Biology and Function of Fetal and Pediatric Skin

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INTRODUCTION

Fetal and pediatric skin are commonly believed to have advantageous properties for wound repair, with the ability of fetal skin to undergo scarless wound repair and the inherent youthful appearance of pediatric skin. However, infant and pediatric skin are also considered to be more sensitive and prone to injury than adult skin with the cosmetic industry marketing an extensive line of delicate products exclusively for the care and hygiene of infants and children.

SKIN DEVELOPMENT

The development of the dermal/epidermal layers is a continuous process starting early in pregnancy with discrete patterns related to gestational age, developing from the cranial to the caudal pole. At 4 weeks gestation, fetal skin can be visualized as 2 distinct layers: a basal cell layer covered by an outer layer, termed the periderm. The periderm is uniquely found in humans; there is no counterpart in animal models such as mice or rats. Keratinization begins at 9 weeks gestation, and at 13 weeks gestation, stratification into different layers becomes apparent. Hair follicles begin to form as epidermal buds along the basal layer at 14 weeks gestation. In the subsequent 2 weeks, these epidermal buds are associated with local proliferation of mesenchymal cells associated with the epidermal bud as hair follicles rapidly develop. This is followed by continued elongation of the hair follicles. The development of eccrine sweat glands begins as epidermal buds in the basal layer at 20 weeks gestation and continue to develop over the next 10 weeks, first by elongating and then by coiling. At 24 weeks gestation, fetal skin continues to heal without scar, as keratinization and stratification into mature morphologic layers continues. After 24 weeks gestation, there is a transitional period when skin heals without characteristic scar deposition but fails to reconstitute the dermal appendages. This transitional period has been found in multiple animal models of fetal wound healing. The scarless wound healing...
phenotype is lost by the third trimester. At 34 weeks gestation, mature keratinocytes characterized by flattened, keratinized morphology are observed in conjunction with adult-type dermoepidermal undulations.5,6

In later gestation, the fetal dermis is primarily thickened by an increase in collagen content.4 This dermis has higher levels of type III collagen, chondroitin sulfate, proteoglycans, and hyaluronan compared with adult dermis.4 Dermal elastin is also absent in fetal dermis.7,8

During the last trimester, the fetus is covered by the vernix caseosa (VC), a protective coat secreted by the sebaceous glands and composed of protein (10%), lipids (10%), and water (80%).9 The VC is uniquely human, with no counterpart identified in animal models. This coat was initially posited to function as a lubricant in the birthing process. However, as the fetus continues to mature, part of the vernix sloughs from the skin surface into the surrounding amniotic fluid.10 This physiologic decrease of vernix with advancing gestational age renders this role unlikely. More recent studies of the VC suggest that the layer facilitates the transition from an aqueous in utero environment to the dry extrauterine environment.11 The vernix helps to protect the fetal epidermis from maceration while immersed in amniotic fluid and permits epidermal cornification and stratum corneum formation.9 The VC also contains high levels of lysozyme, lactoferrin, linoleic acid, as well as other antiinfective agents.9,12

Full-term infants at birth have skin that is anatomically mature when examined histologically with all 5 layers present. These include from deep to superficial: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum.13 As epidermal cells mature, their morphology changes from the columnar stratum basale to the tightly overlapping squamous keratinocytes of the stratum corneum.5,6 The time to

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**Fig. 1.** Fetal development of skin. (A) At 4 weeks’ gestation, skin is composed of 2 layers, the periderm and basal epidermis. (B) At 9 weeks gestation, keratinization becomes apparent. (C) At 14 weeks gestation, stratification of the epidermal layer is apparent along with budding of the basal layer as the primordial hair follicle develops. (D) At 16 weeks gestation, mesenchymal cells may be seen associated with the epidermal bud. (E) At 18 weeks, sebaceous glands become apparent, along with hair follicle elongation. (F) At 23 weeks, the hair follicles continue to elongate while the basal layer buds to form primordial eccrine glands. (G) At 30 weeks’ gestation, the eccrine glands continue to elongate and coil.
fully mature, keratinize, and form this protective horny layer varies depending on body site.14 This occurs more rapidly in facial skin than in the trunk and limbs.6 Neonatal skin has a relatively coarse texture compared with older infants and a more homogeneous smooth structure develops during the first 30 days of life.15 Infants have smaller corneocytes and a significantly thinner stratum corneum until 2 years of age.13

During the next developmental period from infancy to puberty, there is little difference in skin between male and female patients. Both genders demonstrate a steady increase in dermal thickness, with boys developing thicker epidermal and dermal layers.16 At the onset of puberty, there is significant hormonal influence on the skin. After age 12 years, girls accumulate a thick layer of subcutaneous fat, which is absent in boys. On the other hand, boys exhibit a gradual thinning of their thick epidermal and dermal layers. These layers remain a constant thickness in females throughout adolescence and adulthood until menopause.16 In addition, dermal composition begins to change with advancing age starting at puberty; both sexes show similar rates of linear decrease in skin collagen content with age. Women start with a lower baseline collagen density and they seem to age earlier than men.4,16

SKIN FUNCTION

Skin has multiple functions including regulation of body temperature and protection against physical, chemical, and biological insults.17,18 In full-term neonates at birth, the skin is histologically mature, however it remains functionally immature. Neonatal barrier functions are in a constant state of flux, in contrast to mature adult skin.5 It has been proposed that this changing infant skin barrier is not a deficit but a benefit because adaptive flexibility allows constant optimization, balancing growth, thermoregulation, water barrier, and protective functions.

