and physical shield
   - Select product that stays in place and allows for ease of cleansing
   - Use products that can bind or deactivate irritants (bile salts, enzymes) as indicated by patient condition

7. Note area of involvement (% area covered) and severity of damage (faint erythema, definite redness, intense redness, rash, bleeding, etc.)
   - Re-evaluate and modify plan if condition worsens or does not show improvement

Fig 6. Diaper skin care. The management of diaper skin condition is outlined.
Topical Treatment of Skin Compromise

The presence of minor skin damage increases the likelihood of further injury in the high-risk neonate, and prevention/early intervention has been the focus of health care providers who care for them. The published research on the effects of topical products on damaged skin in neonates is very limited, especially for adequately sized randomized controlled clinical trials. The task becomes selecting one of the appropriate and effective products. Consideration of the regulatory guidelines for skin care products may be helpful in making those selections.

Regulatory Guidance for Skin Products

Topical interventions include “barrier creams,” “barriers,” “skin pastes,” “skin protectants,” “moisture barriers,” and “moisturizers.” Many are marketed under the Food and Drug Administration (FDA) Final Monograph entitled Skin Protectant Drug Products for Over-the-Counter Human Use.77 Skin protectants “provide temporary relief from harmful or annoying stimuli.” The “active ingredients” and their allowed levels are listed in Table 2. Those with an asterisk (*) may also claim “temporarily protects minor cute, scrapes, and burns,” and those with pound sign (#) can state “helps prevent and temporarily protects and helps relieve chaffed, chapped, or cracked skin.” The label must also state the following: for external use only, do not use on (deep puncture wounds, serious burns, animal bites), do not get into eyes, keep away from face and mouth to avoid breathing it, stop use/ask doctor if condition worsens or symptoms last more than 7 days or clear and return. Unlike prescription drugs and other categories of OTC drugs, the FDA does not require randomized controlled clinical trials before approval and to demonstrate effectiveness. Therefore, one should be aware that effectiveness has not been shown in controlled clinical trials. The FDA does not review or approve cosmetic claims, such as “soothes” or “dryness.” The paucity of data can be attributed in part to the fact that products can be marketed without demonstrated efficacy.

Treatment of Diaper Dermatitis

Etiology Skin damage in the diaper area is the result of several factors in the “diaper environment.” They include increased skin hydration, contact with skin irritants (urine, feces, enzymes in feces, bile salts, etc), mechanical friction (skin to skin, diaper to skin), skin pH, nutritional status or diet (fecal composition), gestational age (barrier maturation status), use of antibiotic therapy, presence of diarrhea, and medical condition.48,78-83 Diapered skin pH was higher than a nondiapered control site in neonates and older infants, and increased pH was related to the effects of occlusion and increased skin permeability.18,84,85 Higher skin pH was associated with higher skin hydration (wetness) and diaper rash scores.81 Irritants cause skin damage by disrupting the lipid bilayers of the SC, thereby allowing penetration into the viable epidermis. Irritants (eg, sodium lauryl sulfate (SLS)) increase keratinocyte proliferation and alter metabolism and differentiation.86,87 In response, the epidermis up-regulates SC formation, resulting in a defective structure, aberrant water handling, and inadequate desquamation.88-93 Perineal skin excoriation can occur in conditions where pancreatic enzymes are not deactivated in the colon.94,95 When a mixture of pancreatic enzymes and bile salts was applied under occlusion, erythema, blood flow, skin pH, and TEWL all increased.96 Patients who get supplemental digestive enzymes (eg, for metabolic diseases) are at risk for skin breakdown because the unabsorbed enzymes can be excreted in the feces and break down the SC proteins.97 Infants with neonatal abstinence syndrome often have diarrhea and can have severe diaper skin excoriation.98-100 Figs 5A and B illustrate the processes involved in diaper skin breakdown.

Strategy The approach for resolving diaper breakdown is based on minimizing or eliminating the causes and intervening early. Fig 6 shows the aspects of diaper skin care.

