

# Proposal of Slovenian guidelines for the diagnosis of neonatal erythroderma with a case report of Omenn syndrome

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## Abstract

Diagnosing and treating neonatal and infantile erythroderma can be challenging due to the wide variety of potential causes. Neonatal erythroderma is rare and is associated with a high mortality rate due to complications of erythroderma itself and potential life-threatening underlying diseases. Prolonged erythroderma should always be a warning sign and an indication for referral to a hospital where a multidisciplinary team approach is possible. The role of a pediatric dermatologist is to keep in mind the wide spectrum of differential diagnoses that could be causing the condition and the determination of the final diagnosis. To avert a delay in establishing the correct diagnosis, we suggest adhering to specific guidelines. We reviewed available guidelines and adapted a step-by-step approach for use in Slovenia. We also discuss a case of a neonate with erythroderma to illustrate the applicability of the proposed guidelines. Our patient presented with persistent erythroderma, pustules on the trunk and limbs, and intertriginous dermatitis. Despite local corticosteroid treatment, the skin redness persisted. After the exclusion of a systemic infection and additional tests, Omenn syndrome was diagnosed as the underlying cause.

**Keywords:** neonatal erythroderma, immunodeficiency, Omenn syndrome

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## Introduction

Erythroderma is a generalized and persistent erythema of the skin that involves at least 90% of the body surface. It is defined as an inflammatory skin disorder in which there is involvement of total, or near-total, body surface area with erythema and scaling (1, 2). It is a non-specific disease pattern induced by various etiologies (2). Erythroderma, especially in the neonatal and infantile period, can be a potentially life-threatening condition due to complications of the condition itself or due to the underlying disease (2).

Neonatal and infantile erythroderma (NIE) is a clinical phenotype. The causes for it range from benign or transient skin conditions to potentially fatal multiorgan disorders (3). Neonatal erythroderma (NE) presents in the first 28 days after birth and is a pediatric dermatological emergency that requires swift diagnosis and effective, multidisciplinary management (4). It is a diagnostic and therapeutic challenge. The differential diagnostic possibilities of NE are summarized in Figure 1. In the past, erythrodermic neonates and infants were frequently misdiagnosed with eczema. Inappropriate topical steroid treatment can lead to the development of Cushing's syndrome. Delay in establishing the correct diagnosis can be fatal (5). NE is a potentially life-threatening condition that can lead to hypernatremic dehydration, electrolyte imbalance, hyperpyrexia, hypoalbuminemia, and sepsis (6).

According to Cuperus et al. (7), causes of NE can be divided into six main categories (Fig. 1): congenital ichthyoses (including Netherton syndrome), primary immunodeficiencies, metabolic disorders, drug use, cutaneous infections, ectodermal dysplasias and other miscellaneous causes, where many otherwise common skin conditions can be found (7–10). In comparison, Ott and Grothaus describe erythroderma as ichthyosiformic in general and then divide it into three main categories: primary skin diseases, infections, and primary immunodeficiencies (4).

In a recent review article on neonatal erythroderma, a six-step flowchart for the diagnostic approach to neonatal erythroderma during the 1st month of life was proposed. According to that research, all cases of neonatal erythroderma should be referred to teaching hospitals for a multidisciplinary approach and treatment (7).

## Proposed Slovenian guidelines for the diagnostic approach to neonatal erythroderma

Clinical guidelines for NE have not yet been proposed for Slovenia. We reviewed available guidelines and adapted a step-by-step approach proposed by Cuperus et al. (7) for use in Slovenia. The adapted approach is presented in Figure 2.

All cases of persistent neonatal erythroderma should raise a high level of suspicion in the attending physician. Because of the wide variety of underlying etiologies and the fields of medicine they encompass, all cases of neonatal erythroderma involve consultation with a pediatric dermatologist and neonatologist (4). In Slovenia, this means all neonates presenting with NE should be referred to teaching hospitals (the medical centers in Ljubljana or Maribor), where a multidisciplinary approach is possible.

