

**THE PREVALENCE AND RISK FACTORS OF
DERMATOLOGICAL DISORDERS AMONG NEONATES IN A
TERTIARY NEONATAL INTENSIVE CARE UNIT**

Angéla Meszes M.D.

Ph.D. Thesis

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List of abbreviations

BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
DD	Diaper dermatitis
EI	Extravasation injury
ELBW	Extremely low birth weight
HBW	High birth weight
ES	Epidermal stripping
INSURE	Intubation, surfactant, extubation
iv	Intravenous
LBW	Low birth weight
NICU	Neonatal Intensive Care Unit
NPUAP	National Pressure Ulcer Advisory Panel
NBW	Normal birth weight
PU	Pressure ulcer
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome
TEWL	Transepidermal water loss
UAC	Umbilical arterial catheter
VLBW	Very low birth weight

1. Introduction

Preterm birth is one of the most significant perinatal health problems worldwide. According to the WHO data for 2007, the highest rates of preterm birth are observed in Africa and North America (11.9% and 10.6% of all births, respectively), and the lowest in Europe (6.2%), especially in the Scandinavian countries (3-4%).¹ Unfortunately, despite extensive obstetrical and public health efforts, the preterm birth rates remain stable or are even increasing, and impose a considerable burden on both families and society throughout the world. Preterm birth, defined as childbirth occurring before 37 completed weeks of pregnancy or 259 days of gestation, is a major determinant of neonatal mortality and morbidity and has long-term adverse consequences for health. In Hungary, the prevalence of premature birth in the past few years has been estimated as 8-10 % (8.6% in 2010).² Although the prevalence of preterm birth has not been reduced, there has been a marked change in the survival rates of neonates born prematurely or with low birthweight (LBW). The survival rate of infants treated in neonatal intensive care units (NICUs) in Hungary is currently over 95%.¹

In fact, neonatology is one of the most spectacularly developing disciplines of medicine: the recent technological advances and diagnostic and therapeutic innovations have revolutionized the perinatal care of preterm infants and resulted in an impressive improvement in the survival of even very low birth weight (VLBW) infants. The treatment of prematures is performed in NICUs, which are centres that combine advanced technology, diagnostic and therapeutic modalities, and well-trained health-care professionals specializing in the treatment of premature and low birth weight infants and neonates who have medical conditions requiring special medical care. The first NICU was established in 1962, and such centres have contributed markedly to significantly higher rates of survival of preterm infants worldwide. The treatment of premature and severely ill neonates can be carried out in NICUs with different progressivity levels; basically, three levels can be differentiated. The management of neonates born with LBW or extremely low birthweight (ELBW) or who are critically or severely ill is performed in level III. progressivity NICUs. In Hungary, approximately 6500-7000 infants are admitted to level III. NICUs yearly.

Prematurity involves the immaturity of all organs and organ systems. All of the anatomic elements of the skin are fully developed by weeks 22 to 24 of gestation, whereas functional and biochemical maturity requires a much longer time. At gestational week 24, the epidermis is immature, with the stratum corneum consisting of only one to two cell layers. In preterm

infants, the full thickness of the skin (0.9 mm) is much less than that in term infants (1.2 mm), and this is also the case for the thickness of the epidermis and stratum corneum. The uppermost layer of the epidermis, the stratum corneum, which consists of corneocytes, plays a considerable role in the protecting barrier function of the skin. The physical barrier of the skin represented by the stratum corneum is mainly determined by its thickness and integrity. By weeks 33 to 34 of gestation, the stratum corneum has attained structural and functional maturity, although the active adaptation and maturation processes continue after birth. Changes in the skin pH, development of the protecting acid envelope and continuous colonization of the apathogenic microbes play a crucial role in the adaptation process.³

(Figure 1.)

The basic structural differences between the skin of a preterm neonate, a term neonate and an adult skin are of considerable importance in clinical practice. The structure of the skin of a full-term neonate is similar to that of an adult, but it is much thinner and more vulnerable. The skin of a term neonate 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 over 2 to 8 weeks, but this process takes significantly longer for the most premature neonates.⁴⁻⁷

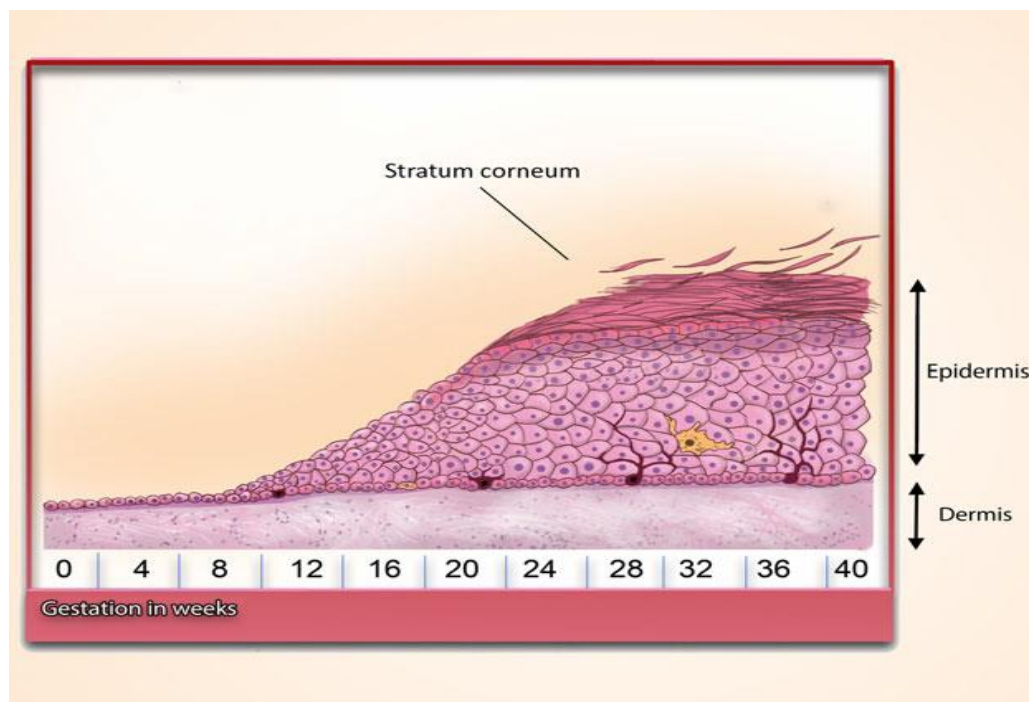


Figure 1. *Development of the epidermis during embryonic and foetal life*

In premature infants, the structural and functional maturation of the epidermis accelerates significantly, taking approximately 2 weeks after birth. As a consequence of this accelerated maturation period, the epidermis of an extremely premature infant undergoes a dramatic development during this 2 weeks, resulting in a markedly decreased transepidermal water loss (TEWL) and a reduced possibility of absorption of various toxic agents.^{3,6,8,9} Preterm neonates are obviously highly vulnerable during this 2-week window period. Septic complications mainly occur in the first few days or 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 TEWL, 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. In extremely premature infants, the TEWL can be as much as 10-15 times more than in full-term infants; a neonate born at 24 weeks of gestation can lose even 13% of the body weight on the first day of life, as a consequence of the high fluid loss due to the practical absence of the epidermal barrier.^{4,5,9-16}

Another anatomical-structural difference is that the dermoepidermal junction is flat, anchoring fibrils, anchoring filaments and hemidesmosomes are fewer and smaller in premature infants, which results in a decreased resistance to shear forces. Due to the immaturity of the dermoepidermal junction, the epidermis and dermis can easily separate from each other; moreover, bullae can develop much more easily after thermal or mechanical impacts. The skin is therefore fragile and prone to be affected by an inadvertent cutaneous injury. The dermis is also thinner, less collagenized and more gelatinous, and this gives rise to an increased risk of oedema, resulting in the risk of an ischaemic injury. Moreover, in consequence of the thin layer of subcutaneous fat and the immature eccrine glands, premature infants have a compromised thermoregulatory capability.^{4,5,10,13,17-20} **(Table 1.)**

	ADULT	TERM NEONATE	PRETERM NEONATE
<i>Skin surface</i>	dry	vernix caseosa	vernix gelatinosa
<i>Thickness of the skin</i>	2.1 mm	1.2 mm	0.9 mm
<i>Thickness of the stratum corneum</i>	9-15 μm	9-10 μm	4-5 μm
<i>Dermoepidermal junction</i>	ridged, antigen expression	slightly ridged, antigen expression	totally flat, reduced antigen expression
<i>Anchoring filaments, fibrils and hemidesmosomes</i>	mature	mature	fewer, smaller
<i>Dermal collagen and elastic fibres</i>	mature	smaller size, immature structure	even smaller size, immature structure

Table 1. Main anatomical differences in the skin between adults, term and preterm neonates (Buonocore, Bracci, Weindling's Neonatology textbook)

It can be seen that the immaturity not only of the internal organs, but also of the skin can result in various clinical consequences during the intensive care of neonates. A thorough knowledge and the exact diagnosis and identification of risk factors of dermatologic disorders in neonates have proved to be extremely important, just as are their correct and professional treatment and prevention.

Premature infants are at high risk of subsequent chronic medical problems. Neurologic, cardiovascular and respiratory diseases, gastrointestinal, metabolic and haematologic problems, developmental abnormalities, the immature immune system and frequent infections demand numerous invasive diagnostic and therapeutic procedures. The treatment and prevention of organ impairments resulting from prematurity and various neonatal diseases are enormous challenges in neonatal care. In consequence of the use of modern invasive diagnostic and therapeutic procedures, respiratory therapy techniques and technical devices ensuring the continuous monitoring of vital parameters, the incidence of iatrogenic events has also increased significantly. The various skin injuries constitute a significant proportion of iatrogenic complications.

Naturally, other severe dermatological disorders besides iatrogenic injuries can also develop in neonates. Serious viral, bacterial or fungal infections, inherited keratinization disorders or dermatologic diseases with the formation of bullae can significantly impair the first and most

important protecting line of the body, and at the same time the function of all the organs. The treatment of these premature or severely ill infants must be performed in highly qualified intensive centres.

2. Aims

2.1. The aim of the current survey was to investigate the prevalence of dermatological disorders among preterm and severely ill term infants in our level III. progressivity NICU. As far as we are 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.

2.2. As most of the dermatological disorders observed in our NICU in the first year of the study period proved to be skin injuries that developed as a consequence of the immaturity of the skin and iatrogenic interventions, we paid particular heed to the prevalence of these injuries in the two years of the study period. We also made a detailed assessment of the aetiology, type and therapeutic possibilities of lesions requiring wound management.

2.3. We also reviewed factors of possible relevance as concerns the development of skin disorders resulting from the immaturity of the skin, and various iatrogenic complications in neonates requiring intensive care. The following factors that may influence (directly or indirectly) the general condition of neonates were analysed: gender, gestational age, birth weight, use of a central venous line, respiratory (mechanical or continuous positive airway pressure ventilation (CPAP)) and circulatory support, positive microbiology culture results, the appearance of early complications (pneumothorax, pulmonary haemorrhage, intracranial haemorrhage or respiratory distress syndrome (RDS)), surgical interventions and the length of NICU stay.

3. Patients and Methods

3.1. Patients and dermatological examinations

Our prospective cross-sectional cohort survey was carried out in the level III. NICU at the Department of Paediatrics at the University of Szeged between 31 January 2012 and 31 January 2014 after approval and permission had been obtained from the Institutional Review Board of Albert Szent-Györgyi Medical Centre. This NICU is a 17-bed tertiary, university-affiliated centre, 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 consecutive newborn term and preterm infants hospitalized in the NICU during the 2-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. Decisions relating to diagnoses and therapies were made in consultation with neonatologists. In view of the relatively high number of surgical procedures required among the NICU patients, paediatric 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 paediatric surgeons.

The gestational age, sex, birth weight, area of involvement, aetiology of the disorder, causative factors, diagnosis at admission and comorbidities were recorded, together with the nature of the management (dressings, ointments, medications and surgical interventions).

3.2. Investigation of the prevalence of iatrogenic dermatological lesions requiring wound management among neonates

During the first year of the study period, a great proportion of the dermatological disorders proved to be lesions associated with immaturity of the skin and consequences of iatrogenic injuries which require special wound management.