When damage is noted, the presence of infection (eg, yeast, bacterial) must first be determined. Rash due to Candida...
Candida albicans can include bright red color, patchy pattern (areas may be surrounded by scales), and pustules. Topical antifungal agents are the treatment of choice and include nystatin, miconazole, clotrimazole, and ciclopirox for infants. Nystatin is prescribed most frequently by pediatricians. Combinations of antifungals and mid-high potency corticosteroids are not recommended because they can cause skin atrophy and penetrate more easily under the occlusive diaper conditions.

A placebo-controlled trial of subjects with acute rash showed significantly lower rash scores for treatment with 0.25% miconazole nitrate in zinc oxide/petrolatum than the controls with the zinc oxide/petrolatum vehicle, and subjects with moderate to severe rash had the greatest improvement. A separate safety study showed low systemic absorption of miconazole nitrate in infants. Treatment of bacterial infections is based on the organisms involved.

The goal for managing diaper skin breakdown is to somehow allow for healing despite the continuing exposure to the offending agents. Ideally, topical treatments (a) provide a semipermeable "film" or "layer" over the damaged skin to allow SC barrier repair, (b) provide a physical shield between the skin and the irritants, (c) remain in place on the skin (not removed by feces), and (d) allow for ease of skin cleansing (minimize stripping). Complete occlusion of damaged skin can cause delay in healing. Skin repair occurs more quickly when treated with barriers, creams, or films that are semipermeable to water vapor. An algorithm for the management and selection of treatments is shown in Fig 7. Once a plan is in place, it can be helpful to monitor the effects by noting the area of involvement (% area covered) and severity of damage (faint erythema, definite redness, intense redness, rash, bleeding, etc). For example, Fig 8 shows a scheme for evaluating erythema.

**Topical treatment** The diaper rash creams and moisture barriers usually contain a skin protectant (ie, one of the "active ingredients" covered by the FDA monograph), commonly zinc oxide, petrolatum, or dimethicone alone or in combination. The published data on topical protectants are virtually nonexistent for adequate controlled trials in infants, especially the high-risk population. In vivo studies (usually adults) on treatment irritant dermatitis with barrier creams have shown mixed results, with skin improvement in some and worsening in others. Hoggarth et al evaluated six commercially available products for irritant protection, prevention of maceration, and protection against topical agents. However, the test applied them once a day and then exposed the skin to irritant (sodium lauryl sulfate surfactant) for 24 hours daily for 4 days. Patches are completely occlusive and probably caused the irritant to pass through the barrier cream as well as through the SC.