Every patient presenting with NE should undergo a full physical examination with a thorough medical history taken, and baseline blood tests should be performed (3, 7).

In a recent study, Ott (3) proposed a flow chart that could lead to a working diagnosis, asking the following five questions: 1) Has widespread erythema with dry skin been present from birth? 2) Has the affected neonate or infant developed failure to thrive? 3) Does the child reveal extracutaneous complications; for example, neuropathy, enteropathy, or hepatopathy? 4) Have severe and/or atypical infections of the skin or other organs been observed? 5) Have bullous skin changes or pathologies of the skin appendages

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occured?

If no diagnosis is acquired, extended blood tests should be performed, skin biopsy taken, and hair sent for trichoscopy (7). A recent prospective study found that in 70% of NE cases a mutation could be discovered by next-generation sequencing (NGS), with a selected panel of 60 genes (12). The financial aspects and familial consent should always be taken into account when considering genetic analysis.

Skin biopsy is helpful for etiologic diagnosis of early erythroderma of infancy, particularly in immunodeficiencies and Netherton syndrome (NS), the most common causative diseases (4). Consequently, these results justify an early skin biopsy for better and earlier management. In primary immunodeficiencies (PIDs), the sensitivity and specificity of these investigations were 58.5 and 98.5%, respectively (13).

Trichoscopy, for example, can be prognostic in NS, where trichorrhexis invaginata (“bamboo hair”) is specifically observed (3, 4, 14, 15). In the case of trichothiodystrophies, trichoscopy shows linear fractures of the hair shaft (trichoschisis), and in Menkes disease kinky hair (pili tarti) can be seen on microscopic examination (15).

If no diagnosis is established and there are syndromic, extracutaneous, or systemic symptoms, consult appropriate specialists to exclude PIDs, metabolic disorders, or syndromic ichthyosis (7). For example, a biotinidase deficiency can present as patchy alopecia and acrodermatitis enteropathica, and it occurs earlier in breastfed babies than in formula-fed babies because human milk contains biotins. As with all metabolic disorders, it is more common that psoriasis-like scaling appears periorificially before it generalizes (7, 14, 16).

If no diagnosis can be made at this point, consider congenital non-syndromic ichthyosis or rare diagnoses in the neonatal peri-

od, such as generalized forms of atopic dermatitis, psoriasis, and seborrheic dermatitis (4, 7).

Atopic dermatitis (AD) presents within the first 6 months of life in 60% of children. (14). AD may have its onset in the 1st month; however, it is rarely erythrodermic in neonates (16).

When the diagnosis is established and appropriate treatment is started, perform regular-follow ups and re-evaluation of the patient to confirm the diagnosis (7).

## Case report

A 5-week-old infant presenting with erythroderma, pustules of the trunk and limbs, and intertriginous dermatitis was transferred to the children’s ward of the Dermatovenerology Clinic for after being hospitalized at the Clinic for Infectious Diseases, where blood cultures for exclusion of a systemic infection were taken, skin smears were performed, and parenteral treatment with intravenous flucloxacillin was started.

Ten days before admission, at 3.5 weeks of age, the child developed a red papular exanthem on his forehead (Fig. 3), which later spread across the entire face (Fig. 4) and then across the entire body. The skin intermittently improved, but later small pustules (Fig. 5) and scaling (Fig. 6) appeared. He had no signs of systemic involvement.

On admission to our ward, the skin of the entire body was dry, scaly, and erythematous (Fig. 4). The scalp was partially covered with white-yellowish scales. The skin behind the ears was macerated, eroded, and covered with whitish-yellow scales. The trunk, mostly on the back, head, and limbs, was covered with tiny pustules.

