Update on the Use of Topical Agents in Neonates

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Skin: A Primary Care Interface

- Bathing, Lotions, Sunscreens, Bedding
- Barrier Breakdown, Diaper Rash, Ostomies
- Prematurity, Immature Skin
- Adhesives, Topical Meds, Dressings, Casts
- Noninvasive Monitoring, ICUs
- Pain Control & Massage Therapy
- Wounds, Burns, Pressure Ulcers, Incisions

Skin: A Primary Care Interface
Objectives

1. Describe skin structure and function in general and for premature and full term neonates

2. Explain how common “topical agents”, encountered in the care of neonates, influence neonatal skin health and describe the potential effects of their use

3. Develop and implement a strategy for decision making regarding the use of specific topical agents on neonates
Perspective: Touch

• Touch is the first sense to develop.
• Touch is a central component of the infant-mother co-regulatory system.
• Therefore, the skin is important in how the infant perceives and reacts to the environment of care and, consequently, in neurodevelopment.

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
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

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

• How do we achieve optimum adaptation to a dry environment at birth?

• How do we facilitate barrier development in the premature infant?
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/m²/hr
- remains low over month 1
- lower than adult values of 6-8 g/m²/hr
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.

Newborn Skin Adaptation: pH

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

Premature Infant Skin

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

Topical Treatments for Infants

Products

**Working Definition:**
Anything that touches the skin surface, including

- environment (e.g., humidity)
- creams, lotions, oils
- diapers, bedding, cloths, wipes
- cleansers, water
- tapes, adhesives
- devices (masks, PICC lines)

OR ???
“Dressing” the NICU Patient
Significance

1. NICU patients at risk for skin breakdown
   - Prematurity, irritants (e.g., feces), stress
2. Epidermis is less well developed in premature versus 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
Skin Breakdown: Examples

- Erythema, inflammation, irritant dermatitis, diaper irritation
- Dryness/scaling
- Tape stripping
- Occlusion induced irritation
- Allergic contact dermatitis
- Pressure ulcers
G-tubes, Trachs: Irritant Dermatitis

- Secretions from G-tube sites, moisture under covers and friction (between skin and cover) can cause irritant dermatitis.
- Similarly, skin irritation can occur at trach sites.
“Normal” Skin Moisture

- In normal, healthy skin, water (from respiration) is lost from the viable tissue through the skin barrier.
Occlusion

- Occlusive (non-breathable) items prevent normal water loss
- Water accumulates and compromises the barrier
- Increased permeability
- Risk of
  - Irritation
  - Infection
Occlusion: Irritation

- Occlusion of normal skin with a tape barrier can cause transient water to build up under the film.
- Over time, the barrier becomes less permeable and more occlusive
- As a result, the skin becomes overhydrated, is more permeable and begins to breakdown.

Irritation from film on face
Tapes: Removal

- Removal of dressings and tapes can cause stripping of some of the outer layers of skin, creating a superficial wound.
- As a result, the skin is more permeable to irritants and susceptible to infection.
Skin Compromise

Water & cleansers disrupt lipid structure

Skin barrier with defects

Irritants can penetrate

Microorganisms can enter to reach the Langerhans cells and epidermis
Skin Compromise: 2

Irritants Have Entered

Mediators increase erythema via vasculature

Cells release mediators of inflammation

Irritants act on living cells

Damaged Barrier
Skin Compromise: 3

Prematurity
Fewer layers, poor

Water, cleansers disrupt lipids

Enzymes: Degrade SC proteins

Damaged Barrier

Tape Stripping: Removes layers

Irritants can penetrate
Skin Compromise 4: Stress

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

Skin Care Products & Regulations

• Topical skin products:
  – barrier creams
  – barriers
  – skin pastes
  – skin protectants
  – moisture barriers

• Many marketed under FDA Final Monograph: “Skin Protectant Drug Products for Over-the-Counter Human Use” (21 CFR Parts 310, 347, and 352)
Skin Care Products & Regulations

- Under this monograph, skin protectants: “provide temporary relief from harmful or annoying stimuli”
- Some can claim: “temporarily protects minor cuts, scrapes, and burns”
- And/or: “helps prevent and temporarily protects and helps relieve chaffed, chapped, or cracked skin”
## Skin Protectant “Active Ingredients”