We laid special emphasis on the investigation of lesions requiring wound care, among other dermatological conditions. All wound-care objectives, management plans and wound assessment details were documented precisely, including the aetiology, the type (acute or

chronic) and exact localization of the wound, the wound dimensions (width, length and depth) in centimetres, the nature of the wound bed, the status of the surrounding skin, the exudate characteristics (amount, colour, consistency and odour), and the presence of infection. Photodocumentation was made at every, or every second examination. Follow-up visits were made 1, 3 and 6 months after wound healing.

3.3. Investigation of the factors of possible relevance as concerns the development of iatrogenic injuries

During the 2-year study period, we investigated the prevalence of lesions associated with skin immaturity and as a result of iatrogenic injuries, such as epidermal stripping (ES), extravasation injuries (EIs), pressure ulcers (PUs), diaper dermatitis (DD), macerations in skin folds, infection-induced cutaneous eruptions, thermal and chemical burn injuries, surgical wounds, UV light-induced exanthema and haematomas.

To analyse the data on the patients' characteristics and case history, the official medical records were used. We investigated the potential role of the following factors in the background of iatrogenic injuries: gender, gestational age, birth weight, length of hospital stay, intensive therapeutic interventions (ventilation and circulation support, surgical interventions), complications (pulmonary haemorrhage, pneumothorax and intracranial bleeding), factors influencing attendance and prognosis (patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD) and infections).

3.4. Statistical analysis

Data were collected and documented through the use of Excel tables, and SPSS 22.0 was used for statistical analysis. The correlations between the prevalence of cutaneous injuries and the demographics and patient characteristics, and data relating to intensive therapeutic interventions, complications, factors influencing the attendance and the prognosis were calculated by using Pearson's chi-squared test and Fischer's exact test. All p values calculated were 2-sided, and a significance level of 0.05 was assumed.

4. Results

4.1. Patient characteristics and demographics

During the 2-year study period, a total of 460 neonates of Caucasian origin were admitted to the NICU (mean birth weight: 2236.86 ± 965.53 (SD) g, range: 500-5470 g, mean gestational age: 33.83 ± 4.39 (SD) weeks, range: 22-41 weeks, gender distribution: 250 males and 210 females). (**Figure 2.**) Distribution by birth weight: 16 (3.48 %) neonates with high birth weight (HBW, > 4000 g), 159 (34.56 %) with appropriate weight for gestational age (i.e. normal birth weight, NBW, 2500-4000 g), 154 (33.48 %) with LBW (1500-2499 g), and 131 (28.48 %) weighing less than 1500 g: 81 (17.61 %) with very low birth weight (VLBW, 1000-1499 g) and 50 (10.87%) with extremely low birth weight (ELBW, <1000 g), of whom 17 (3.7 %) weighed < 750 g (**Figure 3.**). The mean birth weight of the admitted male infants (2360.7 ± 990.87 (SD) g) was significantly higher than that of the female infants (2089.4 ± 915.13 (SD) g. ($p=0.003$).

40.7 % of the infants were born after 36 weeks of gestation, 29.5 % of them between 32 and 35 weeks, 19.16 % of them between 28 and 31 weeks, 9.69 % of them between 24 and 27 weeks, and 2 infants before 24 weeks of gestation. There was no significant difference between the mean gestational ages of male (34.02 weeks) and female (33.59 weeks) infants. (**Figure 4. A-B.**)

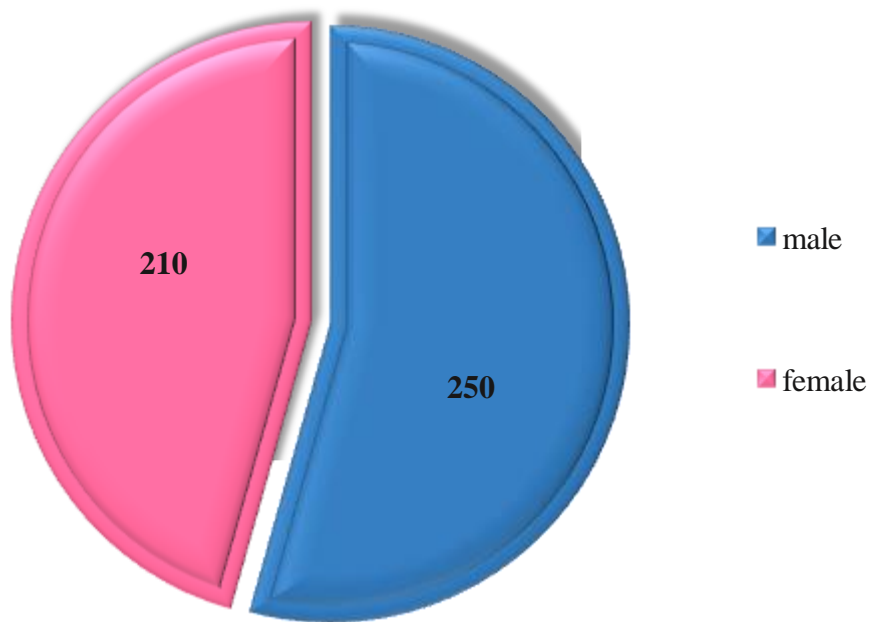


Figure 2. Distribution of all newborn patients by gender who were hospitalized in the NICU during the 2-year study period (N=460)

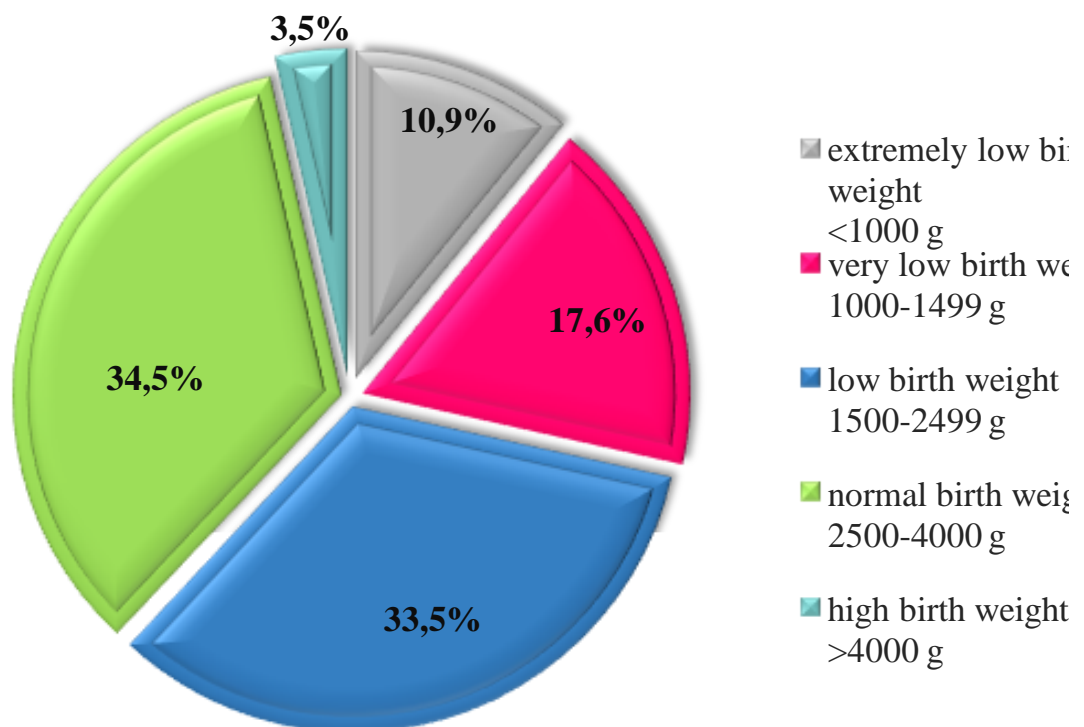


Figure 3. Distribution of all newborn patients by birth weight, who were hospitalized in the NICU during the 2-year study period (N=460)

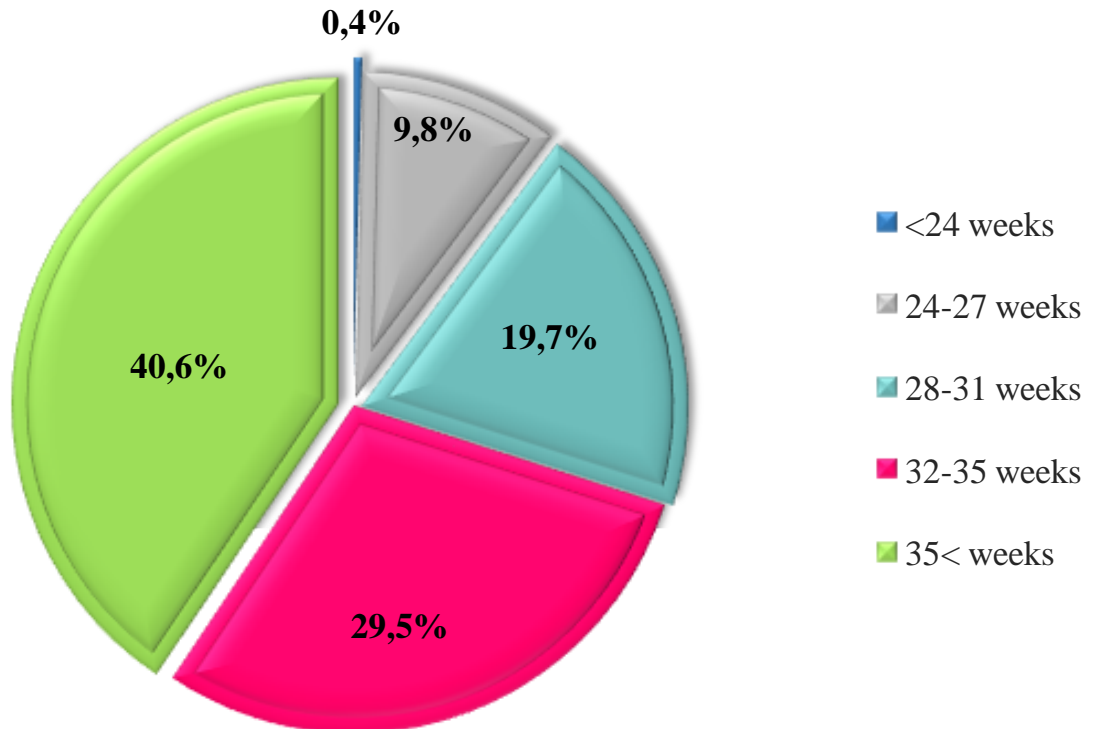


Figure 4. A. Distribution of all newborn patients by gestational age, who were hospitalized in the NICU during the 2-year study period (N=460)

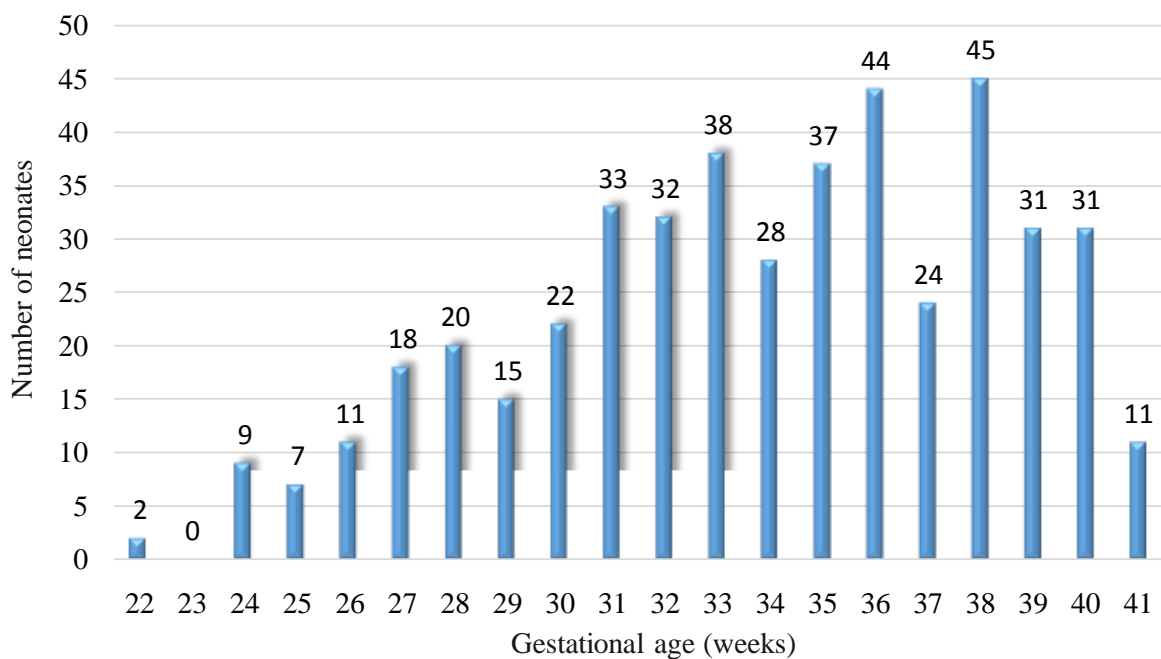


Figure 4. B. Distribution of all newborn patients by gestational age (weekly) who were hospitalized in the NICU during the 2-year study period (N=460)

