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NeoQuest November 2021: A Blistering Neonatal Rash

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A term male infant born via planned caesarean section has neck and buttock skin findings at birth (Figure 1). Based on a family history of similar lesions, as well as a skin biopsy with immunofluorescence testing revealing IgG antibodies, the dermatologist counsels the family that the lesions are expected to resolve spontaneously by one month of age with supportive wound management.

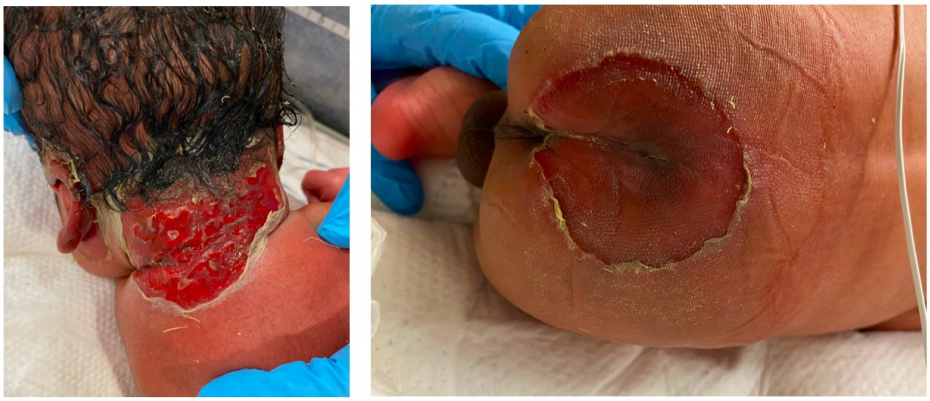

Figure 1. Mientus A, Duncan S. Skin erosions in a newborn. *Neoreviews*. 2021;22(11):e76. doi:10.1542/neo.22-11-e76

What intervention should be recommended to this mother to decrease the risk of similar skin findings in future children?

A. Administer topical and systemic corticosteroids during future pregnancies
B. Avoid delivering vaginally with subsequent pregnancies
C. Collect third trimester nasal swabs for microbiological cultures in future pregnancies
D. Obtain a rapid plasma reagin test prior to conception and during pregnancy
E. Refer for pre-conception genetic counseling and testing

Answer: A. Administer topical and systemic corticosteroids during future pregnancies

Explanation:

Figure 1 illustrates superficial skin erosions with central granulation tissue at the nape of the infant's neck and buttocks. The differential diagnosis of skin blisters and erosions in a neonate is vast and includes infectious, immune-mediated, and genetic etiologies. Given the family history of similar lesions, a skin biopsy

notable for IgG antibody presence on immunofluorescence testing, and anticipated spontaneous resolution with minimal intervention, these lesions are most consistent with neonatal pemphigus vulgaris (PV).

Neonatal PV is a rare transient blistering skin condition that occurs when a fetus is exposed to maternal IgG autoantibodies from a pregnant woman with PV. PV is an autoimmune bullous disorder characterized by the loss of cell adhesion in the intraepithelial layer due to IgG autoantibodies against desmoglein-1 (Dsg1) and/or desmoglein-3 (Dsg3), which are glycoproteins integral in maintaining tissue integrity.[2] When maternal autoantibodies against Dsg1 and Dsg3 are present during pregnancy, they can passively cross the placenta and bind to the fetal epidermis, resulting in bullae, blisters, and skin erosions at birth. Diagnosis of neonatal PV requires a high clinical suspicion and can be confirmed on skin biopsy utilizing hematoxylin and eosin stains, as well as direct or indirect immunofluorescence to identify autoantibodies.[3] The degree of severity of the neonatal presentation and outcome are independent of the maternal disease burden.[3–6] Unlike other etiologies of blistering, most neonatal PV resolves within 3–4 weeks with supportive care focused on wound healing and infection prevention.[6] Typically, neonatal therapy does not require systemic immunosuppressive agents.[6] Although neonatal PV has an overall favorable prognosis, fetal outcomes in a pregnancy complicated with PV can include spontaneous abortion, stillbirth, preterm birth, and low birth weight.[7] Therefore, antenatal surveillance, discontinuation of teratogenic PV medications (eg, methotrexate, cyclophosphamide), and initiation of non-teratogenic PV treatment (topical and systemic corticosteroids, intravenous immunoglobulin, or plasmapheresis) are highly recommended **(Option A)** (Figure 2).[7]