Common diaper rash creams, moisture barriers, and their ingredients are shown in Table 3. The "skin protectant" is in bold and must be at FDA monograph level to make the claim. The others are considered to be "inactive," and US regulations require them to be listed in the order of amount, unless they are at 1% or less where they can be in any order. These ingredients give the products the features of thickness, ease of application, and so on, but they also function to provide uniformity. As an example, Table 4 lists the function of each ingredient in two of the products.
<table>
<thead>
<tr>
<th>Name</th>
<th>Ingredient List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desitin (Pfizer, Inc., New York, NY)</td>
<td>Zinc oxide (40%), BHA, cod liver oil, fragrance, lanolin, methylparaben, petrolatum, t alc, and water</td>
</tr>
<tr>
<td>Desitin Creamy (Pfizer, Inc.)</td>
<td>Zinc oxide (10%), Aloe barbadensis leaf juice, cyclomethicone, dimethicone, fragrance, methylparaben, microcrystalline wax, mineral oil, propylparaben, purified water, sodium borate, sorbitan sesquioleate, vitamin E, white petrolatum, and white wax</td>
</tr>
<tr>
<td>Desitin Clear All Purpose (Pfizer, Inc.)</td>
<td>White petrolatum (60.4%), cholecalciferol, cocoa butter, fragrance, light mineral oil, mineral oil, modified lanolin, paraffin, sodium pyruvate, sunflower seed oil, vitamin A palmitate, vitamin E (dl-alpha tocopherol and dl-alpha tocopheryl acetate)</td>
</tr>
<tr>
<td>A&amp;D Ointment Original (Schering Plough, Kenilworth, NJ)</td>
<td>Petrolatum (53.4%), lanolin (15.5%), cod liver oil (contains vitamin A and vitamin D), fragrance, light mineral oil, microcrystalline wax, paraffin</td>
</tr>
<tr>
<td>A&amp;D Diaper Rash Cream with Zinc Oxide (Schering Plough)</td>
<td>Dimethicone (1%), zinc oxide (10%), aloe barbadensis extract, benzyl alcohol, coconut oil, cod liver oil (contains vitamin A and vitamin D), fragrance, glyceryl oleate, light mineral oil, ozokerite, paraffin, propylene glycol, sorbitol, synthetic beeswax, water</td>
</tr>
<tr>
<td>Triple Paste (Sommers Laboratories, Inc., Collegeville, PA)</td>
<td>Zinc oxide, lanolin, and beeswax. Triple paste is fragrance free and contains no added preservatives</td>
</tr>
<tr>
<td>Boudreaux's Butt Paste (Blairex, Edgewood Cliffs, NJ)</td>
<td>Zinc oxide (16%), boric acid, castor oil, mineral oil, paraffin, Peruvian balsam, petrolatum</td>
</tr>
<tr>
<td>Canus Li'l Goat's Milk 40% Zinc Oxide Ointment (Canus, Waitsfield, VT)</td>
<td>Zinc oxide (40%), petrolatum, goats milk (fresh), mineral oil, emulsifying wax NF, fragrance (parfum), beeswax, propylene glycol, diazolidinyl urea, methylparaben, propylparaben</td>
</tr>
<tr>
<td>Aquaphor (Beiersdorf)</td>
<td>Petrolatum, mineral oil, ceresin, lanolin alcohol, panthenol, glycerin, bisabolol</td>
</tr>
<tr>
<td>Balmex (Chattam, Inc., Chattanooga, TN)</td>
<td>White petrolatum (51%), cyclomethicone, dimethicone, mineral oil, polyethylene, silica</td>
</tr>
<tr>
<td>Mustela Bebe Vitamin Barrier Cream (Laboratories Expanscience, Paris, France)</td>
<td>Zinc oxide (10%), water, mineral oil, propylene glycol dioctanoate, methyl glucose dioleate, titanium dioxide, PEG 45 doceyl glycol copolymer, glycerin, ceresin, ethyl linoleate, Shea butter, PEG 8, panthenol, potassium sorbate, fragrance, magnesium sulfate, methylparaben, caprylyl glycol, propylparaben, sodium polyacrylate</td>
</tr>
<tr>
<td>Triple paste medicated ointment (Sommers Laboratories, Inc.)</td>
<td>Zinc oxide (12.8%), white petrolatum, corn starch, anhydrous lanolin, stearyl alcohol, beeswax, bisabolol, cholesterol, water, glycerin, oat kernel extract (Avena sativa), polysorbate 80</td>
</tr>
<tr>
<td>Aveno baby soothing relief Diaper Rash Cream (Johnson &amp; Johnson Consumer Companies, Inc., New Brunswick, NJ)</td>
<td>Zinc oxide (13%), A sativa (oat) kernel extract, beeswax, benzoic acid, dimethicone, Epilobium angustifolium flower/leaf/stem extract, glycerin, methylparaben, microcrystalline wax, mineral oil, Oenothera biennis (evening primrose) seed extract, potassium hydroxide, propylparaben, sorbitan sesquioleate, synthetic beeswax, water</td>
</tr>
<tr>
<td>Burt's Bees Baby Bee (Burt's Bees, Durham, NC)</td>
<td>Zinc oxide, sweet almond oil, beeswax, tocopheryl acetate, tocopherol (vitamin E), jojoba oil, lavender oil, retinyl palmitate (vitamin A), extract of rosemary, lavender, calendula, chamomile, rose petal, comfrey root</td>
</tr>
<tr>
<td>Mustela Dermo-Pediatrics Stelactiv Diaper Rash Cream (Laboratories Expanscience)</td>
<td>Zinc oxide (10%), water, mineral oil, propylene glycol diethylhexanoate, methyl glucose dioleate, titanium dioxide, PEG 45 doceyl glycol copolymer, glycerin, ceresin, panthenol, Lupinus albus seed extract, PEG 8, Butyrospermum parkii fruit (Shea butter), ethyl linoleate, potassium sorbate, caprylyl glycol, methylparaben, magnesium sulfate, propylparaben, sodium polyacrylate</td>
</tr>
<tr>
<td>Palmer's Bottom Butter (E.T. Browne Drug Company, Inc., Edgewood Cliffs, NJ)</td>
<td>Petrolatum (30%), dimethicone (1%), water, mineral oil, aluminum stearic octenylsuccinate, PEG 30 dipolyhydroxy stearate, stearyl alcohol, Theobroma cacao (cocoa) seed butter, microcrystalline wax, fragrance, Zea mays (corn) oil, retinyl palmitate, cholecalciferol, panthenol, beta carotene, vegetable oil, isopropyl myristate, propylene glycol, methylparaben, propylparaben, diazolidinyl urea</td>
</tr>
<tr>
<td>Jason Natural Cosmetics Earth's Best Organic Diaper Relief Ointment, Aloe Vera and Vitamin E (The Hain Celestial Group, Inc., Melville, NY)</td>
<td>Zinc Oxide (12%), lavender extract, caprylic/capric triglycerides, C12 15 alkyl benzoate, sorbitan isostearate, sorbitan sesquioleate, water (purified), ethylhexyl palmitate, calcium stearic octenylsuccinate, ethyl macadamiate, stearalkonium hectorite, glyceryl laurate, oat kernel oil, tocopheryl acetate (vitamin E), beta glucan, chamomile flower extract (certified organic), marigold flower extract (certified organic), propylene carbonate, magnesium sulfate, benzyl alcohol, potassium sorbate, sodium benzoate</td>
</tr>
</tbody>
</table>

