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## Neonatal Erythroderma: Diagnostic and Therapeutic Challenges

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### Abstract

Erythroderma a life-threatening entity during the first one month, and many a time, a manifestation of genodermatosis, immune deficiency, psoriasis, metabolic diseases, and infections. Atopic dermatitis presenting as erythroderma is usually observed later, after this one-month period, and hence not a common differential for neonatal exfoliative dermatitis. Although a rare entity, there is a paucity of studies on this and in contrast to adults, some may manifest as cardinal signs of primary disease conditions.

**Keywords:** Neonatal, erythroderma, omenn syndrome, biotin metabolism

### Introduction

Erythroderma in the neonatal period is an important entity which needs to be properly recognized by dermatologists and pediatricians alike. It refers to inflammation of the skin producing a fair amount of erythema and scaling involving more than 90% of the surface area of the skin.[1] This condition in the neonate warrants careful diagnostic workup, and very often, urgent medical attention to avoid fatalities in some. The primary workup and differential diagnosis helps to differentiate from eczemas and forms the cornerstone of pinpointing the proper diagnosis of these 'red babies'. [2]

This is definitely a life-threatening entity during the first one month, and many a time, a manifestation of genodermatosis, immune deficiency, psoriasis, metabolic diseases, and infections. Atopic dermatitis presenting as erythroderma is usually observed later, after this one-month period, and hence not a common differential for neonatal exfoliative dermatitis.[3] Although a rare entity, there is a paucity of studies on this and in contrast to adults, some may manifest as cardinal signs of primary disease conditions.[3,4]

The causes of neonatal erythroderma can be broadly segregated pathogenetically for evaluation into different categories as stated subsequently.[5]

### Causes of Neonatal Erythroderma

#### Cutaneous disorders

- Infantile seborrheic dermatitis
- Atopic dermatitis
- Psoriasis
- Pityriasis rubra pilaris
- Generalized mastocytosis
- Ichthyosis: nonbullous ichthyosiform erythroderma, Conradi-Hünemann syndrome, bullous

ichthyosiform erythroderma

- Netherton syndrome
- Toxic epidermal necrolysis, ectodermal dysplasia

### Infections

- Staphylococcal scalded skin syndrome (SSSS)
- Toxic shock syndrome
- Candidiasis

### Immunodeficiency

- Omenn syndrome
- Graft-versus-host reaction

### Metabolic disorders

- Disorders of biotin metabolism
- Essential fatty acid deficiency
- Acrodermatitis enteropathica
- Liener's disease

### Drugs

- Ceftriaxone
- Vancomycin

In a retrospective study, Pruszkowski *et al.*[6] could establish the etiological diagnosis only almost after 11 months of onset. This study observed that the cause of erythroderma in the neonate included immunodeficiency (30%), simple or complex ichthyosis (24%), Netherton syndrome (18%), and eczematous or papulosquamous dermatitis (20%), and five patients (10%) had erythroderma of unknown origin. Sarkar *et al.*[2] observed that the causes were infections (40%), ichthyosiform erythrodermas (25%), atopic dermatitis (15%), infantile seborrheic dermatitis (10%), and unidentified (10%).

Infantile seborrheic dermatitis which manifests in the neonatal period usually presents with greasy scales on the scalp (cradle cap), skin folds like the axilla, neck, retroauricular, and diaper areas. Other forms of presentation are a psoriasiform appearance or rarely erythroderma.[7] Atopic dermatitis may have its onset in the first month; however, it is rarely erythrodermic in neonates. The lesions usually are vesicular and exudative in nature. Sometimes there is a significant overlapping between infantile seborrheic dermatitis and atopic dermatitis. The lesions of atopic dermatitis are more obvious on the face and flexures. Significant itch sensation is not appreciated till the child grows out of the neonatal period.[7,8]

Neonatal psoriatic erythroderma is a rare entity and it commonly presents as recalcitrant diaper dermatitis which may become generalized with a widespread pustular form of the disease. This is accompanied by periodic high fever, and the child becomes very toxic with recurrent crops of superficial pustules appearing on erythematous plaques.[9]

Psoriasis and pityriasis rubra pilaris may look similar with erythematous scaly plaques which may enlarge and become generalized to produce erythroderma. Heavy infiltration of the entire skin with mast cells results in diffuse cutaneous mastocytosis. The skin undergoes lichenification and is erythematous, producing urtication and bulla formation on mild trauma.[9,10] Diarrhea, flushing, and respiratory symptoms are the common accompaniments. Darier's sign, a wheal which flares on stroking the skin, is often positive. Although a life-threatening condition, it improves with age.