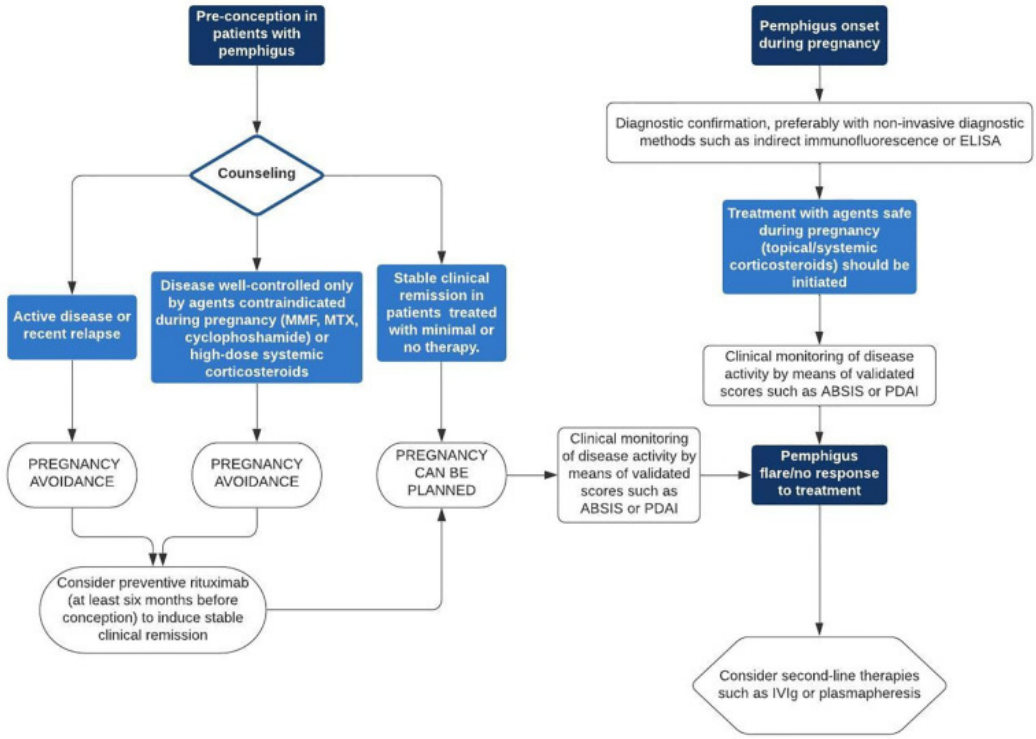

Figure 2. Pre-conception and intrapartum management and treatment strategies in women with PV. ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; ELISA, enzyme-linked immunosorbent assay; IVIg, intravenous immunoglobulin therapy; MMF, mycophenolate mofetil; MTX, methotrexate; PDAI, Pemphigus Disease Area Index. Permission granted for image reproduction from: Genovese G, Derlino F, Berti E, Marzano AV. Treatment of autoimmune bullous diseases during pregnancy and lactation: a review focusing on pemphigus and pemphigoid gestationis. *Front Pharmacol*. 2020;11:583354.[7]

Like immune-mediated disorders, infectious etiologies such as herpesvirus (HSV), S*taphylococcus aureus* (*S. aureus*), and congenital syphilis can also present with various degrees of neonatal blistering and skin erosion, although this infant's rash is not typical for these infections (Table).[8] In addition, dermatology notes a favorable prognosis with spontaneous resolution of this infant's lesions, which is not consistent with HSV, *S. aureus*, or syphilis, as these infections require curative antiviral or antibiotic therapy. Additionally, positive immunofluorescence testing for IgG antibodies makes an underlying autoimmune process most likely.

Disease	General Characteristics	Morphology and Location	Confirmatory Tests	Treatment
Bullous Impetigo	First few weeks after birth Term, well-appearing infants Associated with nursery outbreaks	Isolated, fragile, nontender bullae Face, trunk, neck, axillae, groin, and extremities	Gram stain and culture of blister fluid	Topical or oral beta-lactamase-resistant antibiotic
Staphylococcal Scalded Skin Syndrome	First few weeks after birth Term, ill-appearing infants	Descending erythema; fragile, flaccid, tender bullae with progression to erosions; positive Nikolsky sign Flexural distribution on shoulders, buttocks, body folds, hands, and feet	Cultures of blood, nasopharynx, conjunctiva, umbilicus	IV beta-lactamase-resistant antibiotic Fluid and electrolyte monitoring Emollients or nonadherent dressings
Pseudomonal Skin Infection	First week after birth ±VLBW, ill-appearing infants High mortality rate	Hemorrhagic pustules or bullae ± ecthyma gangrenosum Anogenital region, axillae, face, and extremities	Gram stain of blister fluid, blood culture, skin biopsy	IV antipseudomonal penicillin and aminoglycoside
Neonatal Herpes Simplex	At birth or within first few weeks SGA, ± microcephaly, ill-appearing infants 1/3 with CNS involvement	Grouped vesicles or punched-out ulcers involving scalp, face, and buttocks in peripartum HSV Absence of skin or diffuse bullae and erosions, including palms and soles in intrauterine HSV	Tzanck preparation, immunofluorescence, PCR, viral pan-culture	IV acyclovir
Congenital and Neonatal Varicella Zoster	At birth or within first two weeks SGA, ± ill-appearing infants ± Limb, ocular, and neurologic defects	Hemorrhagic vesiculobullae with neonatal VZV Widespread erosions and scarring with congenital VZV Any body site ± dermatomal distribution	Tzanck preparation, serology, PCR, immunofluorescence, viral culture	Supportive ± varicella zoster immune globulin and IV acyclovir
Congenital and Neonatal Candidiasis	First week after birth ± VLBW, ± ill-appearing infants	Vesiculobullae or diffuse erythematous, erosive dermatitis with scaling Intertriginous areas or widespread, including palms and soles	KOH preparation, pan-culture, antigen detection assay, ± skin biopsy	Topical (localized or diaper dermatitis) or IV antifungal agent (systemic or invasive)
Aspergillus	First week to month VLBW, ill-appearing infants High mortality rate	Grouped pustules ± necrotic eschar Any body site, particularly perineum and anogenital region	Pan-culture, antigen detection assay, skin biopsy and culture	IV antifungal agent ± surgical debridement
Congenital Syphilis	At birth or within first few months ± SGA, ± ill-appearing infants (2/3 asymptomatic) Hepatosplenomegaly	Hemorrhagic vesiculobullae Perioral, perinasal, anogenital, trunk, and extremities Also desquamation and erosions of palms and soles	Treponemal serology, dark field microscopy of blister fluid	IM or IV penicillin G

