Neonatal Skin Physiology

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Change the Outcome®
Why Study Infant Skin?

• Skin contact is important for the development and care of premature infants.
At Birth

• The infant moves rapidly from a warm, wet, safe womb to a cooler, dry nursery environment.
• The baby must breathe, eat and maintain body temperature.
Roles of the Skin at Birth

1. Protection - barrier to water loss, light and irritants
2. Infection control and immunosurveillance
3. Resilience to mechanical trauma
4. Sensation and tactile discrimination
5. Thermal regulation
6. Acid mantle formation
**Stratum Corneum:**
- Physical barrier to irritants
- Tactile discrimination
- Acid mantle formation

**Viable Epidermis:**
- Physical barrier
- Tactile discrimination
- Sensation
- Acid mantle formation

**Dermis:**
- Resilient foundation
- Thermal regulation
- Sensation
- Blood supply

**Melanocyte:**
- Protection – light
- Color

**Langerhans Cell:**
- Barrier – immunological
Pigmentary System

**Melanocytes**

- In lower epidermis – basal layer
- Produce melanin
- Determine inherent skin color
- Become activated when the skin is exposed to sunlight (ultraviolet radiation)
- Transport melanin to shield the living epidermal cells, protecting the DNA.
- Darkening (tanning) is a result of this process.
Pigmentary System

• The pigmentary system is affected by irritation and inflammation, e.g., from ultraviolet light, chemical irritants, burns, wounds.

• It may respond by producing more pigmentation (skin darkening) or less pigmentation (skin lightening).
Langerhans Cells

- Located in the viable epidermis below the stratum corneum (SC)
- Also called antigen presenting cells
- Part of the immune system and
- “Line of defense” if the SC is breached
Stratum Corneum

- Cells – corneocytes
- Lipid bilayers
- Cells connected by desmosomes, molecular “rivets”
- Formed by the viable epidermis
- “Replaced” every 14 days
Stratum Corneum

- Has ~ 16 cell layers
- Thickness 10–40 microns, about 1/5 as thick as paper
- Variable thickness depending on body site
- Mechanically tough, difficult to penetrate
- Contains antimicrobials
  - lysozyme, lactoferrin, etc.

From: The Epidermis, ed. W. Montagna, W.C. Lobitz
Stratum Corneum Formation
Transepidermal Water Loss (TEWL)

- Water of respiration normally moves through the stratum corneum from below.
- The rate of transepidermal water loss (TEWL, g/m²/hr) is a measure of skin barrier integrity.
- TEWL is higher (faster) when the barrier is damaged.
Full Term Infant Skin

Healthy infants

- Well-formed stratum corneum.....note multiple layers
- Thick epidermis
- Structural proteins present in the dermis
Full-Term Newborn SC Barrier

**TEWL**

- very low at birth
- 4-6 g/m$^2$/hr
- remains low over month 1
- lower than adult values of 6-8 g/m$^2$/hr
Biological Question

• How does the infant develop excellent skin while soaking in water and urine before birth?
Long-Term Water Exposure

Water Immersion Foot: Skin Damage from Long-Term Water Exposure

Newborn Infant: Exquisite Skin
SC Damage from Water Exposure

- Water exposure disrupts the lipid bilayers between the corneocytes.
- Holes or “defects” are created and damage continues.
- SC formation or repair of damage cannot occur.
SC Formation

• The stratum corneum forms during the last trimester.
• Infants born too early, at 23 or 24 weeks, have little if any SC.
• Their TEWL is very high, ~ 75 g/m²/hr, similar to values with no barrier
SC Formation – **Dry Conditions**

- When the epidermis (no SC) is exposed to dry conditions, e.g., normal humidity, the stratum corneum formation process is triggered.
- New SC forms to cover the epidermis and *eventually* has ~ 16 layers.
- This process occurs for premature infants without a SC.
How Does This Occur???

- Somehow, the full term infant is born with a well-developed and fully functional stratum corneum in a water environment.

- *Consider Vernix Caseosa*
Vernix Composition

- Water: 80.5%
- Proteins: 10.3%
- Lipids: 9.1%
  - Other lipids: 6.4%
  - Barrier lipids: 2.7%

Vernix Structure

• Corneocytes imbedded in an amorphous lipid matrix.
• Corneocytes are swollen with lower keratin density than adult cells.
• No desmosomes are observed between the corneocytes.
• Fluid, not rigid like SC

Vernix Lipids

- Vernix contains non-polar and polar lipids: triglycerides, sterol esters, wax esters, squalene, cholesterol, free fatty acids, ceramides
- Lipid compositions of vernix and SC are shown in b with the ceramides in c

Ontogeny of Vernix

During gestation, vernix starts to appear on the brow around the hair.