BIOPHYSICAL SKIN PARAMETERS

Skin can be defined by a variety of biophysical skin parameters, which permit the study of skin in a noninvasive manner. Multiple parameters, including transepidermal water loss, hydration, and skin acidity, are affected in skin diseases such as atopic dermatitis, psoriasis, and allergic or irritant contact dermatitis.2

**Transepidermal Water Loss**

Transepidermal water loss (TEWL) describes the amount of water loss through the epidermis through evaporation and depends on multiple factors, including skin temperature, skin blood flow, local hemodynamics, degree of corneocyte formation, and stratum corneum lipid content.19 TEWL is measured by electrical skin impedance; lower impedance indicates higher skin hydration.20 There is a direct relationship between TEWL and skin development. In full-term infants, there is a significant decrease in TEWL indicating a functional barrier to evaporative water loss. At birth, the sweat glands are anatomically mature, however only a small fraction of these glands are functionally mature with secretory activity.20 During the first few months of life, impedance values begin to decrease corresponding to the recruitment and maturation of sweat glands. These values stabilize at 4 months in full-term infants.20

Premature infants, less than 32 weeks’ gestation, have lower impedance and high TEWL at birth. This excess loss is a result of immature barrier function and thinner epidermal layers,20 relatively increased blood flow to the skin compared with other infants, as well as a high ratio of total body surface area to volume. These factors lead to increased insensible water loss. TEWL in these premature infants can exceed 30% of their total body weight within a 24-hour period. TEWL decreases as skin continues to mature, with improved barrier function. The barrier function regulating evaporative losses varies according to anatomic location. In general, TEWL is higher in the facial region, compared with the body.19 The highest TEWL is reported in the nasolabial fold and perioral regions, with the lowest TEWL over the cheeks. There are no gender differences noted in the neonatal or pediatric period.21

Skin Hydration

At birth, skin is transitioned from continuous immersion in an aqueous solution to exposure to relatively low humidity ambient air. Maintenance of skin hydration is critical for skin function, including plasticity, flexibility, prevention of fissures, and proper desquamation.22 Neonatal skin responds with a dramatic decrease in hydration at birth.8 Skin hydration then quickly increases for up to 90 days after birth, as the eccrine glands mature.23 This increased skin hydration persists for up to the first year of life5 and subsequently stabilizes to adult levels.24

The sebaceous glands also play an important role in maintaining optimal skin hydration, secreting lipid-rich sebum. The highest sebum levels in the face are located in the nasolabial area.19 These glands are hormonally regulated and are active in utero, producing the VC.5 After
birth, there are low levels of sebum protection until puberty, when it markedly increases to adult levels, particularly in boys.\textsuperscript{6,24,25}

**Skin Acidity**

Fully mature skin is characterized by a physiologic acid mantle with the pH maintained between 4.5 and 6.0.\textsuperscript{2,26} This acid mantle is an important mechanism in the skin’s defense against infection. The enzymes in the upper epidermis are optimized to function at pH 5.6. Neonatal skin is characterized by a higher pH compared with older pediatric and adult patients, regardless of gestational age, sex, mode of delivery, or body weight.\textsuperscript{27} This newborn skin has a different chemical composition of skin surface lipids.\textsuperscript{2} Maturation and maintenance of the acid mantle depends on lactic acid, free amino acids, and fatty acids found in sebum and sweat. Once established, the acid mantle is more uniformly distributed anatomically in the early pediatric population.\textsuperscript{2} At the onset of puberty, the intertriginous areas, such as the axilla and inguinal region, approach a neutral or even alkaline pH, as found in adults.\textsuperscript{28}

**THERAPEUTIC OPTIONS**

As the survival rate of premature infants continues to increase at earlier gestational age, the issue of immature pediatric skin becomes more prevalent. The therapeutic options focus on supporting the barrier function of the infant skin, including thermoregulation, hydration, and attenuating risk of infection. In the neonatal period, thermoregulation can be supported by the use of low-energy infrared radiation, which warms the ambient air.\textsuperscript{17} Skin temperature can vary greatly depending on anatomic location; the skin overlying the liver correlates most closely with core temperature.\textsuperscript{17}