(continued on next page)
Most contain zinc oxide, petrolatum, or mixtures and compositionally appear to be similar. This is, perhaps, not surprising given the number of ingredients that can be used to make a "skin protectant claim." Thicker products (pastes, creams, ointments) usually have low water content. Pastes and petrolatum barriers can be very occlusive. Some clinicians recommend against their use for long periods and only in situations where soils (feces) are high in water and irritants. Thicker products (pastes, creams, ointments) usually have low water content. Pastes and petrolatum barriers can be very occlusive. Some clinicians recommend against their use for long periods and only in situations where soils (feces) are high in water and irritants. There are no studies on the use petrolatum-based barriers to prevent diaper dermatitis in normal diapered skin. Some patients have conditions that affect fecal composition (eg, gastrointestinal conditions) and may benefit from topical agents designed to mitigate the specific irritants. For example, cholestyramine binds with bile acids to make them inactive, and

<table>
<thead>
<tr>
<th>Name</th>
<th>Ingredient List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method Squeaky Green Diaper Cream, Rice Milk + Mallow (Method Products, Inc., San Francisco, CA)</td>
<td><strong>Zinc Oxide (10%)</strong>, <em>Althaea officinalis</em> extract, caprylic/capric triglycerides, cetyl alcohol, caprylylhydroxyethylcellulose, decylene glycol, dimethicone, glycerin, <em>Helianthus annuus</em> (sunflower) seed oil, <em>Oryza sativa</em> (Rice) bran extract, <em>O sativa</em> (Rice) germ oil, phenoxyethanol, polysorbate 60, sorbitan stearate, water (agua), xanthan gum</td>
</tr>
<tr>
<td>Lansinoh Diaper Rash Ointment (Lansinoh Laboratories, Alexandria, VA)</td>
<td><strong>Dimethicone (5.5%)</strong> (skin protectant), USP modified lanolin (15.5%) (skin protectant), <strong>zinc oxide (5.5%)</strong> (skin protectant), allantoin, beeswax, bisabolol, caprylyc/capric triglycerides, esters, glycerlyl behenate/decysodecanoate, <em>Jojoba Chamomilla recutita</em> flower extract (Matricaria), petrolatum, polydecene, polyethylene, propylparaben, stearyl glycerylstearate, tocopherol acetate (vitamin E), <em>Z mays</em> (corn) starch</td>
</tr>
<tr>
<td>Sensi-Care Skin Protectant (ConvaTec, Skillman, NJ)</td>
<td><strong>Petrolatum (49%), zinc oxide (15%)</strong>, carboxymethylcellulose sodium, water, stearic acid, glycerin, cetyl dimethicone copolyol, polyglyceryl-4-isostearate, hexyl laurate, phenoxyethanol</td>
</tr>
<tr>
<td>Aloe Vesta Skin Protectant (ConvaTec)</td>
<td><strong>Petrolatum (43%)</strong>, water, mineral oil, hydroxylated lanolin, sorbitan sesquioleate, ozokerite, PEG-30 dipolyhydroxystearate, glycerin, steareth-20, magnesium sulfate, DMDM hydantoin, iodopropynyl butylcarbamate, <em>Aloe barbadensis</em> leaf juice</td>
</tr>
<tr>
<td>Carrington Moisture Barrier Cream (Carrington Laboratories, Irving, TX)</td>
<td><strong>Petrolatum (90%)</strong>, mineral oil and paraffin, aemnanan hydrogel, butylparaben, lecinith, propylparaben, purified water, quaternium 15, sodium chloride</td>
</tr>
</tbody>
</table>

