

## **Overview of dermatological disorders of neonates in a central regional intensive care unit in Hungary**

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## **Abstract**

**Background:** The immaturity and vulnerability of the skin and the epidermal barrier function, and the frequent iatrogenic complications following diagnostic and therapeutic procedures are often associated with various skin manifestations among infants in Neonatal Intensive Care Units (NICUs).

**Objective:** The aim of our current survey was to investigate the dermatological disorders among neonates in our NICU.

**Methods:** A prospective, cohort study was carried out in the NICU at the Department of Pediatrics at the University of Szeged between January 2012 and January 2013. All term and preterm infants hospitalized in the NICU underwent whole-body skin examinations, and all dermatological disorders and treatment modalities were recorded.

**Results:** Among the 211 neonates admitted to the NICU, 89 different dermatological conditions were detected in 64 infants. These conditions were accompanied by a wide spectrum of clinical symptoms among the preterm and severely ill term infants. A considerable proportion of the disorders that were seen were results of the immaturity of the skin and various iatrogenic complications.

**Conclusion:** Dermatological disorders are frequent among neonates requiring intensive care. The prevention, early detection and optimal treatment of these disorders with modern, standardized skin care management strategies can result in significant improvements in the barrier function and in the integrity of the skin, and can therefore increase the overall efficacy of neonatal intensive care.

## Introduction

Neonatal Intensive Care Units (NICUs) are centers which combine advanced technology, diagnostic and therapeutic modalities and well-trained health-care professionals specializing in the treatment of premature and low birth weight infants, or neonates who have medical conditions requiring special medical care. The first NICU was established in 1962, and such centers have contributed markedly to significantly improved rates of survival of preterm infants worldwide. A notably high proportion of neonates require NICU care: in Hungary, some 7000 infants are admitted yearly. It is well known that prematurely born infants are at a significantly increased risk of subsequent chronic medical problems. Neurological, cardiovascular and respiratory diseases, gastrointestinal, metabolic and hematologic problems, developmental abnormalities, the immature immune system and frequent infections demand numerous invasive diagnostic and therapeutic procedures. The immaturity of the skin and the epidermal barrier function, and the frequent iatrogenic complications following treatment are often associated with various skin manifestations, though only a few data concerning such skin manifestations are available in the literature at present, mainly relating to sporadic case reports. The aim of our current survey was to investigate dermatological disorders among preterm and severely ill term infants in our NICU. As far as we aware, these are the first literature data on the prevalence of skin disorders in a tertiary NICU during an exact and comparatively long-term study period.

## Methods

The survey was carried out in the NICU at the Department of Pediatrics at the University of Szeged between January 31, 2012 and January 31, 2013, after approval and permission had been obtained from the Institutional Review Board of Albert Szent-Györgyi Medical Center. This NICU is a 17-bed tertiary center, which annually admits 200-270 neonates in severe perinatal conditions from the south-eastern region of Hungary (with a population of almost 1.5 million). All newborn term and preterm infants hospitalized in the NICU during the 1-year study period were included in the study. Each of them participated in whole-body skin examinations, always carried out by the same two experienced dermatologists from the Department of Dermatology and Allergology at the University of Szeged. The dermatologists took part in the visits at the NICU twice weekly and, if needed, unscheduled visits were also made. In the event of diagnostic challenge, the two dermatologists always consulted before agreeing on the final diagnosis. Decisions relating to diagnoses and therapies were made in consultation with neonatologists. Taking into consideration the relatively high number of surgical procedures required among the NICU patients, pediatric surgeons also make a ward round daily in the NICU. The treatment of iatrogenic skin lesions and wound care is carried out with the collaboration of dermatologists and pediatric surgeons. The gestational age, sex, birth weight, area of involvement, etiology of the disorder, causative factors, diagnosis at admission and comorbidities were recorded, together with the nature of the management (dressings, ointments, medication and surgical interventions). The NICU made the official medical records of patients available for final evaluation.

## Results

During the 1-year study period, a total of 211 neonates of Caucasian origin were admitted to the NICU (mean birth weight:  $2353.6 \pm 981.6$  (SD) g, mean gestational age:  $34.5 \pm 4.3$  (SD)

weeks, range: 23-41 weeks, gender distribution: 125 male and 86 female neonates). Distribution by birth weight: 7 (3.3%) neonates with high birth weight (>4000 g), 86 (40.6%) with appropriate weight for gestational age (2500-4000 g), 66 (31.3%) with low birth weight (1500-2499 g), and 52 (24.6%) weighing less than 1500 g: 32 (15.2%) with very low birth weight (1000-1499 g) and 20 (9.5%) with extremely low birth weight (<1000 g), of whom 5 (2.4%) weighted < 750 g.