Several varieties of ichthyoses can manifest as erythroderma. Patients of nonbullous congenital ichthyosiform erythroderma have finer scales and are more inclined to develop erythroderma. The newborns have a collodion membrane which desquamates, revealing the erythroderma. It fades in mild disease but in the severe classic form, large platelike scales with erythema persist. Harlequin ichthyosis

infants with hyperkeratotic fissured plates often die due to respiratory problems; if they survive with treatment, they manifest generalized erythroderma. Epidermolytic hyperkeratosis or bullous ichthyosis have widespread denuded areas which resolve slowly, manifesting underlying erythroderma. In the rare syndrome of keratitis-ichthyosis-deafness (KID) erythema, atypical ichthyosis, follicular keratosis, and palmoplantar keratoderma are common.[11,12] Associated congenital sensorineural deafness and keratoconjunctivitis during infancy justifies the nomenclature of KID syndrome.[13] Collodion membrane is absent in the Sjogren-Larsson syndrome but manifests in infancy with fine or platelike scaly erythroderma. Spasticity, mental retardation, and macular retinal lesions are often noted. Enzyme assay can clinch the diagnosis, revealing deficiency of enzyme fatty alcohol oxidoreductase. Chanarin-Dorfman syndrome encompasses ichthyosis with neutral lipid storage disease and systemic manifestations like myopathy, cataracts, deafness, and growth retardation. Lipid vacuoles can be seen on skin biopsy and peripheral blood smear. Tay syndrome can present with collodion membrane leading to erythroderma. This condition of trichothiodystrophy has ataxia and brittle hairs along with ichthyosis. Conradi-Hünerman syndrome has skeletal abnormalities (chondrodysplasia punctata with epiphyseal stippling), cataracts, bandlike erythroderma along Blaschko's lines, or diffuse involvement which may resolve later followed by follicular atrophoderma. Erythrokeratodermas have more of localized involvement as in CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) and Gottron's syndrome. However in peeling skin syndrome of inflammatory variety, widespread scaling and erythematous plaques are often observed.[12,14] Netherton syndrome presents with features of generalized erythroderma, fragile hair with trichorrhexis invaginata ('bamboo hair'), and severe rhinorrhea, asthma, anaphylaxis due to food, and so on. Erythroderma at birth is often the onset and it is a diagnostic dilemma where sparse hair with shaft defects may take several microscopic examinations, especially of eyebrows and lashes, before clinching the diagnosis. These patients are atopic and often have intercurrent infective episodes with high rates of mortality. The serum IgE levels are markedly raised and are even more than seen normally in atopic subjects.[15]

Toxic epidermal necrolysis, usually a disease of adults, may present in infancy as reported in a two-month premature who developed erythroderma with bullae associated with *Staphylococcus aureus* sepsis. A positive Nikolsky's sign is diagnostic. Polysorbate toxicity in premature infants producing toxic epidermal necrolysis (TEN) has also been recorded. Scaling and erythema in a family with ectrodactyly, ectodermal dysplasia, and cleft lip have also been reported.[16]

Some neonatal skin infections may proceed to exfoliative dermatitis. Staphylococcal scalded skin syndrome (SSSS, Ritter's disease), in infancy, manifests as an acute-onset generalized erythema with skin tenderness and sloughing in a toxic and febrile patient. Exfoliative toxins (ETA, ETB) act as 'super antigens' to release lymphokines from T cells. Though common in childhood, congenital and neonatal cases have been reported.[17] Boric acid poisoning from powders and lotions can cause erythema and desquamation with vomiting, diarrhea, and shock, and can be a close differential diagnosis for SSSS. Widespread staphylococcal pustulosis can result in rapid erythematous desquamation.[16]

Congenital cutaneous candidiasis results as a sequela to infection from the amnion, manifesting as a maculopapular eruption which progresses to pustulation and confluence of the lesions result in exfoliative erythroderma. The lesions begin on the trunk and progress acrally. The condition resolves spontaneously but systemic or pulmonary candidiasis may carry a greater risk of systemic candidiasis. The neonatal form of generalized cutaneous candidiasis is acquired at the time of delivery.[16,18]

Because of the protective effect of maternal immunity, congenital immunodeficiency syndromes are rarely symptomatic at birth. Graft-versus-host reaction from maternal engraftment can, however, occur even during intrauterine development. Omenn syndrome is a familial reticuloendotheliosis with eosinophilia having erythroderma, failure to thrive, lymphadenopathy, and recurrent infections. Marked leukocytosis, eosinophilia, anemia, and hypogammaglobulinemia are some of the findings in this histiocytic disorder. Hypogammaglobulinemia can start with diarrhea and periodic fever together with erythroderma. Dermatitis begins by four weeks of age and rapidly generalizes. DiGeorge syndrome and severe combined immunodeficiency may also present with eczematous dermatitis leading to erythroderma.[16,19]

Graft-versus-host reaction may occur in T cell immunodeficiency or as a result of transplacental transfer of maternal lymphocytes as a sequela of exchange transfusion. An erythematous nonspecific morbilliform rash may lead to erythroderma and epidermal sloughing. Neonatal cutaneous T cell lymphoma can present with congenital ichthyosis with atypical Sezary-like lymphoid cells in skin and lymph nodes and other immunological abnormalities.[5,20]