Apart from substantial white fluid that was obstructing the outer ear canal with no signs of ear infection and a distended belly,

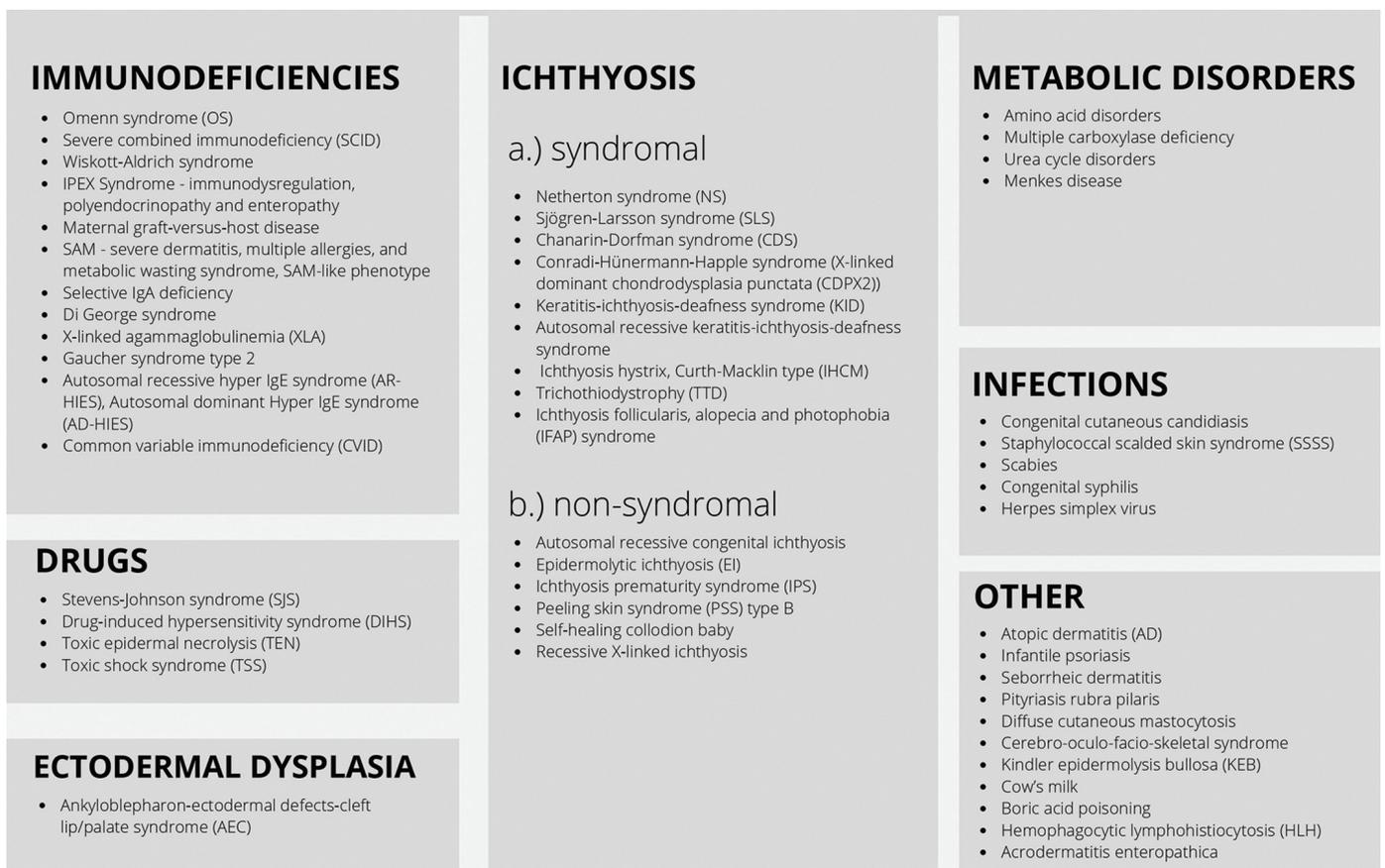


Figure 1 | Differential diagnosis of neonatal erythroderma (3, 7, 11).

which was soft, painless on palpation, and with significant flatulence, there were no signs of systemic involvement in the general examination.

Upon admission, the infant was bathed in an antiseptic bath and the skin lesions were treated locally with a combination of a corticosteroid and antibiotic ointment. As recommended by the infectious disease specialist, we switched to enteral antibiotic treatment. The next day, the pustular lesions started drying, but the erythema persisted despite local corticosteroid treatment.