Altogether 64 (30.3%; 30 male and 34 female; mean birth weight: 2139.14±1159.4 (SD) g, mean gestational age: 33.09±5.4 (SD) weeks, range: 23-41 weeks) neonates exhibited some kind of dermatological disorder, 5 (7.8%) of these neonates suffering from 3 and 15 (7.1%) of them from 2 different dermatological conditions during the period of hospitalization.

Overall 89 different dermatological cases were detected, 63 of whom needed some form of dermatological treatment, while in 26 cases the conditions were merely closely followed. As concerns the distribution of the diseases, significantly intercorrelated iatrogenic injuries and dermatological conditions associated with the immaturity of the skin were observed in the great majority (67/89 [75.3%]) of the dermatological disorders. The average gestational age of the neonates suffering from the above-mentioned conditions was 32.6 weeks. Altogether 35 (35/89 [39.3%]) cases of iatrogenic injuries and complications were treated (Figure 1.), such as epidermal stripping (7/89) (Figure 2.), extravasation injuries (6/89), pressure ulcers (5/89), thermal burns (1/89), surgical wound infection (1/89), blue light-induced exanthema (2/89), contact dermatitis (2/89) and mechanical impact-induced suffusion (1/89). In the cases of 8 neonates, skin reactions presumed to be induced by infection were observed, manifested as erythematous macules, papules, pustules, or in one extremely severe case purpura fulminans (Figure 3.). Cutis marmorata was diagnosed in a hypoxic neonate (1/89) treated with transient hypothermia. One neonate was born in a polytraumatic condition following an intrauterine infection, in whom disseminated intravascular coagulopathy developed and resulted in

extensive purpurae and hematomas. Additionally, other common conditions that developed as a result of the immaturity of the neonatal skin (32/89 [36.0%]) were dry, scaly skin (18/89), diaper dermatitis (10/89) and maceration (4/89).

One neonate (1/89) presented with purpura and petechiae over the entire surface of the body who had anti-HPA-Ia-induced neonatal alloimmune thrombocytopenia, which was treated effectively with intravenous immunoglobulin and a special thrombocyte infusion. One neonate displayed petechiae on the neck and face, caused by the umbilical cord curling around the neck. Of the common transient benign neonatal skin conditions, erythema toxicum neonatorum developed in 5 neonates (5/89). Vascular malformations were diagnosed in 4 (4/89), vascular tumors (Figure 4.) in 8 (8/89) and other benign congenital tumors in 3 neonates (3/89); in these cases, no treatment was needed, but only observation. One neonate (1/89) was born with dermal melanocytosis in the lumbo-sacral region.

## Discussion

Prematurity involves the immaturity of all organs and organ systems. All of the anatomical elements of the skin are fully developed by 22-24 weeks of pregnancy, whereas functional and biochemical maturity requires a much longer time. At gestational week 24, the epidermis is quite immature, the stratum corneum consisting of only 1-2 cell layers. By weeks 33-34 of gestation, the stratum corneum has attained structural and functional maturity, although the active adaptation and maturation processes continue after birth (Figure 5.). The structure of the skin of a term newborn is similar to that of an adult, but much thinner and more vulnerable. The skin of a full-term newborn is structurally and functionally more ready to adapt to an air environment than the skin of a premature infant, which is in homeostasis with a fluid environment. After delivery, premature skin matures rapidly during 2-8 weeks, taking significantly longer for the most premature neonates<sup>1-4</sup>. In premature infants, the structural

and functional maturation of the skin accelerates significantly, taking approximately 2 weeks after birth. Preterm neonates are obviously highly vulnerable during this 2-week “window period”. Septic complications mainly occur in the first few days or in the first 2 weeks of life and are the most common cause of mortality in this special population. The compromised epidermal barrier function results in an enhanced susceptibility to severe, invasive infections, high rates of transepidermal water loss, thermal instability, an electrolyte imbalance, an increased percutaneous absorption of chemicals and drugs, and easily induced skin traumas; these clinical complications are relevant determinants of high morbidity and mortality rates for preterm infants in the NICU <sup>1-13</sup>.

Our aim in this study was to investigate a large population of preterm and severely ill term infants, with a view to attaining a better understanding of the relationships between dermatological and internal diseases, and an overall picture of the frequency of these skin disorders in the NICU. A survey of comprehensive investigations of dermatologic manifestations in preterms is lacking in the literature. The majority of the review articles summarize and describe the etiology of the typical iatrogenic skin injuries in NICUs (thermal burns, chemical burns, light burns, scalp injuries, extravasation injuries, pressure ulcers, epidermal stripping, e.t.c.). <sup>14-17</sup>. Most of the articles that are available have reported on special skin injuries, i.e. extravasation injuries, pressure ulcers or burns. In a retrospective study, Peralta et al. reported on the prevalence of severe, inherited or acquired dermatological disorders in NICU patients <sup>18</sup>. Our own survey reveals that dermatological conditions may be accompanied by a wide spectrum of clinical symptoms, ranging from transient, benign manifestations such as erythema toxicum neonatorum or nevus simplex to extremely severe, rapidly progressing purpura fulminans with a lethal outcome. A considerable proportion of the disorders that were seen were the results of the immaturity of the skin and various iatrogenic complications, these factors obviously being strictly intercorrelated. Around two-thirds of

these neonates (64.2%) were born before gestation week 34 (the stratum corneum achieves anatomical maturity at gestational week 34).