4.2. Dermatological disorders observed in the NICU during the first year of the study period

During the first year of the study period, 211 neonates of Caucasian origin were admitted to the NICU (mean birth weight 2353.6 ± 981.6 g, mean gestational age 34.5 ± 4.3 weeks [range 23–41 weeks], 125 male, 86 female). Seven (3.3%) neonates had HBW (>4000 g), 86 (40.6%) had NBW (2500–4000 g), 66 (31.3%) had LBW (1500–2499 g), and 52 (24.6%) weighed less than 1500 g: 32 (15.2%) with VLBW (1000–1499 g) and 20 (9.5%) with ELBW (<1000 g) of whom 5 (2.4%) weighed less than 750 g.

Sixty-four neonates (30.3%; 30 male, 34 female; mean birth weight 2139.1 ± 1159.4 g, mean gestational age 33.1 ± 5.4 weeks [range 23–41 weeks]) of the 211 infants admitted to the NICU exhibited some kind of dermatologic disorder; 15 (7.1 %) had two and 5 (1.42 %) had three different dermatologic conditions during their hospitalization.

Overall, 89 different dermatologic cases were detected, 63 of whom needed some form of dermatologic treatment, whereas in 26 cases the conditions were merely closely followed. As regards the distribution of the diseases, significantly intercorrelated iatrogenic injuries and dermatologic conditions associated with the immaturity of the skin were observed in the great majority (67/89, 75.3%) of the dermatologic disorders. The average gestational age of these neonates was 32.6 weeks. Thirty-five (39.3%) cases of iatrogenic injuries and complications were treated, such as ES (n = 7), EIs (n = 6), PUs (n = 5), thermal burns (n = 1), surgical wound infection (n = 1), blue light-induced exanthema (n = 2), contact dermatitis (n = 2) and mechanical impact-induced suffusion (n = 1). Skin reactions presumed to be induced by infection were observed in 8 neonates, manifested as erythematous macules, papules, pustules, or in one severe case of purpura fulminans. (**Figure 5.**)



Figure 5. *Acute infectious purpura fulminans due to extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a neonate born in gestational week 29, with a lethal outcome*

Cutis marmorata was diagnosed in a hypoxic neonate treated by using transient hypothermia. One neonate was born in a polytraumatic condition after an intrauterine infection, in whom disseminated intravascular coagulopathy developed and resulted in extensive purpurae and haematomas. Other common conditions that developed as a result of the immaturity of the neonatal skin (n = 32, 36.0%) were dry, scaly skin (n = 18), DD (n = 10) and maceration in the skin folds (n = 4). One neonate who had anti-human platelet antigen-1a-induced neonatal alloimmune thrombocytopenia had purpura and petechiae over the entire surface of the body; it was treated effectively with intravenous (iv) immunoglobulin and a special thrombocyte infusion. One neonate had 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. **(Figure 6.)** Vascular malformations were diagnosed in 4, vascular tumours **(Figure 7.)** in 8, and other benign congenital tumours in 3; no treatment was needed in these cases, but only observation. One neonate was born with dermal melanocytosis in the lumbosacral region. **(Figure 8.)**



Figure 6. *Erythema toxicum neonatorum*



Figure 7. *Infantile haemangioma in the right retroauricular region of a preterm infant born in gestational week 28.*



Figure 8. *Dermal melanocytosis in the lumbosacral region*

The neonates had various diagnoses at the time of admission to our NICU, such as respiratory disorders and RDS, prematurity, intrauterine infection, resuscitation, meconium aspiration, anal atresia, duodenal atresia, choanal atresia, oesophageal atresia, hypothermia, Down syndrome, polytraumatization, hydrocephalus, coagulation disorder and disseminated intravascular coagulation, and myelomeningocele. The most common comorbidities of neonates with dermatological disorders observed in the NICU during the 1-year study period were pneumonia and other infections, anaemia, ductus Botalli persistens, BPD, cerebral or intraventricular haemorrhage, icterus, RDS, pneumothorax and pulmonary hypertension.²²

4.2.1. Lesions requiring wound management during the first year of the study period

32 (17%; 17 male, 53.1%; 15 female, 46.9%) of the 211 infants admitted to the NICU required special therapy for at least 1 wound, 3 of the 32 suffering 2 wounds, i.e. a total of 35 wounds were detected and treated. The gestational age of these 32 neonates varied between 23 and 41 gestational weeks (mean: 33.02 ± 4.9 (SD) g). One of the 32 was born with HWB (3.1%), 10 (31.2%) with NBW, 8 (25.0%) with LBW, 4 (12.5%) with VLBW, and 8 (25.0%) with ELBW. The mean birth weight was 2037 ± 1055 (SD) g.

The 35 wounds were grouped on the basis of the causative factors: ES in consequence of the removal of adhesive dressings, EIs, surgical wounds and infections, burns due to thermal or chemical agents, excoriation in the diaper area, PUs and others. The most common wounds (10 cases, 28.6%) were erosions and excoriations that developed in the gluteal region because of irritative contact dermatitis due to urinal or faecal irritation. Erosions due to ES were observed in 7 neonates (20.0%), in whom injuries developed after the removal of a tape used for cannula fixation. Extravasation wounds were also frequent (6 cases, 17.1%) after paravasation of parenteral feeding solutions such as amino acid, glucose and fatty acid infusions or inotropic drugs such as dobutamine and adrenaline. Another common type of wounds was PUs, which were observed in 5 (14.3%) critically ill neonates (with congenital heart disorders, after resuscitation, or with intrauterine infection); these developed mainly in the occipital region, but 1 occurred in the nose due to a nasal CPAP cannula. PUs were staged on the basis of the National Pressure Ulcer Advisory Panel (NPUAP) Staging Guidelines: 2 patients had a stage I PU ulcer, and 3 ulcers were in stage II. We observed 1 neonate with a deep surgical wound (2,8%) in the lumbo-sacral region, which developed after a closing operation for myelomeningocele²³, and 1 neonate with a thermal burn (2.8%) caused by a pulse oxymeter. There were 5 other iatrogenic lesions (14.3%), which could not be classified into the previous groups: 4 cases of maceration in the folds (12.5%), and 1 suffusion (2.8%).

During the different steps and stages of the wound management, modern wound care methods were used, with close regard to the anatomical and physiological characteristics of the neonates. The wound management included both conventional and modern dressings. The frequency of dressing changes was always determined individually, depending on the wound type and base, the amount of wound exudate, signs of infection and the type of dressing. Swabs were always taken from wound exudates for microbiology, and parenteral antibiotics were commenced in accordance with the bacterial sensitivity if the laboratory findings or skin signs were indicative of systemic infection.²³

A lower gestational age and a lower birth weight proved to be factors predisposing to ES (5/7, 71.4%) and DD (6/10, 60%). Data on all patients and wounds during the first year are presented in **Table 2**.²⁴

AETIOLOGY	NUMBER OF CASES	GENDER (M/F)	GESTATIONAL AGE (weeks) (median, range)	BIRTH WEIGHT (g) (median, range)	LESION	LOCALISATION	CAUSATIVE FACTORS	THERAPY	LENGTH OF STAY (days; median, range)	OUTCOME
<i>Diaper dermatitis</i>	10	7/3	35 (27-41)	2102.5 (910-4340)	erythema (10), erosion (9), papules (1)	gluteal region (10)	irritation (10)	barrier creams, liquid barrier film dressing (10)	43 (11-66)	TSNICU (4), home (6)
<i>Epidermal stripping</i>	7	3/4	28 (23-38)	955 (530-3600)	erosion (7)	umbilicus (3), right cheek (1), left cheek (1), left nipple (1), right foot (1)	tape removal (7)	epithelizing cream, foam dressing (7)	47 (11-49)	TSNICU (5), home (1), death (1)
<i>Extravasation injury</i>	6	3/3	36 (31-36)	2042.5 (1225-2990)	haematoma (2), superficial ulcer (4), deep ulcer (2), bulla (2)	right wrist (3), left hand (1), left upper arm (1), left gluteal region (1)	fatty acid, lipid and amino acid infusion (4), glucose (1), dobutamine (1)	epithelizing ointment (3), hydrogels (2), surgical necrectomy (1), observation (1)	26 (18-41)	TSNICU (4), home (1), surgery (1)
<i>Pressure ulcers</i>	5	2/3	38 (26-40)	3440 (700-3980)	erythema (2), haemorrhagic erosion with crust (3)	occipital region (4), nasal orifice (1)	pressure (5)	herb-containing gel (2), epithelizing ointment (2), hydrogels (1)	47 (28-103)	TSNICU (4), death (1)
<i>Thermal burns</i>	1	0/1	32	1650	ulcer	forearm	pulse oxymeter	epithelizing ointment	12	TSNICU
<i>Surgical wounds</i>	1	0/1	39	3250	ulcer	lumbo-sacral region	postoperative wound infection	hydrofibre dressing, gelling foam dressing	25	TSNICU
<i>Others</i>	5	2/3	31 (26-37)	1650 (1300-1805)	erosion (4), suffusion (1)	neck folds (3), right foot (1), inguinal region (1)	mechanical irritation (4), grabbing the arm (1)	epithelizing ointment (4), observation (1)	12 (10-20)	TSNICU (5)

Table 2. Wounds occurring in the NICU during the first year of study period. Wound characteristics and relevant data on the patients (TSNICU: transfer to secondary neonatal intensive care unit)

4.3. Investigation of lesions associated with skin immaturity and iatrogenic injuries and factors of their development during the 2-year study period

Altogether 83 (18.04%; 41 male and 42 female (**Figure 8.**); mean birth weight: 2055.6 ± 1045.95 (SD) g, mean gestational age: 32.85 ± 5.2 (SD) weeks, range: 23-41 weeks) neonates exhibited some kind of iatrogenic skin disorder, 66 of them suffering from 1, 15 of them from 2, 1 of them from 3, and 1 of them from 4 different dermatological conditions during the period of hospitalization. Distribution by birth weight (**Figure 9.**): 4 (4.8 %) neonates with HBW (> 4000 g), 25 (30.1 %) with NBW (2500-4000 g), 19 (22.9 %) with LBW (1500-2499 g), and 35 (42.2 %) weighing less than 1500 g: 16 (19.3 %) with VLBW (1000-1499 g) and 19 (22.9 %) with ELBW (< 1000 g), of whom 5 (6 %) weighed < 750 g.