Basic blood tests revealed a mildly elevated serum level of CRP (24 mg/l, reference range up to 5 mg/l), the number of lymphocytes was on the lower end of normal values ( $2.8 \times 10^9/l$ , reference range  $2.5-8.0 \times 10^9$ ), there was mild monocytosis, pronounced eo-

sinophilia (29% in the differential blood count, reference range 0-5 %), and extremely elevated levels of serum IgE (1,300 IU/ml, reference range less than 4.1 IU/ml). Specific sensitization to alimentary allergens (cow's milk, eggs, and wheat) was excluded, and liver enzyme tests and serum bilirubin levels were normal. Skin smear analysis was negative for enteroviruses and showed no eosinophilic granulocytes, but it was positive for bacterial flora (*Morganella morganii*, *Acinetobacter pittii*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Enterococcus faecalis*). A Hep-2 test was negative.

Based on all the results and the clinical picture, immunodeficiency was suspected and an additional analysis of peripheral lymphocyte populations was ordered. The test revealed a low

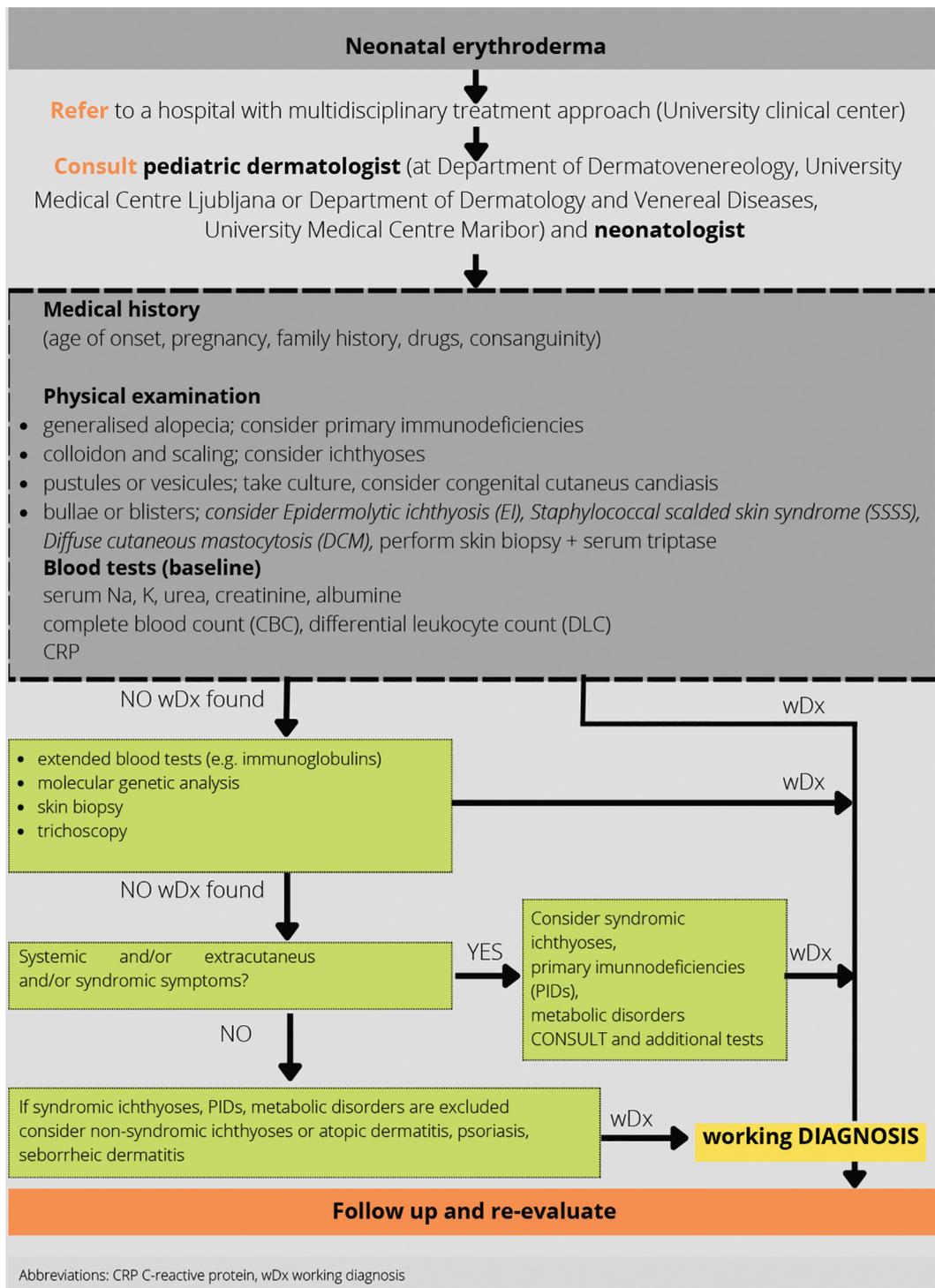


Figure 2 | Proposed Slovenian guidelines for the diagnostic approach to neonatal erythroderma. Adapted from Cuperus et al. (7).

level of CD3+ T cells, absent CD19+ B cells, a low level of CD4+ T cells among CD3+ T cells, and a normal level of CD8+ cytotoxic T cells among CD3+ T cells. The concentration of CD16+ CD56+ NK cells was elevated. These results were diagnostic for a specific type of severe combined immunodeficiency (SCID) called Omenn syndrome (OS). The infant was promptly transferred to the pediatric immunology ward for appropriate care and treatment.

OS is a rare form of SCID. Clinically it can manifest as exfoliative dermatitis, erythroderma, alopecia, lymphadenopathy, hepatosplenomegaly, intractable diarrhea, and recurrent infections. In the analysis of peripheral lymphocyte populations in OS, B cells are typically absent and oligoclonal autoreactive T cells are increased, resulting in eosinophilia and elevated IgE. Mortality is high due to opportunistic infections (17, 18). In recent decades, the survival rate has improved, especially with hematopoietic stem cell transplant therapy (17–19).



Figure 3 | Red papular exanthem on the forehead.