### Table 1
Clinical review of the literature: summary table of various reviews

<table>
<thead>
<tr>
<th>Author</th>
<th>Groups Compared</th>
<th>Findings</th>
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<tr>
<td>Stamatas et al,\textsuperscript{15} 2011</td>
<td>Full-term infants (birth to 3 y) vs Adults</td>
<td>Skin Structure&lt;br&gt;Infants have smaller corneocytes&lt;br&gt;Infants have thinner stratum corneum&lt;br&gt;Skin Function&lt;br&gt;Barrier function: weaker than adults&lt;br&gt;Hydration: decreased at birth, but increased later in infancy&lt;br&gt;TEWL: lower at birth, similar or higher later in infancy (anatomic variance)&lt;br&gt;pH: infant skin is more alkaline&lt;br&gt;Cell proliferation: increased turnover</td>
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<td>Fluhr et al,\textsuperscript{26} 2012</td>
<td>Newborns (1–15 d) vs Infants (5–6 wk) vs Infants (1–2 y) vs Pediatrics (4–5 y) vs Adults (20–35 y)</td>
<td>Skin Function&lt;br&gt;Hydration: newborns have the lowest hydration and water content&lt;br&gt;Skin hydration increases then remains stable through pediatrics and adults&lt;br&gt;TEWL: lowest in the 5–6 wk after birth, highest at 1–2 y&lt;br&gt;pH: skin of newborn infants is more alkaline than all other groups; skin becomes more acidic by 5–6 wk and then remains stable through pediatrics</td>
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<td>Giusti et al,\textsuperscript{2} 2001</td>
<td>Infants (8–24 mo) vs Adults (25–35 y)</td>
<td>Skin Function&lt;br&gt;Hydration: infants have higher hydration&lt;br&gt;TEWL: no difference between infants and adults&lt;br&gt;pH: infant skin is more alkaline at multiple sites</td>
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<td>Firooz et al,\textsuperscript{24} 2012</td>
<td>Pediatrics (10–20 y) vs Adults (20–30 y, 30–40 y, 40–50 y)</td>
<td>Skin Function&lt;br&gt;Hydration: no difference between pediatrics and adults&lt;br&gt;TEWL: no difference between pediatrics and adults&lt;br&gt;Sebum: no difference between pediatrics and adults</td>
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<td>Man et al,\textsuperscript{25} 2009</td>
<td>Prepuberty (0–12 y) vs Young group (13–35 y) vs Middle age (36–50 y) vs Old group (51–70 y)</td>
<td>Skin Function&lt;br&gt;Hydration: higher stratum corneum hydration in young group males compared with females&lt;br&gt;pH: no difference in pH between pediatrics and older groups</td>
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Maintenance of a normal core temperature decreases the mortality rate of these premature infants and helps to minimize insensible water loss by optimizing the TEWL. Although barrier function becomes physiologically mature early in the pediatric period, the increased surface area to volume ratio of younger children continues to put them at a higher risk of excess water loss and dehydration due to insensible losses compared with adults and adolescents. Cognizance of this risk and regular oral hydration are necessary to maintain homeostasis.

From birth to puberty, pediatric skin is at risk of desiccation with lower levels of sebum production. Decreased skin hydration is associated with impairment of the skin’s barrier function and pathologic conditions such as atopic dermatitis. Desiccation of the skin leads to the early appearance of fine cracks and fissures in pediatric skin.9 These defects are a route to infection and irritants. Maintenance of hydration can be facilitated by continual use of moisturizers.

CLINICAL OUTCOMES

Skin development continues from birth throughout life. With interim support of skin function in the neonatal period, even the most premature infant progresses to normal skin capable of thermoregulation, maintenance of hydration, and protection against infection (Table 1).

COMPLICATIONS AND CONCERNS

Pediatric skin has increased permeability with higher TEWL and increased skin hydration. Increased permeability leads to a tendency to develop xerosis, excessively dry skin that presents as white patches with fine white scales, particularly on the exposed facial skin.6 Xerosis leads to increased development of irritant or allergic contact dermatitis.2,6

Without the support of thermoregulation, hydration, and pathogen barriers in the neonatal and early pediatric period, immature skin can result in lethal consequences secondary to extensive transcutaneous fluid loss or infection.18

SUMMARY

Skin development is a continuous process, beginning in utero and continuing throughout life. The skin is anatomically mature at birth, but continues to develop functionally throughout the first year of life. The glandular components of skin are strongly influenced by hormonal changes, with further development seen at the onset of puberty.

REFERENCES

As a group of potentially life-threatening and often easily treatable diseases, infections are often suspected first in a neonate with skin lesions. Recognition of characteristic morphologic features, aided by a few easily performed tests, will greatly enhance correct diagnosis and early initiation of appropriate therapy of the most common cutaneous infections. In this chapter, the focus is on disease caused by the most common pathogens responsible for neonatal infections that manifest with skin lesions: *Staphylococcus aureus*, *Streptococcus* spp. *Candida albicans*, and herpes simplex virus (HSV).