37.8 % of the infants were born after 36 weeks of gestation, 19.51 % of them between 32 and 35 weeks, 23.17 % of them between 28 and 31 weeks, 19.52 % of them between 24 and 27 weeks, and none before 24 weeks of gestation. (**Figure 10.**)

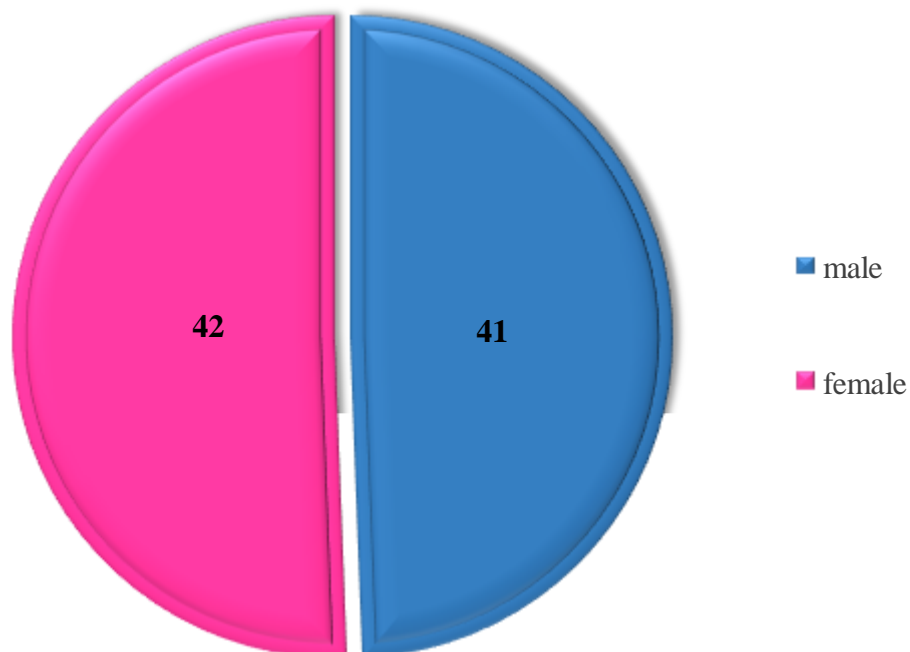


Figure 8. *Distribution of newborn patients by gender with iatrogenic skin injuries (N=83)*

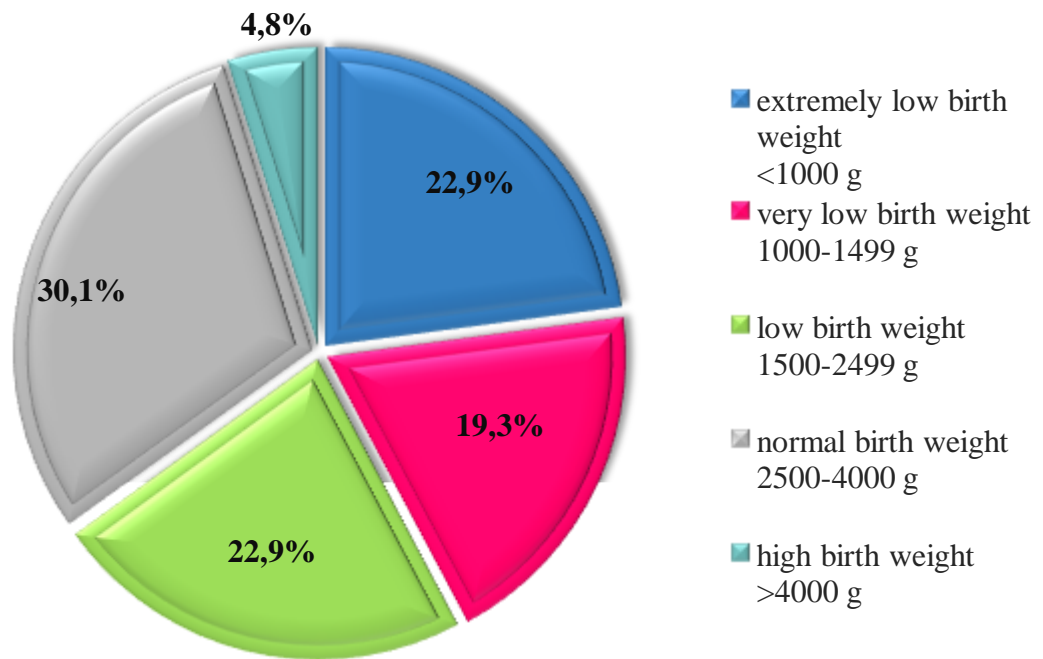


Figure 9. Distribution of newborn patients by birth weight with iatrogenic injuries (N=83)

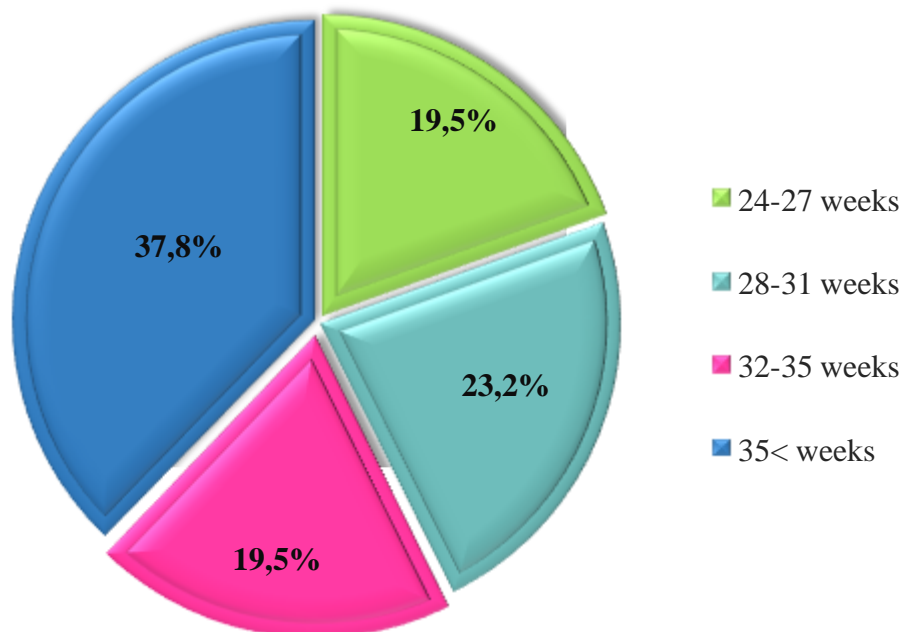


Figure 10. Distribution of newborn patients by gestational age with iatrogenic skin injuries (N=83)

The iatrogenic skin injuries were grouped on the basis of the aetiology and causative factors (**Table 3; Figure 11.**) ES in consequence of the removal of adhesive dressings, EIs, surgical wounds, infection-induced cutaneous eruptions, burns due to thermal or chemical agents, excoriation in the diaper area, macerations and erosions in the folds (**Figure 12.**), PUs, petechiae, haematoma and polytrauma, irritative contact dermatitis, mechanical impact-induced suffusion (**Figure 13.**), hypothermia-induced livedo reticularis and blue-light phototherapy-induced transient rashes. Only one dopamine-related extravasation injury with severe tissue necrosis and ischaemia was recorded during the 2-year study period, which resulted in deep gluteal skin necrosis as a consequence of umbilical arterial catheterization.

Iatrogenic skin injuries	Number of infants	%
<i>Diaper dermatitis</i>	25	24.27
<i>Infection induced cutaneous eruptions</i>	14	13.59
<i>Maceration and erosion in neck folds</i>	13	12.62
<i>Epidermal stripping</i>	11	10.68
<i>Petechiae, haematoma</i>	9	8.74
<i>Pressure ulcers</i>	9	8.74
<i>Extravasation injuries</i>	8	7.77
<i>UV light-induced exanthema</i>	5	4.85
<i>Contact dermatitis</i>	4	3.88
<i>Thermal burns</i>	2	1.94
<i>Cutis marmorata /livedo reticularis</i>	1	0.97
<i>Polytrauma</i>	1	0.97
<i>Surgical wounds</i>	1	0.97

Table 3. Distribution of iatrogenic skin disorders in our NICU patients during the 2-year interval.

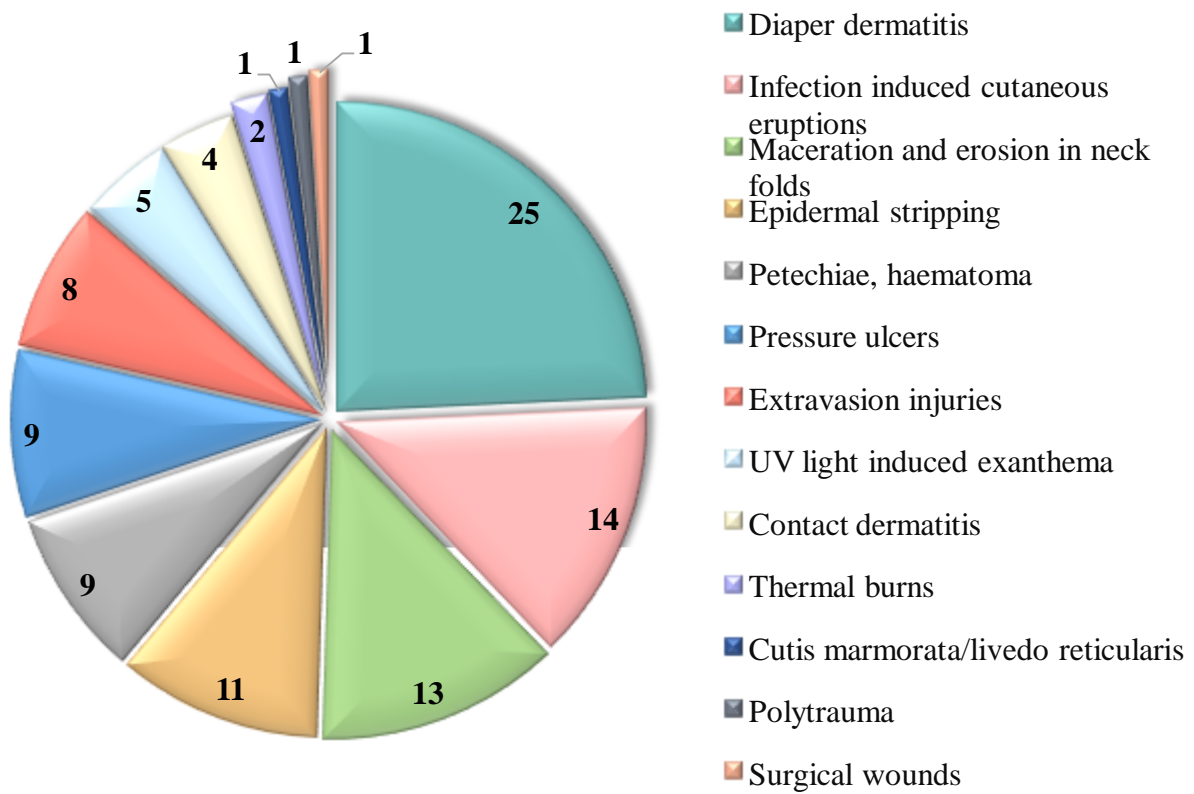


Figure 11. *Distribution of iatrogenic skin disorders in our NICU patients during the 2-year interval.*



Figure 12. *Maceration on the neck as a consequence of mechanic friction*



Figure 13. Mechanical impact-induced suffusion on the left arm after a cannule insertion

The mean gestational age of the neonatal infants with any of the iatrogenic skin injuries was significantly lower than that of the infants without any skin trauma. The mean birth weights in the two groups were not statistically different, but the prevalence of iatrogenic skin injuries was significantly higher among the infants with a birth weight of <1000 g as compared with infants with a birth weight of >1000 g. The length of NICU stay was significantly longer for neonates with iatrogenic skin injuries. The mortality rate of the infants with an iatrogenic skin injury was 9.64 %, while in the infants without skin injuries it was 8.22%; the difference between the two groups was not statistically significant. (**Table 4.**)

	All newborn infant	Neonates with iatrogenic skin injuries	Neonates without iatrogenic skin injuries	p-value
<i>Number of patients (male, female)</i>	460 (250, 210)	83 (41, 42)	377 (209, 168)	
<i>Mean gestational age (weeks)</i>	33.83	32.85	34.04	0.027*
<i>Mean birthweight (g)</i>	2236.6	2055.6	2276.5	0.059
<i>Mean length of hospital stay in the NICU (days)</i>	20.80	32.18	18.29	0.001*
<i>Mortality (%)</i>	8.48	9.64	8.22	0.664

Table 4. Patient characteristics, demographics and outcome (*= statistically significant difference)

