# Vesiculobullous and Pustular Diseases in Newborns

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This article exhibits the most common presentations of vesiculobullous diseases in newborns and reviews the clinical characteristics unique to each diagnosis. Furthermore, a schematic for the workup of neonatal vesicular disorders is presented to empower dermatology residents to execute accurate diagnoses and maximize patient care.

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Vesiculobullous eruptions in neonates can readily generate anxiety from parents/guardians and pediatricians over both infectious and noninfectious causes. The role of the dermatology resident is critical to help diminish fear over common vesicular presentations or to escalate care in rarer situations if a more obscure or ominous diagnosis is clouding the patient's clinical presentation and well-being. This article summarizes both common and uncommon vesiculobullous neonatal diseases to augment precise and efficient diagnoses in this vulnerable patient population.

## Steps for Evaluating a Vesiculopustular Eruption

Receiving a consultation for a newborn with widespread vesicles can be a daunting scenario for a dermatology resident. Fear of missing an ominous diagnosis or aggressively treating a newborn for an erroneous infection when the diagnosis is actually a benign presentation can lead to an anxiety-provoking situation. Additionally, performing a procedure on a newborn can cause personal uneasiness. Dr. Lawrence A. Schachner, an eminent pediatric dermatologist at the University of Miami Miller School of Medicine (Miami, Florida), recently lectured on 5 key steps (Table 1) for the evaluation of a vesiculobullous eruption in the newborn to maximize the accuracy of diagnosis and patient care.[1]

First, draw out the fluid from the vesicle to send for bacterial and viral culture as well as Gram stain. Second, snip the roof of the vesicle to perform potassium hydroxide examination for yeast or fungi and frozen pathology when indicated. Third, use the base of the vesicle to obtain cells for a Tzanck smear to identify the predominant cell infiltrate, such as multinucleated giant cells in herpes simplex virus or eosinophils in erythema toxicum neonatorum (ETN). Fourth, a mineral oil preparation can be performed on several lesions, especially if a burrow is observed, to rule out bullous scabies in the appropriate clinical presentation. Lastly, a perilesional or lesional punch biopsy can be performed if the above steps have not yet clinched the

**TABLE 1. Five Steps for the Evaluation of a Vesiculobullous Eruption in the Newborn[1]**

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|---|
| Step 1: Draw out fluid for bacterial cultures and sensitivity, Gram stain, and viral culture |
| Step 2: Snip the roof of the vesicle for potassium hydroxide examination and frozen pathology |
| Step 3: Scrape the base of the vesicle for Tzanck smear and identification of predominant cell type |
| Step 4: Scrape the lesion for a scabies preparation |
| Step 5: Biopsy the lesion |

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diagnosis.[2] By utilizing these steps, the resident efficiently utilizes 1 lesion to narrow down a formidable differential list of bullous disorders in the newborn.

## Specific Diagnoses

A number of common diagnoses can present during the newborn period and can usually be readily diagnosed by clinical manifestations alone; a summary of these eruptions is provided in Table 2. Erythema toxicum neonatorum is the most common pustular eruption in neonates and presents in up to 50% of full-term infants at days 1 to 2 of life. Inflammatory pustules surrounded by characteristic blotchy erythema are displayed on the face, trunk, arms, and legs, usually sparing the palms and soles.[3] Erythema toxicum neonatorum typically is a clinical diagnosis; however, it can be confirmed by demonstrating the predominance of eosinophils on Tzanck smear.

Transient neonatal pustular melanosis (TNPM) also presents in full-term infants; usually favors darkly pigmented neonates; and exhibits either pustules with a collarette of scale that lack surrounding erythema or with residual brown macules on the face, genitals, and acral surfaces. Postinflammatory pigmentary alteration on lesion clearance is another clue to diagnosis. Similarly, it is a clinical diagnosis but can be confirmed with a Tzanck smear demonstrating neutrophils as the major cell infiltrate.

**TABLE 2. Summary of Vesiculobullous Eruptions in the Newborn**

| Diagnosis | Etiology | Onset | Clinical Features | Workup |
|---|---|---|---|---|
| ETN | Unknown | 24–48 h after birth | Full-term infants; inflammatory pustules with blotchy erythema | Tzanck smear: eosinophils |
| TNPM | Unknown | At birth | Darkly pigmented, full-term infants; pustules with collarette of scale | Tzanck smear: neutrophils |
| Miliaria | Obstructed eccrine sweat ducts | Days to weeks of life | Tiny superficial crystalline vesicles | Clinical diagnosis |
| Neonatal cephalic pustulosis (neonatal acne) | Possible reaction to *Malassezia* | Weeks of life | Pustules on cheeks, forehead, and scalp | Clinical diagnosis |
| Neonatal candidiasis | Infection with *Candida albicans* | Days to weeks of life | Oral thrush; diaper dermatitis | KOH: yeast and pseudohyphae |
| Congenital candidiasis | Infection with *C albicans* | At birth | Diffuse erythroderma | KOH: yeast and pseudohyphae |
| Infantile acropustulosis | Unknown | Months of life | Recurring crops of pustules on hands and feet | Rule out scabies with mineral oil preparation |
| DIRA | Autoinflammatory syndrome | Days to weeks of life | Pustules with erythema, lytic bone lesions, ↑ESR, ↑CRP, FTT | Genetic studies; response to anakinra |
| Eosinophilic pustular folliculitis | Unknown | Days to weeks of life | Follicular pustules on the face and scalp | Tzanck smear: eosinophils; H&E: eosinophilic follicular infiltrate |
| Incontinentia pigmenti | *NEMO* genetic defect | At birth | 4 stages: vesicular, verrucous, hyperpigmented, and hypopigmented lesions | Clinical and genetic studies |
| Behçet disease | Transfer of maternal antibodies | At birth | Ulcerations in the mouth and genital area | Maternal history |

Abbreviations: ETN, erythema toxicum neonatorum; TNPM, transient neonatal pustular melanosis; KOH, potassium hydroxide; DIRA, deficiency of IL-1ra; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FTT, failure to thrive; H&E, hematoxylin and eosin; *NEMO*, nuclear factor κβ essential modulator.