**STAPHYLOCOCCUS AUREUS INFECTIONS**

*S. aureus* is a ubiquitous organism, harbored as a commensal organism by greater than 30% of the general population (Ladhani, 2000). Colonization of the anterior nares and perineum is common, with frequent hand carriage (Dancer and Noble, 1991). This bacterial species is responsible for a variety of skin lesions. Infants become colonized with *S. aureus* during the first few weeks of life, following inoculation at the perineum or from handling. Cutaneous signs of *S. aureus* infection are mediated by local or circulating bacterial toxins that act directly on components of the epidermal keratinocytes, or as “superantigens” to stimulate exuberant immunologic responses (Tokura et al, 1994).

**BULLOUS IMPETIGO**

Impetigo is a group of superficial skin infections caused by group A streptococci or *S. aureus*, or both. However, neonatal bullous impetigo is primarily caused by coagulase-positive *S. aureus*. This form of impetigo can occur in nursery-based, epidemic patterns, often attributed to nasal carriage of *S. aureus*.

**Clinical Findings**

Impetigo is one of the most common neonatal skin infections. It occurs during the latter part of the first week or as late as the second week of life, manifested as vesicles or pustules on an erythematous base, most often seen in the periumbilical area, diaper area, or skin folds. Because the blisters are superficial, intact lesions are usually less than 1 cm in diameter. Larger lesions are flaccid and rupture so easily that they are usually seen as erosions, with a red moist base that develops a thin, varnish-like crust (Figure 99-1). These lesions heal rapidly without scarring. Lesions are usually not closely grouped, differentiating them from the vesicles of herpes simplex infection.

**Etiology**

*S. aureus* is the primary cause of both bullous and nonbullous impetigo. Group A streptococci usually are associated with the nonbullous form, especially affecting patients with atopic dermatitis. Bullous impetigo is caused by toxigenic strains of coagulase-positive hemolytic *S. aureus*. Most often, the organism can be classified as one of the group II phage types (71 and 55). The incubation period is 1 to 10 days. Skin lesions are the result of local production of an epidermolytic exotoxin that cleaves a desmosomal protein connecting cells in the granular layer of the epidermis, producing superficial blisters. This is the same toxin produced in staphylococcal scalded skin syndrome (Amagi et al, 2000; Yamaguchi et al, 2002).

**Epidemiology**

Persons with skin lesions are highly contagious, but the disease also can be transmitted by asymptomatic carriers. The anterior nares of 30% of the general population are colonized with *S. aureus*, providing a reservoir for hand carriage and nosocomial spread (Doebbeling, 1994; Kragballe et al, 1995). Colonization of health care workers by strains of methicillin-resistant *Staphylococcus aureus* (MRSA) poses a potentially serious problem, and outbreaks of MRSA have occurred in neonatal intensive care units (NICUs) caused by an MRSA strain previously found in the community (Regev-Yochay, 2005; Yamaguchi et al, 2002).

Sporadic cases of impetigo are common, but many nursery epidemics have been reported and should be treated aggressively (Dave et al, 1994). Infected infants may not develop skin lesions until after discharge, so infection control surveillance should include all exposed patients. Overcrowding, insufficient nursery personnel, and inadequate hand washing contribute to nosocomial spread. Treatment of the umbilical cord with an antimicrobial agent has been shown to control epidemic *S. aureus* infections in the NICU (Haley et al, 1995). In the setting of an outbreak, nursery personnel should be surveyed for colonization of the hands and nares. Application of mupirocin ointment to the anterior nares twice daily for 5 days will eliminate nasal carriage for up to 1 year (Doebbeling et al, 1994). Effective hand washing can prevent nosocomial spread; chlorhexidine is among the safest and most effective antimicrobial cleansers for hospital use (Doebbeling et al, 1992). The use of antiseptic hand rub has also been shown to be as or more effective than washing with soap. A study by Girou et al in 2002 showed that during routine patient care, hand rubbing with an alcohol-based solution was significantly more efficient in reducing bacterial counts than hand washing with antiseptic soap.
Diagnosis
The diagnosis is supported by the presence of gram-positive cocci in clusters on Gram stain of the fluid from a pustule or vesicle or under crusted plaque of impetigo. Confirmation is made by bacterial culture taken from blood, skin, and soft tissues, especially in the case of suspected MRSA.

Treatment
Bullous impetigo is benign if treated early, but local proliferation with exotoxin production or dissemination can be life-threatening. Treatment should be instituted promptly and isolation maintained until the lesions have resolved. Infants should be closely monitored and a high index of suspicion maintained for evidence of systemic disease. Infants with periumbilical lesions are at risk for bacterial omphalitis. Extremely limited infections may be treated with topical mupirocin, but this form of therapy should be used with caution in neonates. More extensive lesions require a systemically (most recommend parenterally) administered penicillinase-resistant antibiotic for 7 to 10 days. Sensitivities of the organism cultured should ultimately determine the choice of antibiotics, especially with the rising incidence of MRSA. In this case vancomycin or linezolid would be considered.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME
Staphylococcal scalded skin syndrome (SSSS) occurs as a generalized manifestation of a circulating toxin produced by S. aureus that specifically cleaves cell-to-cell adhesion proteins in the epidermis. Affected infants are erythrodermic, a striking cutaneous finding that suggests a long list of differential diagnostic possibilities. Early diagnosis and treatment of SSSS can be lifesaving.