The following factors, interventions and conditions proved to be associated significantly with the development of iatrogenic skin injuries: use of the INSURE (intubation, surfactant, extubation) technique, surfactant use, mechanical ventilation, insertion of an umbilical arterial catheter (UAC), circulatory/cardiac support with dopamine or dobutamine, PDA, pulmonary haemorrhage, intracranial haemorrhage, BPD and positive microbiology culture results. (Pearson's chi-squared test and Fischer's exact test). (**Table 5.**)²¹

Intensive therapeutic interventions, complications, factors influencing attendance and prognosis	Total N (%)	Neonates with iatrogenic skin injuries N (%)	Neonates without iatrogenic skin injuries N(%)	p-value
INSURE	85 (16.27)	24 (29.27)	61 (16.27)	0.006 *
Surfactant	164 (35.96)	41 (50.00)	123 (32.89)	0.003 *
nasal-CPAP	211 (46.27)	43 (52.44)	168 (44.92)	0.216
Mechanical ventilation	204 (44.74)	45 (54.88)	159 (42.51)	0.041 *
Umbilical arterial catheter	27 (5.92)	9 (10.98)	18 (4.81)	0.04 *
Umbilical venous catheter	366 (80.09)	68 (82.93)	298 (79.7)	0.478
Dopamine and/or Dobutrex	96 (21.05)	24 (29.27)	72 (19.25)	0.044 *
PDA	134 (29.39)	35 (42.68)	99 (26.47)	0.004 *
Pneumothorax	29 (6.36)	7 (8.54)	22 (5.88)	0.372
Intrapulmonary haemorrhage	28 (6.14)	10 (12.20)	18 (4.81)	0.02 *
Intracranial haemorrhage	46 (10.09)	14 (17.07)	32 (8.56)	0.02 *
BPD	23 (5.04)	9 (10.98)	14 (3.74)	0.012 *
Operation	99 (21.71)	21 (25.61)	78 (20.86)	0.344
Positive microbiology culture results	214 (46.93)	52 (63.41)	162 (42.32)	0.001 *

Table 5. Factors concerning the development of iatrogenic skin injuries (*= statistically significant difference)

5. Discussion

Preterm birth rates have increased in the past two decades in many countries, in contrast with reports of decreasing rates of preterm deliveries in Finland and The Netherlands.²⁵ This tendency can be explained by many reasons, e.g. increasing multiple pregnancy rates associated with the use of *in vitro* fertilization, later maternal age at childbirth and an increase in maternal body mass index (BMI). Moreover, there are further factors that can increase the risk of premature birth, such as a previous preterm birth, cervical insufficiency, maternal diabetes, renal disease, hypertension and smoking. While the rate of preterm births for singleton deliveries is 5-10%, the rate for preterm multiples is 40-60%.²⁶

The survival rate of premature neonates has risen markedly in recent years due to medical advances in perinatal care, such as the use of antenatal corticosteroids and surfactants. Premature infants are generally at higher risk of mortality and morbidity. This is especially true for the very preterm neonates (< 32 weeks), but moderate (32-33 weeks) and late (34-36 weeks) preterm neonates may also have worse neurodevelopmental and educational outcomes as compared with neonates born after at least 37 weeks of gestation.¹ A notably high proportion of neonates therefore require care in NICU in their early extrauterine life. In Hungary, 6500-7000 infants are admitted to level III. NICUs yearly. NICUs are centres specialized for the treatment of premature and low birth weight infants, or newborns who have conditions requiring special medical care. Such centres have made a marked contribution to the significant improvement of the survival rate of preterm infants throughout the world.

As one of the largest and most important organs, the skin has various functions: it takes part in the fluid-electrolyte homeostasis and thermoregulation, and provides protection against mechanical impacts, the colonization and penetration of pathogenic microorganisms, ultraviolet irradiation, and the absorption of various toxic agents. Moreover, the skin comprises a basic and significant part of the immune system. Like other organs, the skin develops continuously during embryonic and foetal life. A review of the steps of development of the skin and the physiological consequences of the immaturity of the skin clearly demonstrates that the status of the epidermal barrier significantly influences the general health status of neonates.

The mortality rate of infants is one of the most important quality indicators of paediatric and public health. Premature neonates or infants who are born with severe diseases or developmental disorders and who are treated in intensive care units nowadays account for a

great majority of the neonatal or infant mortality in developed countries. While there have been numerous thorough studies on adaptation and disorders of many organs and organ systems, neonatal dermatology is a much less well studied and reviewed field of medicine.

5.1. Dermatological disorders among neonates requiring intensive care

Our primary aim in this study was to investigate a large population of preterm and severely ill term infants, with a view to acquiring 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. This is the first comprehensive study of dermatological disorders and diseases in neonates observed in a NICU during a 1-year study period. The majority of the review articles survey the aetiology of the typical iatrogenic skin injuries in NICUs (thermal burns, chemical burns, light burns, scalp injuries, EIs, PUs, ES, e.t.c.).²⁷⁻³⁰ Peralta et al. reported on the prevalence of severe, inherited or acquired dermatological disorders in NICU patients.³¹ Our own survey has revealed that dermatological conditions may be accompanied by a wide spectrum of clinical symptoms, ranging from transient, benign manifestations such as erythema toxicum neonatorum or naevus simplex to extremely severe, rapidly progressing purpura fulminans with a lethal outcome. A considerable proportion (67%) of the disorders that were seen was the results of the immaturity of the skin and various iatrogenic complications, these factors obviously being strictly intercorrelated. Later, we present these skin injuries and disorders in detail.

A compromised epidermal barrier function results in an increased susceptibility to severe, invasive infections, high rates of TEWL, thermal instability and an electrolyte imbalance, the 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.

A 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 naevus simplex, infantile haemangioma, or haemangioma 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, it should be emphasized 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.

The prevalence of birthmarks varies between races, and only limited data are available concerning birthmarks in preterm neonates. Enjoras and Mulliken concluded that preterm neonates are more prone than full-term neonates to present with vascular birthmarks, though other studies did not confirm this finding.³² We found the prevalence of salmon patch in the NICU to be 1.8% (4/211), which is much lower than previously reported in Caucasians.³² Haemangiomas were observed in 3.8%, and Mongolian spot in 0.5% of the cases. 5 infants (2.4%) were seen with erythema toxicum neonatorum, somewhat surprisingly, 4 of them were premature, the prevalence having been found earlier to be lower in preterm neonates.^{22,33,34}

5.1.1 Lesions requiring wound management

Most of the skin disorders that occur in NICUs develop as a consequence of the immaturity and vulnerability of the neonatal skin. Despite the novel techniques utilized in neonatal care leading to a significant reduction in neonatal mortality, especially in premature infants, the various diagnostic and therapeutic procedures may also be conducive to iatrogenic damage, skin traumas and wounds.^{27, 28, 35-39} This is the first assessment of the aetiology and frequency of iatrogenic skin injuries and lesions that needed wound management in preterm and term neonates during a relatively long study period.

32 of the 211 infants (17%) admitted to the NICU needed special therapy for at least 1 wound, but 3 of the 32 neonates suffered 2 wounds during hospitalization, i.e. a total of 35 wounds were detected and treated during the first year of the study.

The most common acquired wound types in NICUs have been demonstrated to involve ES, as a consequence of the removal of adhesive tapes and dressings used to secure life support and monitoring devices, EIs, surgical wounds, thermal and chemical burn injuries, DD and PUs.^{11, 35, 40-42} Data on the overall prevalence of these disorders in hospitalized neonates are lacking. In a prevalence study, Noonan et al. observed that 43% of the infants and children

admitted had a wound and/or surgical incision, but most of the wounds needed only nursing observations.⁴³ In contrast, our study indicated 32 cases among 211 neonates (17 %; 17 male, 53.1 %; 15 female, 46.9 %) in the NICU, i.e. a prevalence of 170 per 1000 infants hospitalized.

Most skin injuries observed in our NICU proved to be erosions or superficial ulcers, and healed in a short time without any complications or sequelae following the use of local epithelizing ointments or non-adhesive silicone, foam or hydrogel dressings. Fortunately, we did not detect any worsening in wound healing, even in the more severe cases. Besides the use of modern wound dressings suitable for wound stages, the good efficacy of wound healing in neonates is also a factor contributing to a good prognosis. Naturally, the relatively small number of neonates involved is a limitation of our study.²⁴

In the following part of the thesis, the most common wound types of preterm infants will be characterized.

5.1.1.1 Diaper dermatitis

DD is one of the most common dermatological conditions in infants and children, with a prevalence of 14-42 %.⁴³ The prevalence has decreased significantly following the use of disposable diapers with a high hygroscopic capability. We found skin breakdown caused in the gluteal region by urinal or faecal irritation to be the most common skin lesions in our NICU (25/460, 5.43 %).

The symptoms typically occur in the gluteal, perianal and genital regions, but in extensive cases the upper part of the thighs and the lower abdomen are also affected. **(Figure 14. A-B.)** Excoriation of the diaper area may be caused by various factors. Wet skin, occlusion, an elevated skin pH, exposure to urine and faeces and the secondary activation of faecal enzymes all break down the stratum corneum, making the skin vulnerable to the colonization of pathogenic microorganisms, especially *Candida albicans*.^{5, 44}



Figure 14. A: *Severe extensive erosive DD in a neonate born with myelomeningocele and faecal incontinence.*



Figure 14. B. *Erosive DD in a preterm neonate.*

The prevention of DD includes maintenance of a dry skin surface, with frequent (every 4-6 hours) diaper changes to minimize the exposure to faeces and urine, and occasional ventilation of the affected areas is also advised, even in the incubators. Cleansing of the region and the removal of the remaining faeces or diaper creams are highly important, but

should be careful and gentle so as not to cause further skin injuries. Lukewarm tap water should be utilized. Wipes are not recommended because they contain unnecessary chemicals. After cleansing, the region should be dried carefully, and the use of zinc oxide paste, hydrocolloid paste or diaper creams then provides a good barrier on the skin. Mild corticosteroids can be applied if inflammation is significant. Fungal and bacterial superinfections can be resolved with local antifungal (clotrimazole, ketoconazole, nystatin or miconazole) or antibacterial products (mupirocin or bacitracin).^{4, 5, 12-14, 41, 45}

It is also relevant to protect skin folds, e.g. the inguinal, axillary or cervical regions, which are prone to maceration and erosion. Barrier film products may be used, such as Cavilon 3M spray, an acrylate copolymer and siloxane-containing fluid, that dry easily, are not sticky, do not contain alcohol and provide a colourless, transparent barrier film on the skin with good moisture vapour permeability.^{13, 21, 22, 24, 46, 47}

5.1.1.2. Epidermal stripping

ES is often encountered when the epidermis separates partly or completely from the dermis, following removal of the fixation of intravenous lines, catheters, blowpipes, tubes, electrodes, pulse oxymeters or urine-collecting bags.^{4, 5, 13, 14} (**Figure 15.**) The background of the phenomenon involves the significant immaturity of the dermoepidermal junction: the connection between the epidermis and dermis is weaker than the connection between the plaster and the epidermis.