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<th>Allowed %</th>
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<tr>
<td>Cocoa Butter</td>
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<td>Dimethicone</td>
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<tr>
<td>Glycerin</td>
<td>20 - 45</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>50 - 100</td>
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<tr>
<td>Petrolatum</td>
<td>30 - 100</td>
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</table>

<table>
<thead>
<tr>
<th>Ingredients</th>
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<tr>
<td>White petrolatum</td>
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<tr>
<td>Topical starch</td>
<td>1 - 30</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>5 – 13.56</td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>12.5 - 50</td>
</tr>
<tr>
<td>Hard fat</td>
<td>50 - 100</td>
</tr>
</tbody>
</table>
Examples

**Original Ointment**
- Petrolatum (53.4%), Lanolin (15.5%), Cod Liver Oil (contains Vitamin A & Vitamin D), Fragrance, Light Mineral Oil, Microcrystalline Wax, Paraffin

**Diaper Rash Cream**
- Dimethicone (1%), Zinc Oxide (10%), Aloe Barbadensis Extract, Benzyl Alcohol, Coconut Oil, Cod Liver Oil (Contains Vitamin A & Vitamin D), Fragrance, Glyceryl Oleate, Light Mineral Oil, Ozokerite, Paraffin, Propylene Glycol, Sorbitol, Synthetic Beeswax, Water
Regulations

• Unlike prescription and certain OTC drugs, the FDA does not require randomized, controlled clinical trials that demonstrate effectiveness for approval.

• Do not assume that effectiveness has been shown in adequate, controlled clinical trials.
Significance: Products

• Published information on the specific effects on skin barrier integrity and function within the NICU population is limited.

Assumptions

• Products sold for use on infant skin have extensive clinical trials on infants.
• Products tested on adults are automatically safe for infants.
• Infant skin and adult skin are the same.
Premature Barrier Development

**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

Vernix Caseosa

- Vernix caseosa coats the fetal skin surface during the last trimester.
- Vernix appears ~ 17 weeks in a head to toe, back to front pattern.
- Premature infants have little of no vernix.
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
Premature Skin: Topical Oils

• Daily massage with oils is a traditional cultural practice in many countries
• Benefits are prevention of infections and loss of heat
• However, mustard oil, a type commonly used in India, *delayed* skin barrier maturation.

Topical Oils: Sunflower Seed Oil

1. Sunflower seed oil enhanced skin barrier development.
2. Sunflower seed oil contains fatty acid (linoleic).
3. Application of sunflower seed and safflower oils significantly reduced nosocomial infection in preterm infants (< 33 wks GA) by 41% in Bangladesh.

Premature Infants: Petrolatum

- 2x daily vs no treatment in 60 infants (29 wks)
- Petrolatum (Aquaphor®) group had significantly better skin condition, lower bacterial colonization, fewer positive cultures.
- TEWL decreased significantly for both.
- However, there was no difference when corrected for initial TEWL.

Premature Infants: Petrolatum

**Multicenter Trial**

- Vermont Oxford Network, 54 NICUs
- Infants 500-1000g, mean GA = 26 weeks
- 610 infants: Petrolatum (Aquaphor®) 2x daily, 14 days
- 596 infants: Routine skin care
- A significantly *higher* incidence of nosocomial sepsis occurred in 501-750 g infants with Aquaphor®
- Organism responsible for sepsis was coagulase negative staph.

Premature Infants: Petrolatum

Possible Explanation:

- Aquaphor® behaved as an occlusive film in the trial, delaying barrier development and facilitating growth of microorganisms.

Premature Infants: Topical Oils

- Controlled trial among 457 infants ≤ 33 wks
- Nursery of Dhaka Shishu Hospital (Bangladesh)
- Daily treatment with sunflower seed oil (n = 159) or Aquaphor (n = 157) versus a no treatment (n = 181)
- Mortality rates were significantly reduced: 26% sunflower seed oil, 32% Aquaphor
- The results continue to support these treatments for use in developing countries.

Premature Infants: Topicals

- Application of certain topical treatments appears to be effective for improving skin condition in neonates.