Clinical Findings
Affected infants demonstrate abrupt onset of temperature instability and irritability with generalized skin tenderness and erythema that most often starts on the face and spreads rapidly. Erythema often is accentuated in skin folds. Facial edema, conjunctivitis, and crusting around the eyes, nose, and mouth give the infant a characteristic “sad mask” appearance. Flaccid bullae may develop, followed by widespread exfoliation (Figure 99-2) involving the entire skin surface within hours to days. Hypopigmentation may follow exfoliation in darker races that will repigment in time. Blistering is easily elicited by light stroking of intact skin, a diagnostic feature referred to as a Nikolsky sign. When blisters rupture, the skin peels off in sheets, leaving a painful moist, red base. Widespread skin involvement can exacerbate fluid and electrolyte problems (Frieden, 1989). Whereas in bullous impetigo S. aureus is identifiable in the blisters, in SSSS S. aureus is present at a primary distant site such as the nose, mouth, or conjunctiva.

SSSS must be distinguished from toxic epidermal necrolysis (TEN), a life-threatening condition involving full-thickness epidermal necrosis, most commonly due to a drug reaction. In SSSS, mucosal erythema may be seen but there are no intraoral blisters, whereas in TEN, mucosal blistering is present.

Etiology
The signs and symptoms of SSSS are the result of circulating epidermolytic toxin, produced from an often subclinical focus of S. aureus infection. Fresh skin lesions do not contain bacteria, and the blisters are culture-negative. Two distinct epidermolytic toxins have been identified in SSSS, produced by toxigenic strains of S. aureus, phage group I, II, or III. Approximately 5% of S. aureus isolates produce the toxins (Farrell, 1999). The exotoxin cleaves desmosomal proteins within the epidermal granular layer, resulting in blisters (Amagi et al, 2002; Resnick, 1992). Superantigenic stimulation of cytokine production also has been demonstrated (Dave et al, 1994).
Diagnosis

If the diagnosis is in doubt, skin biopsy prepared for frozen section can be examined emergently. The presence of an intraepidermal rather than full-thickness blister will distinguish SSSS from TEN, allowing rapid initiation of appropriate therapy. Other conditions can be ruled out by examination of formalin-fixed sections. If the clinical impression is strong, surveillance samples will define the primary focus of infection. Gram staining may be performed emergently; cultures will confirm the diagnosis. Common sites of primary infection are the nasopharynx, umbilicus, and ocular conjunctivae; the urine also may demonstrate organisms. Bullous lesions do not contain organisms. Blood culture specimens should be obtained because sepsis, although uncommon, may occur. Phage typing may be of interest in epidemics.

Treatment

Systemic administration of a penicillinase-resistant penicillin is the therapy of choice. Fluid and electrolyte replacement and measures for maintenance of normal body temperature may be required. Approximately 2 to 3 days after initiation of therapy, the denuded areas become dry, and a flaky desquamation ensues. Crusted and denuded areas may be treated with compresses of Burow or normal saline solution. Application of a bland ointment emollient may accelerate the return of the skin to normal during the flaky desquamative phase. Resolution occurs in another 3 to 5 days. Because the intraepidermal cleavage plane is at the level of the granular layer, scarring occurs only in instances of secondary complications (Frieden, 1989).

STREPTOCOCCUS SPP INFECTIONS

Cutaneous streptococcal infections occur in the newborn but are less common than staphylococcal infections. Group A streptococci have been reported to cause disease of epidemic proportions (Dillon, 1966; Peter and Hazard, 1975) following the introduction of the organism into the nursery by maternal carriers or nursery personnel. The umbilicus (omphalitis) is a frequent site of infection. Conjunctivitis, paronychia, vaginitis, and an erysipelas-like eruption also have been described (Dillon, 1966; Geil et al, 1970; Isenberg et al, 1984). Because sepsis and meningitis may result, infected infants should be treated promptly, and strict isolation should be instituted. As with staphylococcal infection, serious efforts should be made to identify the source of the organism. Several nursery outbreaks have been difficult to terminate because colonized infants may show little evidence of disease (Lehtonen et al, 1984). Isolation and treatment of infected infants, disinfection of the umbilical stump as the most likely reservoir of the organism, and penicillin prophylaxis for carriers and exposed infants have been the most effective measures. The infections respond readily to penicillin, which should be administered over a 10-day course.

Group B streptococci are now one of the most frequently encountered pathogens in the newborn nursery. Early-onset disease (during the 1st week of life), probably acquired in utero or during delivery, most commonly becomes manifest as septicemia with respiratory distress and shock. Late-onset disease (7 days to 3 months) is acquired postpartum and more often takes on the form of meningitis. Patients with early-onset disease may harbor the organism on the skin; however, the presence of this agent on the skin is short-lived compared with other sites (Baker, 1977).