Metabolic and nutritional disorders are suspected when the infant has failure to thrive and the dermatitis manifests periorificially at the onset before it generalizes. Severe protein malnutrition during infancy can present with widespread erythema, edema, erosion, and desquamation of the skin. Deficiency of zinc due to malabsorption as in acrodermatitis enteropathica or low concentration of zinc in breast milk can begin with psoriasiform dermatitis in circumoral or periorificial areas which may crust and spread to involve other areas; this has also been reported in children with acquired immunodeficiency syndrome.[21] Diarrhea, failure to thrive, irritability, and photophobia can accompany such dermatitis. Essential fatty acids, mostly found in dairy products and vegetable oils, are supplemented in the diet. Diffuse desquamation, lichenification, and intertriginous dermatitis can develop in such situations. Cystic fibrosis dermatitis presents with psoriasiform diaper rash not responsive to topical steroids or antifungals. This dermatitis may spread and is associated with growth failure and irritability. Deficiency of holocarboxylase synthetase manifests with neonatal erythroderma. The children have alopecia, secondary cutaneous candidiasis, dehydration, and ketoacidosis which can lead to a fatal outcome. Deficiency of holocarboxylase synthetase in skin fibroblasts clinches the diagnosis. Deficiency of biotinidase presents with patchy alopecia and acrodermatitis enteropathica-like skin lesions. These conditions encompass the group of 'multiple carboxylase deficiency' disorders. Human milk has low biotin and so breast-fed infants with deficiency have earlier clinical manifestations than formula-fed babies. Acrodermatitis enteropathica-like exfoliative erythema develops in infants with maple syrup urine disease who are on a diet low in branched-chain amino acid isoleucine. Secondary candidial infection is not unusual in such cases. Similar dermatitis was reported with deficiency of arginine, neonatal citrullinemia, and deficiency of carbamoyl phosphate synthetase.[5,16,22]

Penicillins, aminoglycosides, and cephalosporins often produce erythematous maculopapular skin lesions, but rarely erythroderma. Ceftriaxone and vancomycin in neonates may produce erythroderma, and vancomycin may also induce hypotension on account of histamine release.[23]

Leiner's disease is literally a clinical phenotype of acquired erythroderma, diarrhea, and failure to thrive. Desquamative generalized erythema and dermatitis with weight loss was thought to be common in breast-fed infants due to the deficiency of biotin. Cases of generalized dermatitis in seborrheic pattern due to immunodeficiencies were also included in this category. Later, they were found to be more susceptible to infections as a result of a possible yeast opsonization defect resulting from dysfunction of the fifth component of the complement. Hence the etiology was stamped as multifactorial. The dermatitis develops in the first few weeks together with chronic diarrhea.[16,24]

## The Diagnostic Workup

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Neonatal erythroderma is definitely a diagnostic challenge for pediatric dermatologists. A thorough history, clinical evaluation, and investigative battery form the cornerstone of proper therapeutic intervention.

### Clinical evaluation

Clinical features are often inconclusive but do help to pinpoint a diagnosis/shortlist the possibilities in some cases. The onset with collodion baby often heralds the group of hereditary ichthyoses. Skeletal, neurological, and ophthalmological problems are sometimes present, and where diagnosis is doubtful, skin histology may help. Fever, blisters, and tenderness of skin point toward infective etiology. SSSS demonstrates a positive Nikolsky's sign, whereas mastocytosis may present with blisters, but a positive Darier's sign distinguishes it from similar conditions. Lymphadenopathy and partial alopecia can distinguish Omenn syndrome from others like Netherton syndrome and graft-versus-host disease. The 'red baby' neonatal erythroderma, resulting from vancomycin or ceftriaxone is diagnosed only after a careful history taking.[4,16]

## Investigations

Laboratory tests that maybe useful in the evaluation include taking swabs for bacterial culture, Gram stain or potassium hydroxide skin/hair mounts, complete blood counts, serum immunoglobulins like IgE, and skin biopsy. Assays for zinc, alkaline phosphatase, essential fatty acids, amino acids, and biotinidase are often corroborative in the diagnosis of neonatal erythroderma.

## Skin histopathology

Biopsy of the skin forms the cornerstone of correct diagnostic approach in most cases. Routine histochemistry and immunohistochemical studies are undertaken with the biopsy specimen.

Netherton syndrome and bullous and nonbullous ichthyosiform erythroderma can often be pinpointed by the aid of histopathological examination. Erythrodermas are distinguishable on histology.[\[4,5\]](#)

## Treatment Options

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Managing neonatal erythroderma is a therapeutic challenge as it is very difficult to treat this potentially life-threatening situation. Careful monitoring of the vital signs, maintenance of fluid and electrolyte balance, and prevention of hyperpyrexia are mandatory in the management protocol.

Irrespective of its cause, neonatal erythroderma is a potentially life-threatening condition.

Erythrodermic neonates and infants are at a risk for hypernatremic dehydration and hyperpyrexia.

Maintaining adequate intake of oral or parenteral fluids and monitoring serum electrolytes is therefore mandatory. Application of emollients, wet dressings, topical steroids, and systemic antibiotics are the other modalities. Maintaining the skin barrier and proper hydration is the key to managing most of the conditions. However, reassurance of parents and counseling form the cornerstone of management.

## Footnotes

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