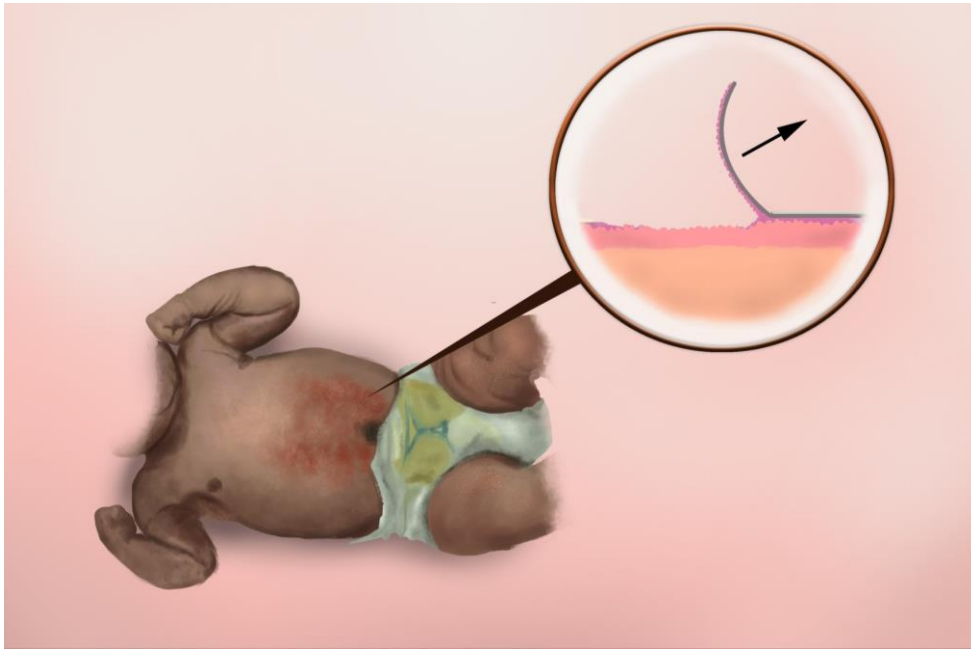


Figure 15. *Mechanism of the development of ES: the epidermis separates partly or completely from the dermis as a consequence of the removal of adhesive tapes and dressings used to secure life support and monitoring devices*

ES has been reported to be the most common cause of skin breakdown in hospitalized neonates⁴⁸, and especially in neonates born before a gestational age of 27 weeks.¹⁴ However, the prevalence data on ES in paediatric care are somewhat controversial, varying from 8% to 17%.⁴³ In our NICU, 11 of 460 infants (2.4 %) suffered ES. The most common localizations for the development are the wrist, foot, umbilicus and the angle of the mouth, i.e. the common sites for cannulae and tubes in neonates. **(Figure 16-17.)**

For the prevention of ES, the use of adhesive tapes should be minimized, preference being given to non-bonding skin dressings of appropriate quality, such as silicone dressings, film dressings, hydrogels and hydrocolloids. Moreover, adhesives should be removed slowly and carefully, after at least 24 hours of use, with a warm water-soaked cotton ball or with emollient products in a horizontal plane.^{4,5,13,14,41,43,49,50} The use of alcohol or organic solvents is absolutely contraindicated, as it is well known that these products can cause chemical burn injuries on the skin; furthermore, the toxic adverse events due to percutaneous absorption should be considered.^{21,22,24,47}



Figure 16. A-B. *ES developed as a result of the removal of adhesive tape*

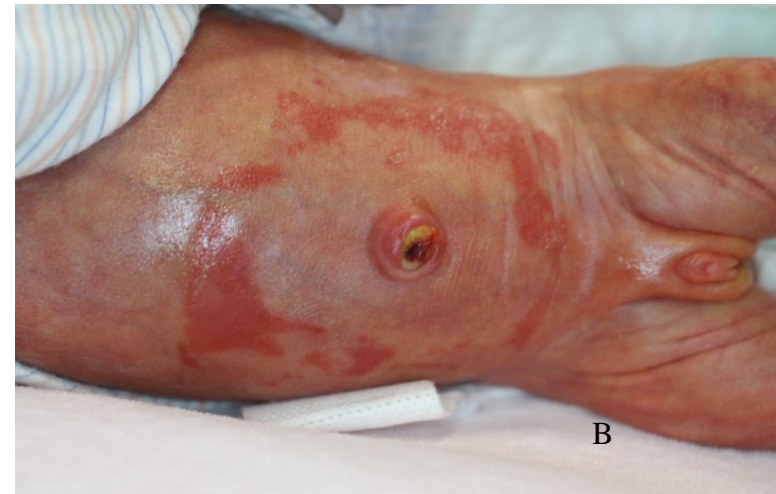


Figure 17. A-B.: *ES around the umbilicus as a result of tape removal in a premature twin pair. C-D.:* *After epithelizing local treatment*

5.1.1.3. Extravasation injuries

EIs develop as a result of the leakage of iv administered drugs into the surrounding tissues, most often inotropes (dopamine, dobutamine or adrenaline) (**Figure 18.**), products used for parenteral nutrition and fluid replacement (dextrose in high concentrations, calcium, potassium, bicarbonate, aminoacids and lipids), and also certain particular medications (acyclovir or vancomycin). In preterm neonates, the walls of the veins are much more vulnerable and fragile, while iv lines are often required for long periods of time, and EIs may therefore occur in spite of the greatest care and circumspection.⁵¹ The degree of tissue damage depends on the physicochemical characteristics (composition, concentration, osmolality and pH) of the extravasated solutions; osmotic damage, ischaemia secondary to an impaired circulation, direct cellular toxicity, mechanical compression and secondary infections are responsible for the development of EIs at a cellular level. The extravasation of calcium gluconate can result in iatrogenic calcinosis cutis.⁵¹



Figure 18. *Necrotic ulcer on the left foot as a result of extravasation of aminoacid and lipid solution*

A survey of regional NICUs by Wilkins et al. indicated a prevalence of EIs that caused skin necrosis in 38 per 1000 neonates. Most injuries occurred in infants born at 26 weeks of

gestation or less.⁵² Similarly, we observed 8 EIs (1.7 %), 2 of which proved to be severe, and the other 6 only moderate. In 2 cases in the literature, the leakage of parenteral nutrition from a percutaneous long line was reported.¹⁰ We observed 1 case of the extravasation of dobutamine, and 1 patient with glucose- and 4 patients with lipid and amino acid infusion-induced EIs. **(Figure 19. A-B-C.)**

Since EIs occur so frequently in this special patient group, an effort to devise protocols promoting the early recognition and provision of such injuries can be observed on the part of NICUs. The most important objectives are the early recognition and continuous control of the position of intravenous lines, in which the use of transparent fixing dressings may assist.^{11, 15, 41, 42, 50, 53, 54}

There is no general agreement as to the best practice for the treatment of EIs in preterm infants. There have been various publications on the successful management of EIs, which can be divided into operative and non-operative groups⁵¹, or expectant, topical care and extravasant removal types⁵⁴. Observation alone until the total area involved is demarcated can be an option, and this is the most common practice in injuries without any obvious skin damage (expectant treatment). A number of different topical agents have been applied with good results, including antiseptic creams with silver sulfadiazine, with or without 0.2 % chlorhexidine, nitroglycerine or enzymatic debridement with an ointment containing fibrinolysin and deoxyribonuclease⁵⁴. In a report from Korea, a combination of antibacterial and herbal ointments was applied.⁵⁵ Additionally, film dressings, hydrocolloids and hydrogels can be used in occlusive dressings, and hydrogels even in a sterile polythene bag.^{13, 52} Operative solutions involve removal of the extravasant by saline flushing, liposuction or skin puncturing and saline infiltration either alone or in some areas combined with hyaluronidase.^{52, 54} In cases of vasoconstrictor drug extravasation, infiltration of the skin with phentolamine can be advised.⁵⁶

In conclusion, the most important suggestions laid down in the protocols include immediate line removal, elevation of the limb, a saline flush via small incisions/punctures around the extravasation site, the use of hyaluronidase, and the local application of phentolamine or nitroglycerine following the extravasation of inotropic agents.^{16, 21, 22, 24, 41, 42, 47, 49, 50}

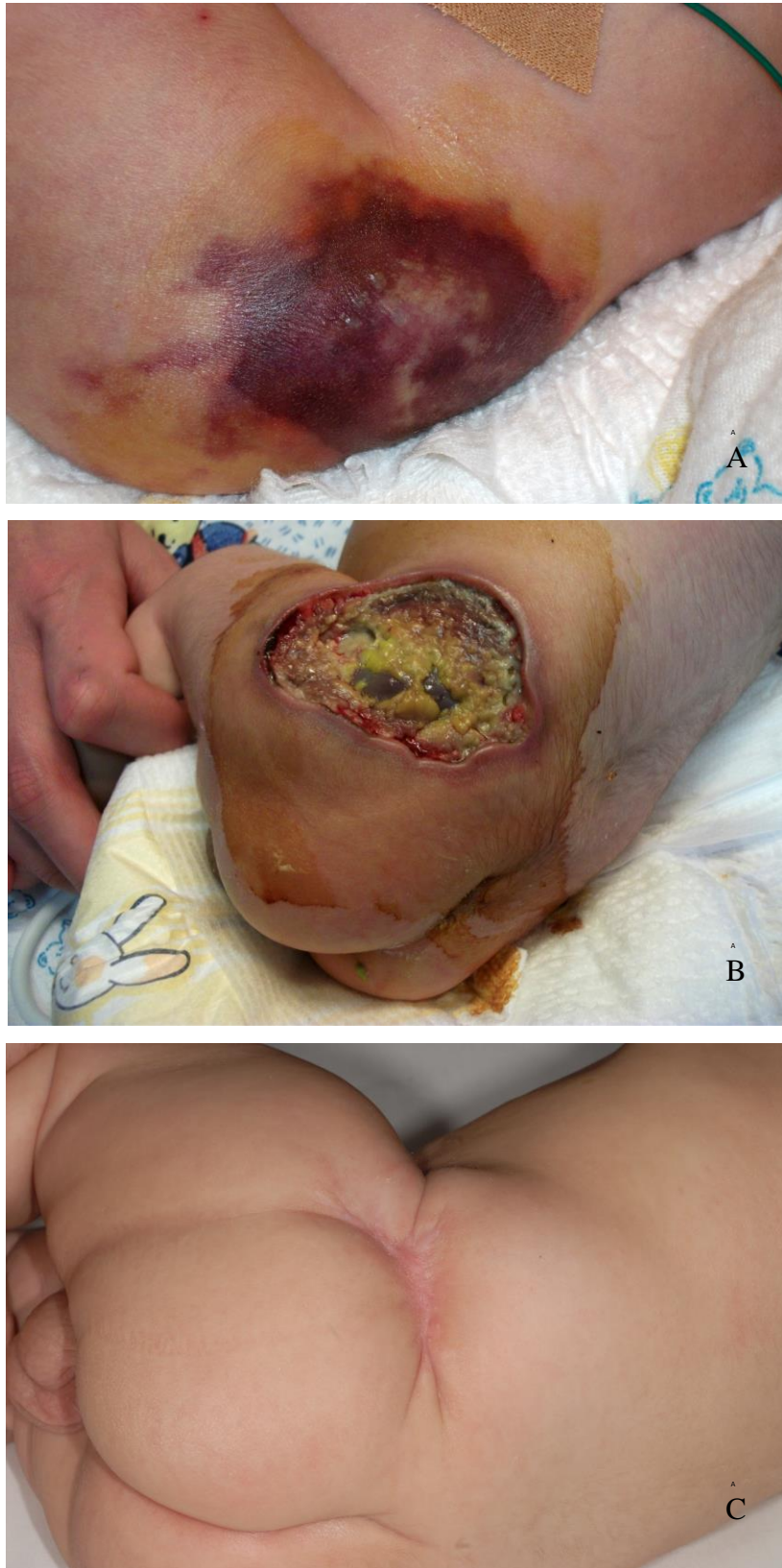


Figure 19. *A. EI in the left gluteal region in consequence of a dobutamine infusion. B. Deep wound after surgical necrectomy. C. After 72 days of treatment, a functionally non-disturbing scar on the left gluteal region.*

5.1.1.4. Pressure ulcers

PU's still present a problem in neonatal care: particularly sedated, paralysed or immobilized neonates are at high risk. Besides a low peripheral blood flow, as a consequence of the low amount of dermal collagen and elastic fibres, there is a high water content in the immature neonatal dermis. This oedema can reduce the blood flow, and increases the risk of ischaemic, pressure-related injuries.¹³ According to a Japanese study, neonates who are nursed in incubators are at a special risk of the development of PU's, because of the high temperature and humidity in incubators and specific intrinsic factors such as the size, physical shape and skin immaturity of premature infants.⁵⁷ The prevalence of PU's has been reported to be 27 % in paediatric intensive care units and 23 % in NICUs.⁴⁰ These wounds mostly occur in the occipital region or on the ear, nose or even the knees if the neonate is nursed prone, but medical devices can also cause PU's.³⁶ In a multisite prospective cohort study, Fujii et al. observed that the cumulative incidence rate of PU's in NICUs was 16 %. The most frequent site of pressure sores was the nose (50 %) (**Figure 20.**), the explanation of which was presumed to be that CPAP or nasal directional positive airway pressure was applied in most cases⁵⁷, these being risk factors for the development of nasal deformations and PU's.⁵⁸ Our 2-year survey revealed 9 patients (1.95 %) with PU's, 6 of which occurred in the occipital region (**Figure 21. A-B.**), and all 9 in critically ill neonates. Despite the frequent use of monitoring or therapeutic devices, we noted only three device-related PU's, obviously thanks to the good nursing care.