**However……**

- The mechanisms in human infants are not well understood.
Skin Care in the NICU Patient: Effects of Wipes versus Cloth & Water on Stratum Corneum Integrity

Subjects

- 130 infants:
  - Wipe A = 45
  - Wipe B = 45
  - Cloth & Water = 40
- Mean gestational age: 34 wks (range 23 – 41)
  - Preterm = 97
  - Full term = 33
- Mean age at enrollment: 38 wks (range 30 – 51)
- Gender:
  - Males: 82
  - Females: 48

Regional Differences: Premature and Full-Term

TEWL differed at for the perineal region, suprapubic area and chest.

Skin pH was significantly higher for diapered skin than the chest.

Results: Local Perineal Erythema

- Local area (perineal) erythema scores were significantly lower for wipes than for cloth and water.

<table>
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<tr>
<th>Day of Treatment</th>
<th>Local Site Erythema Score</th>
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<tbody>
<tr>
<td>1</td>
<td>Wipe A (US)</td>
</tr>
<tr>
<td>5</td>
<td>Wipe B (Euro)</td>
</tr>
<tr>
<td>7</td>
<td>Cloth &amp; Water</td>
</tr>
</tbody>
</table>

- *p ≤ 0.001 US
- *p = 0.04 Euro
- *p = 0.000 US
- *p = 0.04 Euro

Results: TEWL Perineal Site

- TEWL at the perineal site was significantly lower for wipes treated skin than for cloth & water, reflecting a more normalized skin barrier.

Effect of Gestational Age

- Perineal erythema scores were lower for preterm infants than for the full term group.
- The total stool exposure (g) influenced skin irritation.

Diaper Skin Breakdown: Prevention & Treatment

- **Reduce hydration**
  - Use absorbent products to wick moisture from skin
  - Avoid diapers with plastic or non-breathable outer sheet
  - Minimize contact with urine, watery stools
  - Change diaper frequently
  - Insure that diaper fits properly
  - Dry the skin after cleansing

Visscher M. Pediatric Health, Feb 2009, 3(1): 81-98
Diaper Skin Breakdown: Prevention & Treatment

• Use gentle skin cleansing methods
  – Soft implements
  – Avoid products with known irritants, fragrance, alcohol
  – Wipes without fragrance, irritants had lower erythema and rash than soft cloth and water
  – Minimize rubbing
  – If cream in place, remove only the soiled portion to minimize rubbing

Visscher M. Pediatric Health, Feb 2009, 3(1): 81-98
Diaper Skin Breakdown: Prevention & Treatment

- **Apply topical treatments for barrier recovery and prevention of damage**
  - Provide a semipermeable layer
  - Provide a shield between skin and irritants
  - Use amount to balance “semipermeability” and physical shield
  - Use product that stays in place
  - Use products that can bind or deactivate irritants (bile salts, enzymes)

Visscher M. Pediatric Health, Feb 2009, 3(1): 81-98
Importance of an Acidic SC pH

- The rate of SC barrier recovery after tape stripping was increased with the application of an acidic (pH 5.5) buffer.
- Use of skin acidic (pH ~ 5) treatments may be a useful strategy for damaged infant skin.

Effect of Chlorhexidine Gluconate (CHG) on the Skin Condition at PICC Line Sites
Results: Skin Erythema

- At week 1, the sites were significantly different with the highest erythema at the PICC site.
- By week 3, PICC and dressing sites were comparable and higher than the control.

* All sites different week 1, ANOVA, p < 0.001
# PICC and Dressing sites different from control, Linear Mixed Models, p = 0.000

Results: Skin Dryness

• Dryness at baseline
• Week 1: dryness was significantly higher at the PICC site than the dressing and control.
• By week 3, PICC and dressing sites were comparable, with higher dryness than the control.

Implications & Commentary

• The dressings, rather than CHG alone, contribute to skin breakdown.
• These results highlight the skin compromise issues associated with tapes and dressings.
• Dressings with inherently higher permeability may minimize skin breakdown.
• Investigation and/or development of alternatives is essential.
Touch: Infant Skin Interactions

**Specific Modalities:**

- Skin-to-Skin Contact (Kangaroo Care)
- Newborn Individualized Developmental Care and Assessment (NIDCAP)
- Infant Massage
- Tactile Stimulation
Skin-to-Skin Contact

- Skin-to-skin contact
  - immediately following birth resulted in increased temperature and blood glucose, compared to swaddling next to the mother
  - for one hour shortly after birth impacted state organization and time spent sleeping