Overall, it can be stated that all diagnostic or therapeutic interventions and procedures can potentially promote iatrogenic skin disorders. The more premature and smaller a neonate, the more immature the organs, and the more severe the developmental abnormalities, general problems or infections, essential interventions and procedures increase in number. Epidermal stripping develops most frequently as a consequence of the removal of adhesive tapes and dressings used to secure life support and monitoring devices such as cannulas, tubes, probes, catheters, electrodes, pulse oxymeters, etc. All neonates treated or nourished via intravenous lines may suffer extravasation injuries. Low peripheral blood flow, long-standing immobilization, artificial ventilation and insufficient calorie intake can all lead to an increased development of pressure ulcers. Severely ill neonates treated in NICUs generally require intensive care, making some diagnostic or therapeutic procedures inevitable.

In practice, almost every newborn treated in NICUs has at least one intravenous or other type of cannula or tube fixed with tapes; their removal can promote the development of epidermal stripping, particularly in premature infants with an immature epidermis. In our study population, all patients who suffered epidermal stripping, extravasation injuries or pressure ulcers manifested evidence of device-related injury. In 43 % of the cases, epidermal stripping lesions were observed around the umbilical region, as a consequence of umbilical catheter securement. In the other cases, epidermal stripping was noticed on the cheeks (28.5 %) or on the extremities (28.5 %), relating to the fixation of the endotracheal tube or i.v. cannulas. All newborns with extravasation injuries had lesions on the extremities, with the exception of one (16.6 %) with a lesion in the left gluteal region as a consequence of a malpositioned umbilical arterial catheter. Only one newborn (20 %) suffered a pressure ulcer in the left nasal orifice, as a consequence of the use of nasal CPAP prongs. Other procedures, such as resuscitation,



can provoke the development of hematoma, suffusion or maceration, and the use of diaper wipes may result in contact dermatitis. Furthermore, we observed that a lower gestational age and a lower birth weight were factors predisposing to epidermal stripping and diaper dermatitis.

One of the major limitations of our study is the relatively small number of neonates involved, which makes a statistical analysis and interpretation of the results difficult from the aspects of the roles of gestational age, birth weight, length of hospitalization, number of invasive procedures, and other factors influencing the occurrence of skin injuries.

Another relevant limitation of our study is the potentially missed observation of transient benign neonatal skin conditions, i.e. mainly erythema toxicum neonatorum. The individual lesions of erythema toxicum neonatorum disappear rapidly, usually within a few hours or days; the rapid and spontaneous regression of the lesions cannot facilitate the determination of the exact prevalence of the skin condition. The prevalence of erythema toxicum neonatorum is generally lower among preterm infants. Other benign conditions, such as nevus simplex, infantile hemangioma, or hemangioma precursor lesions cannot be recognized in the first few days of life, and in these cases reexamination of the infants is therefore recommended. Overall, the exact time of the skin examination in detecting these transient or not fully developed skin lesions is very important. Neonates with higher birth weight or in a less severe general condition usually spend shorter times in the ward as compared with infants with lower birth weight or severe comorbidities; these latter infants are usually reexamined several times during hospitalization. Moreover, we should emphasize that in the case of some critically ill infants, who can be mobilized only with difficulty, the whole-body skin examination cannot easily be performed.

In order to gain an overall picture of the prevalence of neonatal skin disorders, we set out to investigate a large population of healthy newborns in the Neonatal Care Unit at the

Department of Obstetrics and Gynecology at the University of Szeged between April 2012 and May 2013, besides the present study in the NICU. Overall, 2289 newborn infants underwent whole-body screening skin examinations. At least one skin manifestation was found in 63% of the neonates. The major diagnosis groups were transient benign cutaneous lesions, vascular lesions, pigmented lesions, traumatic, iatrogenic, congenital or acquired disorders with skin injuries, and developmental abnormalities or benign skin tumors. The more frequent of the transient cutaneous lesions were erythema toxicum neonatorum (22.1%) and sebaceous hyperplasia (17.5%), those of the vascular lesions were naevus simplex (31.2%), hemangioma (1.1%) or hemangioma precursor lesion (1.1%), and those of the pigmented lesions were congenital melanocytic nevi (1.2%) and dermal melanocytosis (1.6%). The prevalence of iatrogenic injuries was very low (3.45%). In the vast majority of cases, special treatment was not necessary, but 5.27% of the neonates required particular dermatological therapy, and in 9.2% of them close observation was indicated<sup>19</sup>.