Full term newborns are often covered with vernix at birth.
Infant Skin *in Utero*

- Stratum corneum not yet formed
- Sebaceous Gland
- Hair Follicle
Vernix caseosa coats the epidermis in utero starting around the hair follicle.

Then, it spreads over the epidermal surface between the individual hairs.

Over time, the SC continues to form.
Vernix Research Findings

- **Native vernix is a multifunctional skin cream with the following properties**
  - Skin moisturizer
  - Anti-infective
  - Anti-oxidant
  - Skin cleanser
  - Skin repair and wound healing, semipermeable
  - Barrier protectant, e.g. against enzymes
Vernix *Retained* Skin was:

1. more hydrated

2. less erythematous

3. of lower skin pH

Vernix: Cleanser

- Finger and forearm skin was soiled (top row).
- Treatment with vernix was effective for removing the soil particularly from ridges, furrows and hair follicles.

Vernix: SC Barrier Repair

- Wounds were made at 25 microns of laser energy.
- Vernix and petrolatum-based cream (PBC) had greater recovery than no treatment, day 2 ($p < 0.05$).
- PBC had directionally faster recovery than both others on day 7 ($p = 0.06$).

Vernix: SC Barrier Repair

- Vernix contains fatty acids, including oleic, linoleic and long chain species.
- Fatty acids, particularly linoleic, activate peroxisome proliferator-activated receptor-a (PPARα) which increases the rate of SC barrier formation.
- Linoleic acid has anti-inflammatory properties which may favorably impact SC repair or development.

Vernix: Enzyme Penetration

• Films of vernix impeded the penetration of the exogenous enzyme chymotrypsin (found in meconium, similar proteolytic enzymes present in feces) \textit{in vitro}.

• Additionally, vernix films maintained the activity of native enzymes which are necessary for epidermal development.

Implications

- Overall, vernix facilitates SC development in normal, full term infants through a variety of protective and adaptive mechanisms.
- The findings provide support for the practice of vernix retention at birth.
- The World Health Organization recommends that vernix be retained and bathing delayed for at least 6 hours.
What Happens *After* Birth???

Full Term Infants

Premature Infants
Full-Term Skin Adaptation

- The SC undergoes a rapid transition at birth.
- The water handling behavior changes significantly over the first month.
- By one month, the moisture accumulation rate is significantly higher for the infant vs. mother.

Full-Term Skin Adaptation

• Newborn skin has significantly lower hydration than infants at 1, 2 and 6 months and their mothers.

• The changes in hydration and water binding indicates that the skin is adapting to the new environment.

Importance of Hydration

• Adequate stratum corneum hydration is essential
  – for plasticity and flexibility during movement
  – to prevent cracking
  – for desquamation of the outermost layer

Low Skin Hydration: Potential Explanations

1. Rapid change from high to low humidity at birth may initiate changes such as the proteolysis of filaggrin to natural water binding molecules known as moisturizing factor (NMF).

2. Extensive exposure to amniotic fluid may extract water binding molecules (NMF) from newborn skin.

Water Binding Free Amino Acids

• Free amino acid (FAA) levels are very low at birth and then increase significantly over the first month (p < 0.05).

• FAAs are substantially lower in infants at one month of age than in adults (p < 0.05).

Free Amino Acids: Effect of Vernix

• Vernix retention resulted in significantly higher FAA levels after birth versus infants with it removed.

• Free amino acids in vernix retained skin appear to originate from vernix itself.

Summary

1. FAA production may be initiated with high-to-low humidity transition in the neonatal period.
2. The low levels of FAA in neonatal foreskin is consistent with reports that 100% humidity blocks filaggrin proteolysis (animals).
3. Retention of FAA containing vernix appears to facilitate increased hydration and pH reduction at birth.

Newborn Skin Adaptation: pH

- Skin pH nearly neutral at birth.
- Rapid decrease during first 4 days.
- Regional differentiation with lower pH for nondiaper site.