The "skin protectant" is in bold. USP = United States Pharmacopeia; BHA = butylated Hydroxy anisole; NF = normal form; PEG = polyethylene glycol.

Table 4. Ingredients in a Common Diaper Rash Cream and Their Functions

<table>
<thead>
<tr>
<th>Ingredient Function</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc oxide (10%)</td>
<td>Skin protectant claimed from monograph</td>
</tr>
<tr>
<td>A barbadensis leaf juice</td>
<td>Moisturizer, hydrating agent</td>
</tr>
<tr>
<td>Cyclomethicone</td>
<td>Assists in spreading</td>
</tr>
<tr>
<td>Dimethicone</td>
<td>Assists in spreading</td>
</tr>
<tr>
<td>Fragrance</td>
<td>Provides pleasant odor and/or covers ingredient odors</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>Preservative</td>
</tr>
<tr>
<td>Microcrystalline wax</td>
<td>Viscosity control</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Emollient, solvent</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>Preservative</td>
</tr>
<tr>
<td>Purified water</td>
<td>Solvent</td>
</tr>
<tr>
<td>Sodium borate</td>
<td>Product pH control</td>
</tr>
<tr>
<td>Sorbitan sesquioleate</td>
<td>Moisturizer, emollient</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Vitamin at low level, effectiveness not established</td>
</tr>
<tr>
<td>White petrolatum</td>
<td>Viscosity control</td>
</tr>
<tr>
<td>White wax</td>
<td>Viscosity control</td>
</tr>
</tbody>
</table>

Desitin Creamy ingredients: Zinc oxide (10%), *A barbadensis* leaf juice, cyclomethicone, dimethicone, fragrance, methylparaben, microcrystalline wax, mineral oil, propylparaben, purified water, sodium borate, sorbitan sesquioleate, vitamin E, white petrolatum, and white wax.
Table 5. Surfactants Found in Skin Care Products and the Relative Irritancy Potential

<table>
<thead>
<tr>
<th>Relative Irritancy</th>
<th>Surfactants</th>
</tr>
</thead>
</table>
| High               | Sodium lauryl sulfate  
Sodium dodecyl sulfate  
Sodium alkyl sulfate  
Sodium or potassium cocoate  
Sodium or potassium tallowate  
Sodium palmitate  
Sodium or potassium stearate  
Linear alkyl benzene sulfate  
Triethanolamine laurate  
Benzalkonium chloride  
Dodecyl trimethyl ammonium bromide |
| Moderate           | Sodium ethoxylates  
Sodium laureth sulfate  
Ammonium laureth sulfate  
Sodium cocoyl isethionate  
Sodium alkyl glycerol ether sulfonate  
Sodium cocoyl sulfosuccinate  
Disodium stearyl sulfosuccinate |
| Low                |                                |

Preparations have been used successfully for severe perineal skin breakdown.\textsuperscript{112-114} Cholestyramine ointments can be prepared in hospital pharmacies. Sucralfate (Carafate; Marion Merrell Dow, Kansis City, MO) in the form of an ointment or powder has been used to treat skin damage from gastric secretions. If candidiasis is also present, these patients must be treated with an antifungal as well.\textsuperscript{115,116}