Skin-to-Skin Contact

- Infants 25-33 wks GA (n = 17)
- In mothers,
  - decreased salivary cortisol (32%)
  - decreased heart rate (7%),
  - decreased stress (89%)
  - increased mood (6%)
- In infants,
  - decreased heart rate
  - decreased pain scores
  - either increased or decreased cortisol

Developmentally Supportive Care

- Premature infants cared for with NIDCAP methods had significantly better
  - neurobehavioral function and more mature neuronal fiber structure
  - mother-child interaction (cluster communication), better hearing/speech and lower behavior symptom scores

Tactile Stimulation

• Tactile stimulation via repeated stroking increased circulating lactate levels by 200% in the neonatal rat model

Questions?????????
Additional Information
Premature Infants: Topicals

- 173 infants 25 – 36 wks GA
- 4 weeks with
  - Olive oil (fatty acid, linoleic) 30% and lanolin 70%
  - Bepanthen emollient (dexpanthenol, phenoxyethanol)
- Percent subjects with best skin condition was greater for olive oil vs. Bepanthen
- Both produced less dermatitis than control.

Types of Cutaneous Nerve Endings

- **Free Nerve Endings (pain)**
- **Merkel Disks (touch)**
- **Krause End Bulbs (cold)**
- **Innervated Hair Follicle**
- **Meissner’s Corpuscle (Tactile)**
Skin Statistics

In an area the size of a quarter there are

- Cells: > 3,000,000
- Sweat glands: 100 – 340
- Nerve endings: 50
- Blood vessels: 3 feet
- 640,000 sensory receptors
- 7 – 135 tactile points per cm²
- Sensory fibers from skin to spinal cord > 500,000

**TEST**

**Erythema**
- Area Increments:
  - <2%
  - 2-10%
  - >10%
  - 15%
  - >50%

**Severity Levels**
- Faint-Definite Pink
- Definite Redness
- Very Intense Redness

**Rash**
- Area Increments:
  - one
  - <2%
  - 10-50%
  - >50%

**Severity Levels**
- Papules
- Pustules (automatic ≥ 2 grade)

**Dryness**
- Area Increments:
  - <10%
  - 15%
  - >50%

**Severity Levels**
- Slight powderiness
- Early cracking
- Moderate cracking & scales
- High cracking & lifting scales
- Bleeding cracks

**Erythema = 2.0**
**Rash = 1.0**
**Dryness = 2.5**

**CONTROL**

**Erythema**
- Area Increments:
  - <2%
  - 2-10%
  - >10%
  - 10-50%
  - >50%

**Severity Levels**
- Faint-Definite Pink
- Definite Redness
- Very Intense Redness

**Rash**
- Area Increments:
  - one
  - <2%
  - 10-50%
  - >50%

**Severity Levels**
- Papules
- Pustules (automatic ≥ 2 grade)

**Dryness**
- Area Increments:
  - <10%
  - 10-50%
  - >50%

**Severity Levels**
- Slight powderiness
- Early cracking
- Moderate cracking & scales
- High cracking & lifting scales
- Bleeding cracks

**Erythema = 0.5**
**Rash = 0**
**Dryness = 0**
Tape Irritation

- Removal of dressings and tapes can cause stripping of some of the outer layers of skin, creating a superficial wound.
- As a result, the skin is more permeable to irritants and susceptible to infection.

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<th>Erythema</th>
<th>Area Increments</th>
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<table>
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Erythema = 2.5
Tape Irritation

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<td>None</td>
<td>---</td>
</tr>
<tr>
<td>0.5</td>
<td>Slight powderiness</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>1.0</td>
<td>Slight powderiness or early cracking</td>
<td>10-50%</td>
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<tr>
<td>1.5</td>
<td>Slight powderiness or early cracking</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>2.0</td>
<td>Early cracking or moderate cracking &amp; scales</td>
<td>&gt;50%</td>
</tr>
<tr>
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<td>Moderate cracking &amp; scales</td>
<td>10-50%</td>
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<tr>
<td>3.5</td>
<td>High cracking &amp; lifting scales</td>
<td>10-50%</td>
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<td>4.5</td>
<td>Bleeding cracks</td>
<td>10-50%</td>
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<tr>
<td>5.0</td>
<td>Bleeding cracks</td>
<td>&gt;50%</td>
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Dryness = 2.0

Erythema = 2.5

Control