Importance of an Acidic SC pH

• An acidic pH
  – is required for SC cell cohesion
  – contributes to the SC innate immune function by inhibiting colonization of pathogens, e.g., S. aureus.
  – is necessary for the effective functioning of enzymes in SC formation and integrity, i.e.:
    • lipid metabolism, bilayer structure, ceramide synthesis, desquamation

Elias, PM, Semin Immunopathol. 2007, 29:3-14.
Premature Infant Skin
Premature Infant Skin

- Stratum corneum poorly developed or absent
- Thin epidermis
- Dermis not fully formed and deficient of structural proteins
Significance

1. NICU patients at risk for skin breakdown
   - Prematurity, irritants (e.g., feces), stress
2. Epidermis is less well developed in premature vs full term neonates
3. Skin breakdown can result in
   - Infection, fluid loss, discomfort, stress, delay in start of oral feeding, anxiety for caregivers and families
Premature SC Barrier

- Premature infant skin barrier integrity varies greatly with gestational age.
- TEWL for 24 – 25 wks gestation is very high, comparable to epidermis without a SC barrier.

Premature SC Development

- Premature infants experience high fluid loss, thermal instability, electrolyte imbalance.
- However, the SC barrier forms rapidly after birth.
- Surface hydration decreases over a few days.

Premature SC Barrier Development

- At one month post birth, TEWL is significantly higher for the preterm infant than for the full term newborn.
- May lead to increased susceptibility to infection and penetration of exogenous agents.

Effect of humidity

- Premature infants 23-27 wks GA
- Incubator at ~80% RH for first week
- Randomized to 75% or 50% thereafter
- SC barrier maturation was more rapid at 50% vs 75% RH

Premature Barrier Maturation

- Case study report on 10 infants aged 23-24 wks at birth
- TEWL decreased and conductance increased over time.
- Proposed a maturation time of 9 weeks

Premature Skin Adaptation: pH

- Skin pH profile for the mature infant varies with gestational age.
- Initial pH drop was observed in both groups.
- Smaller babies have a higher pH for a longer time.

Chest Skin pH: Adaptation

- Chest skin pH decreased significantly over 14 days.
- Skin pH over time was influenced by age at birth and time from birth.
- Neonatal skin continues to change long after birth, presumably as it adapts to the dry environment.

Biomarkers of Innate Immunity

- Involucrin was higher in
  - Preterms than full terms
  - both infant groups versus adults.
- Keratin 1,10,11 higher in adults than infants

• IL6 and IL8 were higher in preterms than full terms
• IL1a was higher in both infant groups than adults and may be a marker of barrier maturation.

Skin Integrity in NICU Patients
Skin Compromise

Damaged Barrier

Irritants Have Entered

Irritants act on living cells

Mediators increase erythema via vasculature

Cells release mediators of inflammation
Skin Compromise

Water & cleansers disrupt lipid structure

Microorganisms can enter to reach the Langerhans cells and epidermis

Skin barrier with defects

Irritants can penetrate
Diaper Skin Compromise

• Diaper skin can be damaged by:
  – over-hydration
  – urine
  – feces
  – friction
  – increased skin pH
  – diet
  – medications

• Fecal enzymes can degrade SC proteins and cause inflammation
Skin Compromise

Stratum corneum: cells, lipids, rivets

Prematurity: fewer SC layers

Enzymes:
- Degrade SC proteins
- Water, harsh cleansers damage lipids

Excess rubbing strips skin

Net: Irritants penetrate to the epidermis and cause inflammation
Skin Barrier Repair after Damage

Normal Skin Barrier
- Uniform size
- Regular structure
- Cells connected

Abnormal Skin Barrier
- Defective
  - formed too fast
- Dry with large scales
Skin Compromise: Stress

- Reduced integrity due to decreased
  - cell proliferation: fewer layers
  - lipid synthesis
  - desmososomes (cell connections)
- Decreased antimicrobial agents
- Increased skin infection
- Delayed barrier recovery & wound healing

The Skin – Brain Connection

1. Skin and brain are both derived from ectoderm during gestation
2. Evidence for a brain-skin axis
   – Mast cells, substance P, nerve growth factor
   – An “HPA” axis within the skin that makes:
     • CRH, ACTH, Cortisol
3. A. Slominski: “The skin runs the brain.”

Skin Nerve Response

- Physical stimuli
  - Trauma, mechanical, heat, cold
  - Osmotic changes, hydration changes
  - Hydration changes
- Chemical stimuli
  - Irritants, toxins, allergens, microbes
  - Enzymes
  - Inflammatory mediators
  - pH changes
- Responses
  - Pain, Burning, Stinging, Itch
Cutaneous Nerve Endings

- Note that the nerve endings are not exposed to the environment.
- Sensory signal receptors are expressed in the keratinocytes.

Keratinocyte Response

Net, cells (keratinocytes) sense and respond to environmental, i.e., threatening, effects the communicate to the nervous system.

Questions????????