Topical creams can be limited by poor substantivity and removal by stool. Solutions and sprays that form a semipermeable barrier film upon drying are available. They are intended to be left in place to protect the skin from direct irritant contact with irritants. They are semipermeable to assist barrier repair. Skin stripping during cleansing is minimized. Sureprep No-Sting Protective Barrier Wipe (Sureprep NSPBW, Medline Industries, Inc, Mundelein, IL) comes as a water-based solution, is nonflammable, and has no age restrictions. Another is Cavilon No-Sting Barrier Film (Cavilon NSBF, 3M Corporation, St Paul, MN). The material is in volatile silicone solvent and dries to form the semipermeable film. It can be used on infants older than 1 month (eg, not for use on preterms) and is flammable. Sureprep NSPBW was evaluated in a small study in 10 NICU patients with severe perineal skin breakdown.\textsuperscript{117} The skin condition, based on assessment of area and severity, improved. Two were discharged after 1 day. A trial of suitable size among parallel treatment groups is necessary to determine the effectiveness of Sureprep NSPBW vs other barrier creams, but it represents a potential alternative for diaper skin breakdown in high-risk infants.

**Skin cleansing** Bathing practices vary with the infant's age and medical condition. Skin cleansing products usually contain ingredients, surfactants (surface active agents), to emulsify soils for removal during rinsing. Cleansers can be no-rinse liquids or creams, in bar form, or liquids added to water. Because they emulsify lipids, surfactants can damage the SC barrier and cause skin irritation. Relative skin irritancy has been determined via skin testing, and rankings for common surfactants are shown in Table 5. After cleaning, residual surfactant can remain on the skin, especially when copious rinsing is not practiced.\textsuperscript{118} Liquid products containing surfactants with very low irritancy are recommended for infants. The irritancy can be determined by checking the ingredient label against the list in Table 5.

Diaper skin can be cleansed with a soft cloth and an oil-in-water lotion to assist in soil removal.\textsuperscript{119} Wipes composed of a substrate with cleansing agents and/or emollients have been developed for use on diaper skin. Wipe treatment resulted in significantly lower erythema and surface roughness vs water plus an implement (cotton washcloth, cotton wool balls) in healthy infants.\textsuperscript{120,121} Wipes made of a soft nonwoven substrate containing water, nonionic cleansers, and emollients resulted in reduced skin irritation (erythema, rash) and TEWL vs cloth and water in critically ill premature and full-term neonates.\textsuperscript{122,123} Wipes used on diaper skin should be free of alcohol, fragrance, and ingredients of known irritancy or cytotoxicity and contain only essential materials.\textsuperscript{109}

**Skin pH** Reduction in diaper skin pH may be another strategy for improving skin health. An acidic pH is important for the enzymes involved in SC formation and integrity to be effective. It contributes to the SC's innate immune function by inhibiting colonization of pathogens, for example, *Staphylococcus aureus*.\textsuperscript{124-126} Application of a pH 5.5 buffer solution increased the rate of barrier recovery after damage.\textsuperscript{127} Wipes with pH buffers have been developed.\textsuperscript{128} Routine skin cleansing with a new diaper wipe resulted in significantly lower diaper skin pH than the hospital standard of cloth and water in a trial among high-risk premature and full-term infants.\textsuperscript{123} Provision of an acidic skin pH may also help reduce the activity of fecal enzymes.

**Other product ingredients and use on infants** Published data on the many products that touch, interact with, adhere to, or influence the skin barrier of infants are very limited. Items developed for the health and consumer skin care markets are typically tested on adults and/or rely on marketplace experience (lack of adverse effects) to support use on infants. They may contain ingredients that should be avoided, if possible, or used with caution.\textsuperscript{129} For example, products containing boric acid are not recommended because of its toxicity.\textsuperscript{130,131} Benzalkonium chloride is used in skin products as a disinfectant or preservative and should be evaluated before use on infants. It has been implicated in allergic dermatitis in infants.\textsuperscript{132} The ingredients are listed on the label and should be checked for potential negative effects in the neonatal population before being adopted for routine use.
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37. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol.* 1986;115:84-92.


50. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol.* 1986;115:84-92.

51. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol.* 1986;115:84-92.

52. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol.* 1986;115:84-92.

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65. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol.* 1986;115:84-92.

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