To prevent PU's, patients should be repositioned and turned at least once every 2 hours, medical equipment (cuffs, nasal CPAP equipment, the fixations of endotracheal tubes, the tubes themselves, catheters, cannulae and pulse oxymeters) should be checked and replaced frequently, and the use of special weight-relieving gel pillows and foam mattresses for infants is recommended. Even if these rules are carefully observed, skin damage can easily develop in very preterm and unstable infants.^{14, 21, 22, 24, 41, 47, 49}



Figure 20. A PU on the nose after artificial ventilation.

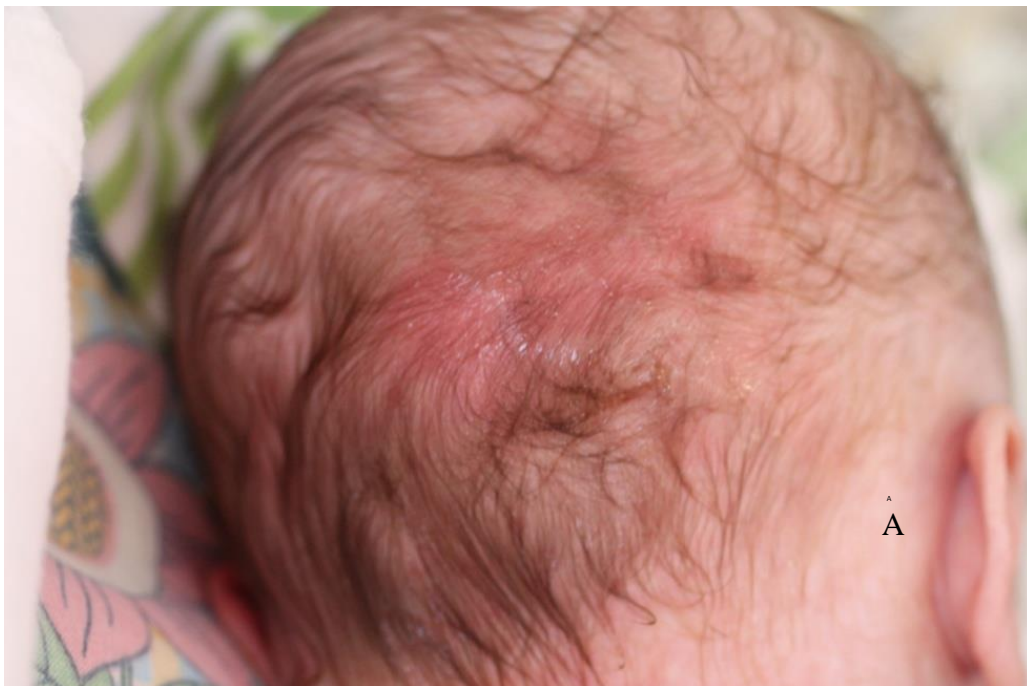


Figure 21. A: A stage I. PU in the occipital region.



Figure 21. B: *Stage III. PUs with crusts in the occipital region.*

5.1.1.4. Burn injuries

Even the relatively low surface temperatures of devices (pulse oxymeters, phototherapy blankets, fluorescent bulbs without plexiglass shielding, infrared heating lamps, alcohol lamps, laryngoscopes, transillumination devices, various electrodes and warming bottles) applied during various diagnostic and therapeutic procedures may cause burn injuries in premature neonates.^{11, 59} **(Figure 22. A-B.)** Our survey detected 2 neonates with thermal burn injuries, caused by a pulse oxymeter. **(Figure 23.)** Close control during the application of heating lamps or monitoring devices is indispensable for averting thermal burns.⁴¹



Figure 22. *Burn injury on the right feet (A.) and on the left hand (B.) as a consequence of pulse oymeter use.*

Antiseptic solutions, including alcohol, or alcohol-based solutions of chlorhexidine gluconate or povidone-iodine, may cause chemical burns in premature infants. Skin disinfectants and antiseptics should be used only with strict adherence to the indications. Consideration must be given not only to their local toxic effects, but also to their systemic side-effects resulting from

absorption, and they may lead to the drying-out and irritation of the skin, or to further impairment of the barrier function. In connection with the use of antiseptics containing alcohol, haemorrhagic skin necrosis or (due to the increased absorption) alcohol intoxication can develop.^{50, 60} Through the use of aqueous skin preparations and disinfectant products, and the rinsing of alcohol-based ones with saline water immediately after use, chemical burns can be prevented.^{21, 22, 24, 47}



Figure 23. *Thermal burn injury on the right feet as a consequence of pulse oximeter use*

5.1.1.5. Surgical interventions and wounds

Surgical interventions frequently become necessary in neonates treated in NICUs. Most of the developmental disorders which may be diagnosed in foetal life (diaphragmatic hernia, oesophageal, duodenal, anus atresia, myelomeningocele, ectopic urinary bladder, and heart developmental disorders) require surgical interventions after birth. However, disorders that need invasive interventions or even operations (pneumothorax, haemothorax or necrotizing colitis) can also develop in the postnatal period.

Surgical wounds develop mostly after suture opening as a result of infection or mechanical stretches. **(Figure 24. A-B.)** To prevent surgical wounds, sutures should be observed carefully for signs and symptoms of infection by applying transparent dressings.^{23,41,50}



Figure 24. **A.** *Necrotic, superinfected, exuding ulcer with inflamed surroundings that developed in the lumbosacral region after closing surgery for myelomeningocele.* **B.** *After 72 days of treatment: an epithelized wound with a residual scar 1 cm in diameter.*

5.2. Characteristics of wound care in neonates

With the increase in the survival rate of premature neonates in recent years, the skin care and wound management in this special patient group pose an ever greater challenge to practitioners. Skin and wound complications remain a significant source of morbidity and mortality in these vulnerable infants.

The principles of wound care management are relatively new, and are not known widely. Due to the researches and studies performed in the last two decades, moist wound healing principles have become the main evidence-based treatment modality. Numerous types of modern dressings have been introduced. These modern dressings have many advantages, such as decreased tissue damage and the lower possibility of infections and pain accompanying dressing changes. Furthermore, they provoke the removal of discharge, tissue regeneration and epithelization, and reduce the hospitalization time, which is essential for the normal psychosocial development of neonates. The clinical practice of wound care in adults cannot be applied directly to neonates in view of the anatomical and physiological differences of their skin^{10, 11, 50}

Wound management usually starts with a precise description and documentation of the wound, including the aetiology, the type (acute or chronic) and the exact localization of the wound, the wound dimensions (width, length and depth) in centimetres, the nature of the wound bed, the status of the surrounding skin, the exudate characteristics (the amount, colour, consistency and odour), and the presence or not of infection. In cases of special wound types, the stage of the wound should be determined on the basis of various staging guidelines, such as the NPUAP guidelines for the staging of PUs.⁴³

Wound cleansing should be gentle, with sterile saline irrigation alone or following the use of antiseptic solution. Disinfectants and antiseptic products can be used only in the case of the strict observation of indications. Extensive and unjustified use of these products is not only unnecessary, but can also result in several adverse events. Besides the local toxic effects, the systemic complications should be taken into consideration in consequence of the possibility of their absorption, or they may even cause dryness and irritation of the skin, or impairment of the barrier function. 10 % povidone-iodine, Prontosan solution (polyhexanide) and Octenisept solution (0.1 % octenidine dihydrochloride + 2.0 % phenoxyethanol) are currently available as potentially good solutions in wound and skin disinfection. It should be emphasized that antiseptic agents should be thoroughly washed off with sterile, lukewarm saline solution or distilled water after the necessary action time. After the topical use of povidone-iodine, an

increase in the serum iodine level and the development of hypothyroidism and transient hypothyroxinaemia have been observed in neonates. Alcohol, hexachlorophene-containing products and hydrogen peroxide should be avoided. The guidelines recommend that 0.5-2 % chlorhexidine solution can be used most safely for skin disinfection with a broad spectrum of antiseptic effects against both Gram-negative and Gram-positive bacteria.^{4, 5, 14, 45, 49}

The surrounding skin should be protected with hydrophobic creams or non-alcohol liquid barrier films, such as Cavilon 3M, an acrylate copolymer and siloxane-containing fluid. The latter can also be successfully applied to prevent ES or DD as it provides a colourless, transparent barrier film on the skin with good moisture vapour permeability. Mechanical or chemical debridement or surgical necrectomy demands appropriate experience.²⁴ The steps of wound care in neonates are presented in **Figures 25 and 26**.

Dressings applied to neonates should protect the wound and its surroundings, should be easily applicable and removable, and should not need to be changed too frequently. If transparent dressings are used, the wound can readily be observed for inflammation and the nature and quantity of wound exudates.^{11, 50, 61} The literature recommends non-adhesive and non-interactive dressing products, such as hydrogels, soft silicone wound contact layers, hydrocolloids, foams, hydrofibres and semipermeable films for routine use. In the daily routine, modern, intelligent dressing products should be used in this special population, as we preferred. All of them meet the requirements of moist wound healing principles and also result in autolytic debridement. Silver-sulfadiazine creams, iodine or ionic silver-containing dressings, which are widely utilized in adults, should be avoided, especially in preterm neonates. When wounds are superinfected and odorous, extreme care must be taken regarding the systemic absorption of chemical agents used on wounds, and consequently their toxicity as concerns the increased circulation of the wound.^{50, 61} Dressing should be gently fixed with gauze or elastic conforming bandages, avoiding adhesive dressing.

The frequency of change of dressings should always be determined individually, depending on the wound type and base, the amount of wound exudates, signs of infection and the type of dressing. Swabs always have to be taken from wound exudates for microbiology, and parenteral antibiotics are commenced in accordance with the bacterial sensitivity if the laboratory findings or skin signs are indicative of systemic infection. Dressing changes should be performed under appropriate pain control.²³



Figure 25. **A:** After cleansing of the wound, the wound surroundings are protected with hydrophobic cream. **B:** Aquacell Ag hydrofibre dressing is placed on the cleaned wound base. **C:** A sterile covering with gauze and dressing fixation.