CNS=central nervous system, HSV=herpes simplex virus, IM=intramuscular, IV=intravenous, KOH=potassium hydroxide, PCR=polymerase chain reaction, SGA=small for gestational age, VLBW=very low birthweight, VSV=varicella zoster virus

Table. Summary of common infectious etiologies of neonatal blisters and erosions. Table from: Ahmad R, O'Regan G, Bruckner A. Blisters and Erosions in the Neonate. *Neoreviews.* 2011;12: e453-462.[8]

If a neonate is positive for HSV lesions, maternal antenatal surveillance for active lesions during future pregnancies and labor is critical. In the presence of active genital ulcers at the onset of labor, it is recommended to avoid vaginal delivery. In this situation, delivery via cesarean section without labor or rupture of membranes would be helpful to decrease the risk of the neonate contracting HSV and developing clinical symptoms (**Option B**).[9]

Toxins released by *S. aureus* can cause bullous impetigo, and in more severe cases, staphylococcal scalded skin syndrome (SSSS). One prospective study noted an increased neonatal *S. aureus* carriage risk to those born vaginally to pregnant women with culture-proven vaginal *S. aureus*.[10] However, there is no evidence that *S. aureus* nasal swab screening or decolonization of a mother is an effective intervention in preventing skin lesions from forming in future children **(Option C)**.

Syphilis must be evaluated in all pregnant women, especially in women who have previously given birth to a child with congenital syphilis. Obtaining a rapid plasma reagin (RPR) test during future pregnancies will detect if a woman is reinfected and aid in the prevention of vertical transmission to her fetus **(Option D)**.

Inherited skin conditions like epidermolysis bullosa, bullous congenital ichthyosiform erythroderma, and incontinentia pigmenti must be considered in any neonate with bullous and ulcerative lesions. In these conditions, the type of blister formation, extent of disease, and prognosis can vary, depending on the mutation or defect. Thus, genetic counseling and testing for these aforementioned inherited skin conditions will provide guidance in the care of the neonate affected and assist in determining the risk of recurrence in future offspring **(Option E)**. Generally, even mild presentations of inherited skin disorders do not resolve completely (in contrast to the dermatologist's prognosis), and individuals may have cutaneous and/or multisystemic effects into adulthood. As PV is an immunologic disorder, rather than an inherited skin disorder, genetic counseling and testing are not routinely recommended.

Did you know?

- Neonatal PV typically presents with a diffuse distribution of lesions affecting both skin and mucosa, which contrasts with adult PV where lesions tend to localize to the mucosa. This difference in presentation is a direct result of the variation in expression of Dsg3 in neonates (diffuse distribution throughout the entire epidermis) and adults (localized expression in the deep layers of the epidermis).[11]
- If there is a strong suspicion for neonatal PV based on maternal history, testing the neonate's serum for Dsg1 and Dsg3 antibodies via enzyme-linked immunosorbent assay may help establish a diagnosis when the option to perform a skin biopsy is limited or unavailable.[5, 6]

A neonate is noted to have multiple skin erosions and red-brown papules in the diaper region. What key feature on skin biopsy aids in the diagnosis of this skin finding? Once a diagnosis is made, what further systemic evaluation must be performed?

To learn more about this and other etiologies of blisters and skin erosions, read the following article:

- Ahmad R, O'Regan G, Bruckner A. Blisters and erosions in the neonate. *Neoreviews*. 2011;12(8):e453–462.

NeoQuest November Authors

Neena Jube-Desai, MD, MBA, FAAP, University of Maryland

Elizabeth V. Schulz, MD, FAAP, Uniformed Services University

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