Skin infections caused by group B streptococci are uncommon but have been documented (Belgaumkar, 1975; Hebert and Esterly, 1986; Howard and McCrackin, 1974). The most common skin manifestation of GBS is cellulitis, usually of the face (Shet and Ferrieri, 2004). Vesciculopustular lesions and small abscesses and necrotizing fasciitis all have been noted. A 10-day course of procaine penicillin or clindamycin is considered the treatment of choice.

OMPHALITIS

CLINICAL FINDINGS

Omphalitis is infection of the umbilical stump that presents around day 3 of life. Clinically there is erythema, edema, and tenderness around the umbilicus with or without discharge. Infection can extend into the subcutis or along the abdominal wall causing necrotizing fasciitis.

ETIOLOGY

S. aureus, Escherichia coli, Klebsiella spp., and S. pyogenes are common organisms that cause omphalitis. Preterm infants, low-birthweight infants, and infants from home births and complicated deliveries are at increased risk (Sawardekar, 2004).

DIAGNOSIS

Gram stain and bacterial culture from moist umbilical stump fluid can be obtained, but because this area can be contaminated easily, clinical correlation is needed. True infection must be differentiated from embryonic duct remnants or umbilical papilloma.

TREATMENT

Ampicillin and gentamicin can be used initially until culture and sensitivities are obtained. Intravenous antibiotics can be switched to enteral once the skin improves clinically. In a Cochrane review, no difference was demonstrated in cord and other skin infections within 6 weeks of observation between cords treated with antiseptics as compared with dry cord care or placebo. However, there was a trend toward reduced colonization with antibiotics compared to antiseptics and no treatment (Zupan et al, 2004).

CANDIDA ALBICANS INFECTIONS

C. albicans is a frequent pathogen of the female genital tract, especially during pregnancy. Infantile infection may be acquired in utero, during delivery, or postnatally.
Infections of the Skin

LOCALIZED CANDIDA INFECTION
(PRIMARY CUTANEOUS)

Oral Candidiasis (Thrush)

*C. albicans* colonizes the oral cavity and gastrointestinal tract of most neonates, with peak incidence of thrush occurring at 4 weeks of age (Russell and Lay, 1973). The lesions are readily recognized as asymptomatic to moderately painful plaques of white, friable material on an erythematous base over the tongue, palate, buccal mucosa, and gingivae.

Diaper Dermatitis

Localized cutaneous candidal infections are common in infants, with peak incidence at 3 to 4 months of age. Characteristic primary lesions are tiny vesicopustules that erode and merge, forming bright, erythematous plaques often with a scalloped edge in the moist intertriginous areas of the perineum and perianal and inguinal creases (Figure 99-3). White scale and “satellite” pustules may be seen along the periphery. Thrush may also be present in conjunction with *Candida* diaper dermatitis. Other intertriginous areas such as the neck folds and axillae can also be infected with *Candida*, as well as the nails.

Diagnosis of Localized Cutaneous Candida

Presumptive diagnosis often is made by physical examination and history, but microscopic examination of scrapings suspended in 10% potassium hydroxide for yeast and pseudohyphal forms is useful. The diagnosis may be confirmed by identification of the organism on culture.

Treatment

Nystatin is an antibiotic derived from *Streptomyces noursei* with activity against *Candida* but not dermatophytes. Oral lesions usually respond promptly to a course of nystatin suspension, 100,000 to 200,000 units, administered by mouth four times daily for 14 to 21 days. In refractory cases, an increased dosage of nystatin or systemic therapy may have to be instituted (Hebert and Esterly, 1986). Localized cutaneous candidiasis in an otherwise healthy infant is most easily treated with a topical candidicidal agent, such as nystatin, one of the imidazoles (e.g., miconazole, clotrimazole, ketoconazole), or ciclopirox olamine (Gibney and Siegfried, 1996). Nystatin in an ointment vehicle may be the least irritating. If the breastfeeding mother is affected, treatment of the mother with nystatin cream or oral fluconazole may be indicated. Gentian (crystal) violet is a triphenylmethane antiseptic dye effective against *Candida* species. In a 0.5% or 1% aqueous solution it has been a time-honored, safe, and effective treatment for thrush. Gentian violet is infamous for deep purple staining of the skin, which is transient. Prolonged use of gentian violet has been associated with nausea, vomiting, diarrhea, and mucosal ulceration. Carcinogenicity in mice has been reported (Rosenkranz and Carr, 1971).

CONGENITAL (INTRAUTERINE) CANDIDIASIS

Congenital candidiasis is *Candida* infection acquired in utero from an ascending infection, crossing the fetal membrane and infecting surfaces that come in contact with amniotic fluid and manifests with symptoms in the first days of life. Even though the rate of vaginal colonization is 33%, congenital candidiasis is uncommon. Risk factors include the presence of a foreign body in the maternal uterus or cervix. Systemic dissemination of yeast is rare in the majority of term infants.