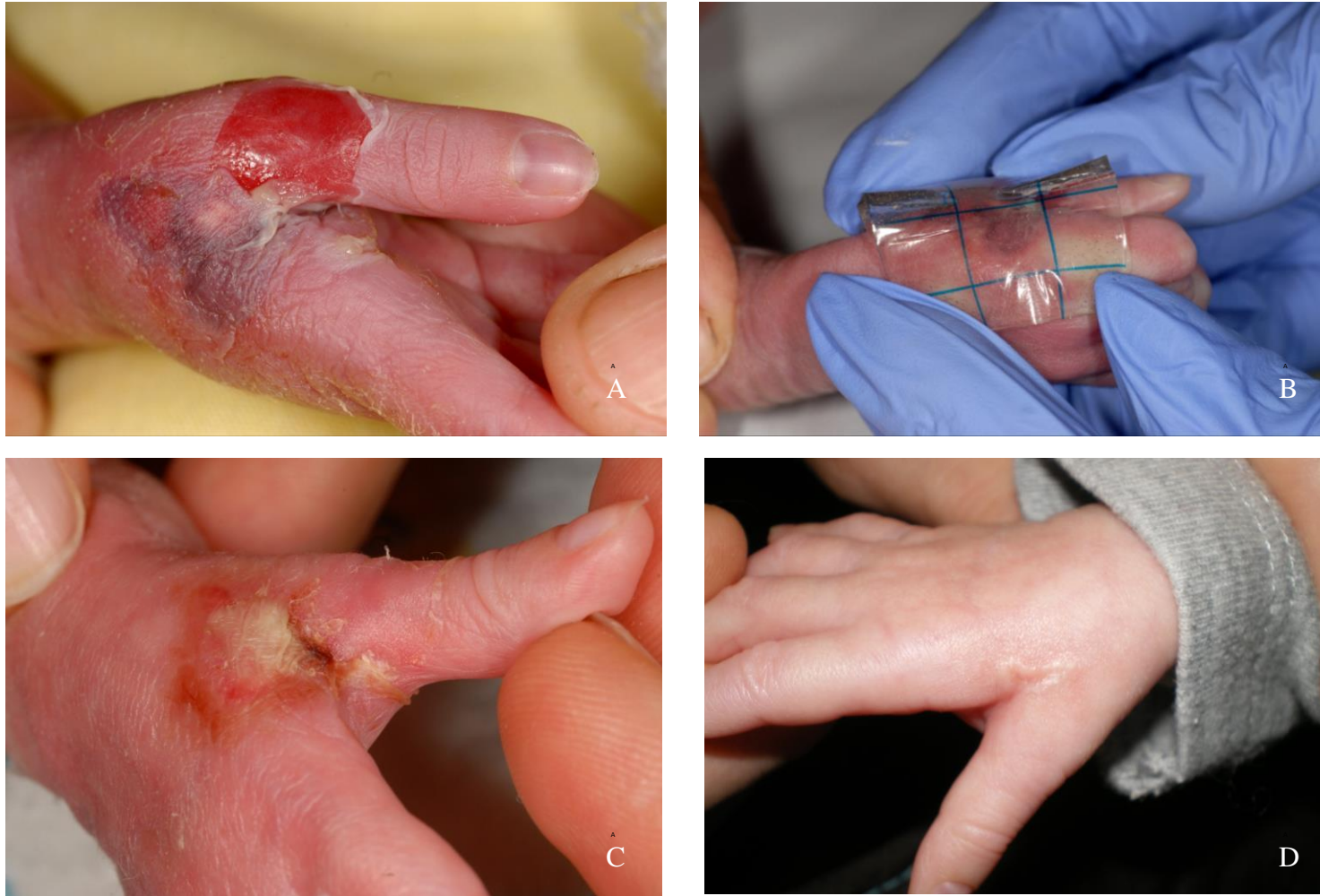


Figure 26. **A:** *Haematoma and erosion in the right foveola radialis.* **B:** *A hydrogel dressing is placed on the wound.* **C:** *A yellowish discharge on the wound base.* **D:** *A small, non-disturbing scar remains.*

5.4. Iatrogenic skin injuries

The impressive improvement of neonatal care during recent decades has led to a significant improvement in the survival of very low birth weight infants.⁶²⁻⁶⁵ Neonatal intensive care is a relevant risk factor for the development of iatrogenic cutaneous injuries. An iatrogenic event may be defined as any event that occurs during hospitalization that compromises the safety of the patient, even if the patient is not harmed.^{28, 37-39}

The enhanced susceptibility to iatrogenic skin lesions in infants of very low birth weight or in a critical condition is multifactorial. Overall, it may be stated that all diagnostic or therapeutic interventions and manoeuvres can potentially promote iatrogenic skin injuries. The more premature and smaller a neonate, the more immature the organs and the more severe the developmental abnormalities, the higher the numbers of general problems, infections, essential interventions and procedures. Only a few literature data are available concerning the prevalence of iatrogenic events and iatrogenic skin injuries in this special patient population. There has been no literature survey of comprehensive investigations of dermatologic manifestations in preterms. Most review articles tend to summarize and describe the aetiology of the typical iatrogenic skin injuries in NICUs.^{27, 30, 38}

In an observational, prospective study, Ligi et al. assessed the incidence, nature, preventability and severity of iatrogenic events in a tertiary neonatal centre in France. 388 neonates were enrolled in the study, with a total of 10 436 patient-days. 267 iatrogenic events were recorded in 116 neonates, with an iatrogenic event incidence of 25.6 per 1000 patient-days. Cutaneous events were most common, with a prevalence of 24 % in the study population. An extremely low gestational age, a low birthweight, a longer length of hospital stay, a longer duration of respiratory support or conventional ventilation, and a longer duration of venous catheterization were all associated with a significantly higher prevalence of iatrogenic events³⁵. The retrospective, multicentre study by Srulovici et al. reported that the frequency of iatrogenic events was associated with a lower gestational age, exposure to mechanical ventilation, total parenteral nutrition and morbidities, including intraventricular haemorrhage, patent ductus arteriosus, RDS, infection, jaundice and bronchopulmonary dysplasia. Multivariate logistic regression analysis revealed that the length of hospital stay was significantly and independently associated with iatrogenic events.⁶⁶

A wide variety of medical procedures may be utilized during the routine care of neonates in the NICU, including heel prick blood sampling, endotracheal suction, iv cannula insertion,

peripheral venous blood sampling, intubation, venous long line insertion, peripheral arterial line insertion, umbilical catheter insertion, lumbar puncture and chest drain insertion.

In 100 consecutive children at 16-29 months of age, Cartlidge et al. investigated the prevalence of scars attributable to intensive therapeutic procedures performed during the neonatal period. Surprisingly, scars (needle marks, EIs, heelprick marks, adhesive tape damage, or lesions related to the application of central venous catheters or chest drains) were present in every child, and in 11 children these lesions were cosmetically or functionally significant. The number of lesions was inversely related to the child's gestational age and directly related to the length of intensive care received.⁶⁷

The patients with the lowest birth weight, who require complex interventions and substantial physiological support and invasive procedures, are more likely to undergo iatrogenic events. In the survey by Barker and Rutter, the pattern and frequency of invasive procedures were investigated in 54 consecutive infants admitted to a NICU. Over 3000 procedures were recorded; one infant (born in the 23rd gestational weeks, birth weight 560 g) underwent 488 procedures.⁶⁸

The most common iatrogenic skin injuries include thermal, chemical and ultraviolet burns, ES, EIs, heel prick injuries, PUs, and umbilical and peripheral arterial catheter-related injuries.⁴² ES develops most frequently as a consequence of the removal of adhesive tapes and dressings used to secure life support and monitoring devices such as cannulae, tubes, probes, catheters, electrodes and pulse oxymeters. **(Figure 27.)** All neonates treated or nourished via iv lines may suffer extravasation injuries. Low peripheral blood flow, long-standing immobilization, artificial ventilation and an insufficient calorie intake can all lead to an increased development of PUs. **(Figure 28. A-B.)** Moreover, heel prick injuries, the insertion of central lines, iv catheters, thoracic drains, umbilical, central or peripheral vein catheterization or arterial blood sampling may result in scarring or anetoderma of prematurity (monitoring devices may also induce pressure resulting in hypoxaemia). Multiple heel pricks can induce iatrogenic calcinosis cutis of the heels. Other procedures, such as resuscitation, can provoke the development of haematoma, suffusion or maceration, and the use of diaper wipes may result in contact dermatitis.



Figure 26. *ES developed as a consequence of the removal of adhesive tape used to secure intratracheal tube*



Figure 27. A. *PU developed as the consequence of nasal-CPAP cannule use*



Figure 27. B. *Stage III. PUs developed in the occipital region of the newborn infant*

In the course of our study, significant differences were found between the characteristics of the neonates with and without iatrogenic skin injuries. The gestational age of the neonates who suffered iatrogenic injuries was significantly lower, their birth weight was lower (limit of significance), and the length of their hospital stay proved to be significantly longer. Obviously, the gestational age, the birth weight and the length of hospital stay correlate strongly with each other; the more premature and smaller the neonate, the longer the care and the more complex the interventions required; the likelihood of injuries developing therefore increases. The parameters relating to the necessary therapeutic interventions and the frequent early complications during the intensive care can be used well for the purpose of characterizing the condition of the neonate. Neonates requiring INSURE usage, surfactant application, mechanical ventilation, umbilical arterial catheter insertion and circulatory support with inotropes significantly more frequently sustained iatrogenic skin injuries. Positive microbiological culturing results relevant in terms of the condition of the neonates were also found in significantly more cases in this patient group. Among the neonates with intracranial or pulmonary haemorrhage, PDA and BPD iatrogenic injuries were likewise higher. Severe congenital disorders and accompanying diseases, complications and infections necessitate further diagnostic and therapeutic interventions, resulting in a further increase in the chance of various skin injuries developing.

A significant proportion of the iatrogenic injuries that occur in NICUs results from skin injuries. A majority of these complications are of a minor character, but in severe cases the functional impairment of the epidermal barrier may result in important physiological consequences and induce significant pain in these fragile and vulnerable premature infants and may lead to prolonged hospitalization. Intensive, prospective surveillance methods are demanded with a heightened awareness of iatrogenesis. Every effort should be made to achieve the prevention or at least the early recognition of iatrogenesis and to devise and adhere to the skin care and wound management guidelines in the NICU with meticulous care. 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.²¹

5. 5. Prevention of iatrogenic skin injuries

The treatment of dermatological disorders emerging during hospital care of preterm or severely ill neonates is particularly challenging, and skin care and wound management in neonates are also complicated. Most of the injuries suffered by neonates are iatrogenic, and a recent study concluded that the majority (83 %) of such iatrogenic events are preventable.^{30, 40} The first step in the prevention is the investigation and precise knowledge of the types, causative factors and prevalence rate of skin injuries that occur in NICUs. It can be seen that the prevention and treatment of each type of skin injury are very complex problems.

The introduction of the new generation of minimally or non-adhesive dressings led to a significant reduction in the development of ES, while the use of transparent film dressings facilitates regular observation of the iv cannula site^{9, 11, 27, 48} Superficial erosions, the early stage of PUs are relatively easy to manage, partly because of the excellent regeneration and repairing ability of the neonatal skin. The treatment of stage III-IV PUs, EIs 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 aesthetic damage.

Regular examination of the skin, the largest organ, can be easily performed without medical devices. Thorough skin care, cleansing of the skin, use of emollient agents, care of the umbilical cord stump and the diaper-covered gluteal and genital regions are all significant parts of the daily routine and thus of the prevention of skin injuries.

It is important to emphasize the roles of preventive skin care and the adequate treatment of dermatological conditions during neonatal intensive care, since the integrity of the skin is essential for the stabilization of severely ill or preterm neonates. To maintain skin integrity, at least daily skin assessment is advised, using valid and objective score systems.^{48,49}

The introduction and application of modern, standardized skin care management strategies can result in a significant improvement 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. Maintenance of well-defined, evidence-based, optimized neonatal skin care clinical guideline for the NICU continues to demand the collaboration of well-trained neonatologists, dermatologists and pharmacists, and it is important to take into consideration the regional characteristics of the neonatal intensive care.^{21,22,24,47}

6. Summary

The survival rate of premature infants has recently increased significantly as a consequence of the advances made in neonatological care. In Hungary, as elsewhere worldwide, a large proportion of neonates need intensive care for various durations in their initial extrauterine life. Not only does the immaturity of the lungs or other internal organs pose a significant problem during neonatal intensive care; the immaturity of the skin also results in a number of clinical consequences, including a high epidermal water loss, which may lead to a fluid and electrolyte imbalance, instability of the core temperature and a high potential for evaporative heat loss. These clinical complications are relevant determinants of high morbidity and mortality for preterm infants in the NICU.

The management of dermatological disorders frequently comprises a great challenge to practitioners during neonatal care. The immaturity of the neonatal skin is a significant risk factor in terms of the development of iatrogenic injuries, while impairment of the skin barrier may result in such important physiological consequences as detailed above. The anatomical and functional characteristics appreciably increase the possibility of the development of skin injuries and wounds, and also significantly influence the wound healing processes in premature and severely ill term neonates. Skin injuries can induce appreciable pain; their treatment requires further interventions and prolongs the length of hospitalization, and in serious cases, permanent aesthetic and functional complications may occur. The prevention of

iatrogenic skin injuries, the careful consideration of risk factors, and the creation of protocols ensuring efficient treatment are therefore indispensable for a further increase in the standard of neonatal intensive care.

Complete neonatal skin care protocols should include recommendations relating to a 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 ES, PUs, EIs, surgical wounds and chemical or thermal burn injuries⁴⁸. The treatment of dermatological disorders emerging during the hospital care of preterm or severely ill neonates 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.

7. Declaration

All clinical pictures originate from our own clinical photo database. Photos were taken with the written permission of the parents or the legal representatives.

Figure 1 and Figure 15 were made by Dr. Zoltán Tóbiás.

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