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In a prospective 1-year multicenter study performed by Reginatto et al,[4] 2831 neonates born in southern Brazil underwent a skin examination by a dermatologist within 72 hours of birth to characterize the prevalence and demographics of ETN and TNPM. They found a 21.3% (602 cases) prevalence of ETN compared to a 3.4% (97 cases) prevalence of TNPM, but they noted that most patients were white, and thus the diagnosis of TNPM likely is less prevalent in this group, as it favors darkly pigmented individuals. Additional predisposing factors associated with ETN were male gender, an Apgar score of 8 to 10 at 1 minute, non–neonatal intensive care unit (NICU) patients, and lack of gestational risk factors. The TNPM population was much smaller, though the authors were able to conclude that the disease also was correlated with healthy, non-NICU patients. The authors hypothesized that there may be a role of immune system maturity in the pathogenesis of ETN and thus dermatology residents should be aware of the setting of their consultation.[4] A NICU consultation for ETN should raise suspicion, as ETN and TNPM favor healthy infants who likely are not residing in the NICU; we are reminded of the target populations for these disease processes.

Additional common causes of vesicular eruptions in neonates can likewise be diagnosed chiefly with clinical inspection. Miliaria presents with tiny superficial crystalline vesicles on the neck and back of newborns due to elevated temperature and resultant obstruction of the eccrine sweat ducts. Reassurance can be provided, as spontaneous resolution occurs with cooling and limitation of occlusive clothing and swaddling.[2]

Infants at a few weeks of life may present with a noncomedonal pustular eruption on the cheeks, forehead, and scalp commonly known as neonatal acne or neonatal cephalic pustulosis. The driving factor is thought to be an abnormal response to *Malassezia* and can be treated with ketoconazole cream or expectant management.[2]

Cutaneous candidiasis is the most common infectious cause of vesicles in the neonate and can present in 2 fashions. Neonatal candidiasis is common, presenting a week after birth and manifesting as oral thrush and red plaques with satellite pustules in the diaper area. Congenital candidiasis is due to infection in utero, presents prior to 1 week of life, exhibits diffuse erythroderma, and requires timely parenteral antifungals.[5] Newborns and preterm infants are at higher risk for systemic disease, while full-term infants may experience a mild course of skin-limited lesions.

It is imperative to rule out other infectious etiologies in ill-appearing neonates with vesicles such as herpes simplex virus, bacterial infections, syphilis, and vertically transmitted TORCH (toxoplasmosis, other infections rubella, cytomegalovirus infection, and herpes simplex) diagnoses.[6] Herpes simplex virus classically presents with grouped vesicles on an erythematous base; however, such characteristic lesions may be subtle in the newborn. The site of skin involvement usually is the area that first comes into contact with maternal lesions, such as the face for a newborn delivered in a cephalic presentation.[2] It is critical to be cognizant of this diagnosis, as a delay in antiviral therapy can result in neurologic consequences due to disseminated disease. The other TORCH diagnoses may present with blueberry muffin lesions, which are blue to violaceous papules on the trunk, arms, and legs due to extramedullary hematopoiesis. Each disease process may lead to its own characteristic sequelae and should be further investigated based on the maternal history.

If the clinical picture of vesiculobullous disease in the newborn is not as clear, less common causes must be considered. Infantile acropustulosis presents with recurring crops of pustules on the hands and feet at several months of age. The most common differential diagnosis is scabies; therefore, a mineral oil preparation should be performed to rule out this common mimicker. Potent topical corticosteroids are first-line therapy, and episodes generally resolve with time.

Another mimicker of pustules in neonates includes deficiency of IL-1ra, a rare entity described in 2009.[7] Deficiency of IL-1ra is an autoinflammatory syndrome of skin and bone due to unopposed action of IL-1 with life-threatening inflammation; infants present with pustules, lytic bone lesions, elevated erythrocyte sedimentation rate and C-reactive protein, and failure to thrive.[8] The characteristic mutation was discovered when the infants dramatically responded to therapy with anakinra, an IL-1ra.

Eosinophilic pustular folliculitis is an additional pustular dermatosis that manifests with lesions predominately in the head and neck area, and unlike the adult population, it usually is self-resolving and not associated with other comorbidities in newborns.[2]

Incontinentia pigmenti is an X-linked dominant syndrome due to a genetic mutation in *NEMO*, nuclear factor κβ essential modulator, which protects against apoptosis.[3] Incontinentia pigmenti presents in newborn girls shortly after birth with vesicles in a blaschkoid distribution before evolving through 4 unique stages of vesicular lesions, verrucous lesions, hyperpigmentation, and ultimately resolves with residual hypopigmentation in the affected area.

Lastly, neonatal Behçet disease can present with vesicles in the mouth and genital region due to transfer of maternal antibodies. It is self-limiting in nature and would be readily diagnosed with a known maternal history, though judicious screening for infections may be needed in specific settings.[2]

## Conclusion

In summary, a vast array of benign and worrisome dermatoses present in the neonatal period. A thorough history and physical examination, including the temporality of the lesions, the health status of the newborn, and the maternal history, can help delineate the diagnosis. The 5-step method presented can further elucidate the underlying mechanism and reduce an overwhelming differential



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diagnosis list by reviewing each finding yielded from each step. Dermatology residents should feel comfortable addressing this unique patient population to ameliorate unclear cutaneous diagnoses for pediatricians.

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