Clinical Findings

Lesions of congenital candidiasis can be seen on the placenta and fetal membranes, including characteristic granulomas of the umbilical cord (Hebert and Esterly, 1986; Schirar et al, 1974). The cord lesions are multiple yellow-white papules, usually measuring 1 to 3 mm in diameter. The cutaneous eruption of congenital cutaneous candidiasis may be sparse or widespread and consists of papules and
vesicopustules on an intensely erythematous base. The face is relatively spared, as are the oral mucous membranes, and there is no predilection for the diaper area. Palmar and plantar pustules, paronychia, and nail dystrophy help distinguish this condition from more common, benign neonatal dermatoses (Figure 99-4). Bullae and desquamation usually are late features (Figure 99-5). Skin lesions usually resolve with desquamation within 1 to 2 weeks (Darmstadt et al, 2000). The prognosis is good in full-term infants. Topical treatment may be used.

Very low-birthweight infants may present with a less specific, scalded skin–like or erosive dermatitis owing to the organism’s penetration of the immature, compromised epidermal barrier, leading to invasive disease. Generalized scaling is the dominant feature, but a careful search may reveal primary vesicopustules and periangual or nail involvement as helpful diagnostic clues (Gibney and Siegfried, 1996).

**Diagnosis**

The differential diagnosis includes conditions that cause blisters and pustules. Napkin psoriasis is also on differential. A potassium hydroxide preparation that reveals budding yeasts and pseudohyphal forms is the easiest and most cost-effective initial step in establishing the diagnosis. Calcofluor white stain and immunofluorescence microscopy is a more sensitive rapid technique. Positive results on cultures from an intact pustule, skin scrapings, or skin biopsy tissue also support the diagnosis. Cultures of blood, urine, and cerebrospinal fluid are usually negative; however, they are indicated when systemic disease is suspected and in all preterm infants.

**SYSTEMIC/DISSEMINATED CANDIDIASIS**

Systemic candidiasis infection (Candida infection in an otherwise sterile body fluid such as blood, urine, or cerebrospinal fluid) affects very low-birthweight infants more commonly than full-term infants. Most neonatal fungal infections are caused by C. albicans and Candida parapsilosis.

Systemic or disseminated candidiasis can be due to congenital candidiasis (acquired in utero) in very low-birthweight infants, untreated localized Candida infection in preterm infants, or nosocomial spread. Risk factors for congenital systemic infection include birthweight of less than 1500 g, indwelling catheters, broad-spectrum antibiotic therapy, steroid administration, and hyperalimentation. Approximately 10% of NICU infants become colonized in the 1st week of life. Candida septicemia represents 10% to 16% of all cases of sepsis in the NICU, and early recognition and appropriate therapy are lifesaving (Gibney and Siegfried, 1996; Leibovitz, 2002). The estimated crude mortality rate for candidemia is 38% to 75% (Lupetti et al, 2002).

**Clinical**

Skin manifestations may occur in 60% of infants, which include burnlike dermatitis followed by desquamation, progressive diaper dermatitis with papules and pustules, and abscess. Systemic involvement occurs via hematogenous or lymphatic spread, most frequently involving the kidney, central nervous system (CNS), and skeletal system. Pneumonia may result from aspiration of infected amniotic fluid and manifests with respiratory distress. Other systemic signs include apnea, bradycardia, temperature instability, hypotension, guaiac-positive stools, and abdominal distention. Laboratory features include an elevated white blood cell count with a left shift reaching the level of a leukemoid reaction (e.g., 120,000/mm³). In addition, persistent hyperglycemia and glycosuria may be present (Darmstadt et al, 2000).

**Diagnosis**

The differential diagnosis includes several other neonatal vesiculopustular eruptions that range from benign, self-limited cutaneous processes to rapidly progressive, life-threatening disease. Early and correct diagnosis is essential. Organisms from skin usually are demonstrable on potassium hydroxide or calcofluor white preparations and cultures of scrapings from involved skin. Disseminated
disease can be difficult to diagnose. Respiratory distress and infiltrates on chest radiograph will obscure evidence of *Candida* pneumonia because hyaline membrane disease often occurs in the same patient population. Ophthalmologic examination, chest radiograph, and blood, urine, and cerebrospinal fluid cultures may be helpful, but negative findings are not uncommon in disseminated candidiasis (Johnson et al., 1984). Histologic examination of specimens from the placenta and umbilical cord prepared with the appropriate stains may demonstrate fungal elements. Urinalysis positive for budding yeast or urine culture positive for *C. albicans* may be quickly dismissed as being due to contaminants, but such findings are strongly associated with systemic disease in infants at risk. The diagnosis of disseminated candidiasis can be expedited by a positive touch preparation of a punch biopsy specimen. Using this technique, the practitioner firmly imprints the dermal side of the specimen on a microscope slide and then looks for yeast after potassium hydroxide preparation or Gram staining (Held et al., 1988).