Figure 4 | Red papular exanthem of the baby's face.

## Discussion

Neonatal and infantile erythrodermas are associated with a wide range of cutaneous and systemic disorders, one of them being PID.

As demonstrated by our case report, a step-by-step approach proposed by Cuperus et al. (7) was adapted for use in Slovenia and is essential for achieving a timely working diagnosis.

Our patient with erythroderma, intertriginous inflammation, and pustules on the trunk was admitted to the infectious diseases clinic, where blood cultures and skin smears were taken to exclude systemic infection and antibiotic treatment was started. After transferring the infant to our ward, a detailed clinical examination was made, which excluded systemic infection. Erythroderma persisted despite local corticosteroid treatment, and the skin smears showed colonization with multiple pathogenic bacteria.



Figure 5 | Exanthem of the face with small pustules.



Figure 6 | Dry, scaly, and erythematous skin of the baby's entire body.

Basic blood tests failed to present us with a working diagnosis. We decided on further extensive blood tests and an analysis of peripheral lymphocyte populations. The results showed high IgE levels, eosinophilia, and hypogammaglobulinemia. In connection with typical results in peripheral lymphocyte populations and a failure to respond to corticosteroid treatment, this is diagnostic for OS.

After establishing the correct diagnosis, the patient was transferred to the immunology ward at the pediatric clinic for further assessment of the disease and appropriate definitive treatment.

## Conclusions

Prolonged erythroderma should always be a warning to a physician, and the role of a pediatric dermatologist is to bear in mind the wide spectrum of differential diagnoses that could be causing the condition. In the case of PID, the diagnostic process must be swift, and referral of the patient to the appropriate pediatric ward must occur as soon as possible to avoid any possible complications and start the appropriate treatment. This can only be achieved through a multidisciplinary approach, which is always needed in such rare and potentially life-threatening cases.

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