In our opinion, it is very difficult to compare the prevalence of dermatological disorders of healthy newborns with those of neonates requiring intensive care. The frequency and distribution of the skin manifestations are fundamentally different. The vast majority of the skin conditions observed among healthy, term infants are transient benign cutaneous lesions and benign vascular lesions that do not require any special dermatological therapy. In contrast, 75.3 % of the dermatological disorders observed in the NICU were iatrogenic injuries and dermatological conditions associated with the immaturity of the skin. Of the common transient benign neonatal skin conditions, erythema toxicum neonatorum developed in only 5 neonates (2.37%) and of vascular lesions, hemangioma was diagnosed in 8 neonates (3.8%). Moreover, there is a significant difference between the numbers of the two neonate populations, which is also a relevant situation as concerns the statistical analysis of the results.

During the past few decades, the rapid improvement of neonatal intensive care has resulted in dramatic decreases in neonatal mortality rates and an impressive improvement in the survival of very premature infants, but the incidence of iatrogenic events has increased simultaneously<sup>14,15,20,21</sup>. Ligi et al. reported that the incidence of iatrogenic events in NICUs was 25.6 per 1000 patient-days, while Kugelman et al. observed a prevalence of 18.8 infants with iatrogenic events per 100 hospitalized infants and an incidence of 2.02 iatrogenic events per 100 hospitalization days for new admissions, and 0.4 events per patient<sup>22</sup>. Cutaneous events and nosocomial infections were the most common, and the majority of the cutaneous injuries were generally minor. Nosocomial infections and respiratory complications proved to be the most severe iatrogenic events<sup>20</sup>. The incidence of iatrogenic complications rises with the number of diagnostic and therapeutic procedures performed, with the length of the hospital stay, and with the level of immaturity. The most common iatrogenic skin injuries include thermal, chemical and ultraviolet burns, epidermal stripping, extravasation injuries, heel prick injuries, pressure ulcers, and umbilical and peripheral arterial catheter-related injuries<sup>23</sup>. Further investigations should be conducted on the dermatological disorders that occur in NICUs worldwide in order to assess the exact prevalence data of iatrogenic dermatological complications, which are also certainly much less frequently reported and registered than other adverse events.

With the most careful treatment, the majority of iatrogenic skin injuries can be prevented, though regular skin examinations are absolutely indispensable for early detection. The introduction of the new generation of minimally or non-adhesive dressings led to a significant reduction in the development of epidermal stripping, while the use of transparent film dressings facilitates regular observation of the intravenous cannula site<sup>5,11,12,24,25</sup>. Superficial erosions, the early stage of pressure ulcers, are relatively easy to manage, partly because of the excellent regeneration and repairing ability of the newborn skin. The treatment of stage

III-IV pressure ulcers, extravasation injuries and infected surgical wounds with deep tissue necrosis is very complicated; adequate wound care methods and evidence-based protocols are essential for the prevention of permanent functional disabilities and esthetic damage.

Complete newborn skin care protocols should include recommendations relating to neonatal skin assessment, bathing, emollient treatment, cord care, care of the diaper area, use of disinfectants, and neonatal wound care protocols integrating guidance for the treatment of epidermal stripping, pressure ulcers, extravasation injuries, surgical wounds and chemical or thermal burn injuries <sup>26</sup>. The treatment of dermatological disorders emerging during the hospital care of preterm or severely ill newborns is particularly challenging, and it is therefore important to emphasize the role of prevention and early detection. The introduction and application of modern, standardized skin care management strategies can result in significant improvements in the barrier function and in the integrity of the skin, and a decrease in the frequency of iatrogenic injuries, and can therefore increase the overall efficacy of neonatal intensive care. Well-defined, evidence-based, optimized neonatal skin care clinical guidelines for the NICU demand the constant co-operation of well-trained neonatologists, dermatologists, nurses and pharmacists, and it is additionally important to take into consideration the regional characteristics of the neonatal intensive care.

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Fig.1. Distribution of iatrogenic skin disorders among our NICU patients during a one-year interval.

Fig.2. Superficial erosion due to epidermal stripping on the right foot in a preterm infant born in the 27th gestational week.

Fig.3. Acute infectious purpura fulminans due to ESBL-producing *Klebsiella pneumoniae* born in the 29th gestational week, with a lethal outcome

Fig.4. Infantile haemangioma in the right retroauricular region of a preterm infant born in the 28th gestational week.

Fig.5. Development of the epidermis during embryonic and fetal life.