**Prognosis and Treatment**

Systemic infection with *C. albicans* in premature infants is a serious infection with high morbidity and mortality rates (Johnson et al., 1984). Congenital or acquired candidiasis warrants parenteral antifungal therapy (e.g., with amphotericin B) for infants with any of the following risk factors for disseminated disease: (1) evidence of respiratory distress or sepsis in the immediate neonatal period; (2) birthweight less than 1500 g; (3) treatment with broad-spectrum antibiotics or corticosteroids; (4) extensive instrumentation during delivery or invasive procedures in the neonatal period; (5) positive systemic cultures; (6) evidence of altered immune response; and (7) birth at less than 27 weeks of gestational age. A critical factor for survival in systemic candidiasis is not limited extent of infection but the early initiation of antifungal therapy (Botas et al., 1995; Johnson et al., 1984). A few single-center studies have demonstrated the efficacy of fluconazole in the prevention of both colonization and infection by *Candida* spp. (Kaufman et al., 2001; Manzoni et al., 2006), and a multicenter, prospective, randomized clinical trial has shown the safety and efficacy of fluconazole in preterm and very low-birthweight infants (Kicklighter et al., 2001).

**HERPES SIMPLEX VIRUS INFECTION**

Early recognition and prompt initiation of therapy for neonatal herpes are critical. The consequences of delaying antiviral therapy can be devastating.

**CLINICAL FINDINGS**

Onset of symptoms usually occurs at 1 to 2 weeks for most neonates, but congenital lesions have been reported (Salvador et al., 1994). Infection is categorized by extent of disease, as follows: skin-eye-mucosae (SEM) disease, CNS disease, and disseminated disease. Neonatal HSV infection often presents with a sepsis-like syndrome or with a new onset of seizures. Skin or mucosal lesions may appear only late in the disease course, or not at all. Only one third of infants present with cutaneous involvement (Frieden, 1989), although more than 80% develop typical skin lesions during the course of their disease (Overall, 1994). Characteristic skin lesions begin as isolated or grouped, tense vesicles on an erythematous base and evolve into pustules, crusts, or small erosions over several days. Forty percent of infected infants have SEM disease. With early treatment, these infants have an excellent prognosis; if the infection is left untreated, it will progress in 75% of cases (Arvin and Prober, 1992). Thirty-five percent of infected infants have CNS disease, with a high incidence of developmental abnormalities. One fourth of the infants present with evidence of disseminated disease (e.g., sepsis, liver dysfunction, coagulopathy, respiratory distress). For this group, the prognosis is poor, with a 60% mortality rate and a 40% risk of long-term neurologic impairment in survivors (Arvin and Prober, 1992; Whitley, 1994). Infants infected in utero have a distinctive clinical presentation. Skin lesions are almost always present at birth and include widespread erosions and bullae, scars, and scalp lesions that resemble those of aplasia cutis. Other frequent findings include chorioretinitis, microcephaly, hydranencephaly, and microphthalmia (Arvin and Prober, 1992).

**ETIOLOGY**

A majority of cases of neonatal herpes simplex are the result of vertical transmission. Two thirds of cases are caused by HSV-2 and one third by HSV-1. The usual route of infection is via intrapartum contact with genital mucosa, but ascending infection accounts for 5% of cases of neonatal herpes. Infants who become infected in utero are more often premature or small for gestational age, with more widespread and severe disease (Arvin and Prober, 1992).

**EPIDEMIOLOGY**

Prospective, single-center studies in the United States have shown rates of neonatal HSV infection as high as 31.2 cases per 100,000 (1 in 3200) live births (Corey and Wald, 2009). Most cases of maternal-fetal transmission involve women with undiagnosed genital herpes, many of whom have acquired primary HSV-1 or HSV-2 near delivery. One half of infected infants are born to mothers with primary infections. These women, who are usually without active lesions, have a 25% to 50% risk of transmitting disease to their newborns (Corey and Wald, 2009). One half of infants with neonatal herpes are born to mothers with recurrent genital herpes, generally from HSV-2. Most of these women also are asymptomatic at the time of delivery and may have no known history of genital herpes. In this group, the risk of transmitting infection is around 2.5%.

**DIAGNOSIS**

A high index of suspicion is required. The differential diagnosis includes the causes of vesicles and pustules in the newborn outlined in Chapter 97. Tzanck smears, viral cultures, and direct fluorescent antibody detection are the most widely used tests to detect herpes infection. The diagnostic yield for each is variable, largely influenced by
Strategies to decrease risk of vertical transmission include cesarean delivery, serologic screening of pregnant women, prophylactic antiviral therapy, and maternal vaccination development. Delivery via cesarean section for women with active lesions or prodromal symptoms and prophylactic antiviral treatment for women with gestational HSV are some accepted approaches (Enright and Prober, 2002). Suppressive acyclovir reduces the frequency of genital lesions near term and the frequency of cesarean delivery, but there are no data to suggest that it reduces the risk of neonatal herpes. Because a direct correlation exists between the development of neurologic deficits and the frequency of recurrent cutaneous HSV, the use of suppressive oral acyclovir therapy after acute neonatal SEM disease may limit long-term morbidity (Kimberlin et al, 1996).

SUGGESTED READINGS


Complete references used in this text can be found online at www.expertconsult.com