The impact of changes in neonatal intensive care practices on short-term outcomes of premature infants

Hrgetić Vitols, Anna Mara

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Anna Mara Hrgetić Vitols

THE IMPACT OF CHANGES IN NEONATAL INTENSIVE CARE PRACTICES ON SHORT TERM OUTCOMES OF PREMATURE INFANTS

GRADUATE THESIS

Zagreb, 2018.

This graduate thesis was made at the Department of Neonatology and Neonatal Intensive Medicine in the University Hospital Centre Zagreb mentored by Assistant Professor Ruža Grizelj, MD PhD and was submitted for evaluation in the academic year 2017/2018.

Abbreviations

BPD = Bronchopulmonary Dysplasia

CPAP = Continuous Positive Airway Pressure

CGA = Corrected Gestational Age

GA = Gestational Age

ICH = Intracranial Hemorrhage

MV = Mechanical Ventilation

nCPAP = nasal Continuous Positive Airway Pressure

NEC = Necrotizing Enterocolitis

NICU = Neonatal Intensive Care Unit

PMA = Postmenstrual Age

ROP = Retinopathy of Prematurity

UHC = University Hospital Centre

VLBW= Very Low Birth Weight

Table of Contents

Summary

Title: "The impact of changes in neonatal intensive care practices on short-term outcomes of premature infants"

Author: Anna Mara Hrgetić Vitols

Objective: To assess the changes in neonatal care practices at the NICU-UHC Zagreb and their impact on short-term morbidity of a cohort of premature infants. A comparison between two epochs was performed, the periods before and after changes in respiratory support, healthcare professionals' attitudes and practices in supporting and promoting the breastfeeding, and laboratory phlebotomy reduction was introduced. ***Methods:*** We performed a retrospective study to investigate short-term morbidity of infants born at GA ≤32 weeks and/or BW ≤1500 g and transferred to UHC Zagreb from local Zagreb hospitals or remote areas in Croatia in the first week of life in the years 2013 and 2017. Continuous data was represented as mean ± SD, or median (minimum-maximum) values for continuous variables, and frequency percentages for categorical variables. Characteristics were compared between groups using the 2- sample *t*-test, Chi square test, or Fisher's exact test. In all cases 2-tailed *P* values <0.05 were considered statistically significant. ***Results:*** The use of nCPAP as primary respiratory support increased from 25% to 72% ($P<0.001$) and surfactant use decreased from 69% to 33% ($P=0.002$) between the two time periods. The overall incidence of comorbidities was lower in 2017; rate of severe BPD (3 *v.* 42%, $P<0.001$), severe ROP (0% *v.* 14%, $P=0.025$), IVH ≥ 3 (11% *v.* 33%, $P=0.023$). The median duration of invasive MV was reduced from 31 days in 2013 to 6 days in 2017 ($P<0.001$), as well as LOS from 74 days in 2013 to 57 days in 2017 ($P=0.001$). Amount of phlebotomy blood loss and total number of PRBC transfusions were markedly reduced (from 1128 ml to 564 ml; $P=0.004$, and form 92 to 36; $P=0.009$, respectively). Incidence of surgical NEC, time to reach full enteral feed, and breastfeeding on discharge remained unchanged. ***Conclusion:*** Changes in care protocols at the hospital since 2013 have improved the outcome of premature neonates. There was a marked improvement in most of the morbidity of very low birth weight infants over time, most likely due to provision of nCPAP as primary respiratory support. Usage of nCPAP as primary ventilation support and better policies on blood diagnostic procedures have lowered the incidence of comorbidities and decreased hospital stays.

Key words: very low birth weight infants, respiratory support, red blood cell transfusion, bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity

Sažetak

Naslov: "Utjecaj promjene prakse intenzivnog liječenja na kratkoročne ishode nedonoščadi"
Autor: Anna Mara Hrgetić Vitols

Cilj: Ispitati utjecaj promjene prakse intenzivnog liječenja u Zavodu za neonatologiju i neonatalnu intenzivnu medicinu KBC-a Zagreb na kratkoročni morbiditet (do otpusta iz bolnice) kohorte nedonoščadi. Usporedili smo ishode nedonoščadi u periodu prije i poslije promjene načina provođenja respiratorne potpore, stavova zdravstvenih radnika i prakse u podupiranju i promicanju dojenja te smanjenja jatrogenog gubitka krvi. ***Metode:*** provedena je retrospektivna analiza kratkoročnih ishoda nedonoščadi GD ≤32 tjedana i/ili RM ≤1500 g koja su premještena u KBC Zagreb iz lokalnih zagrebačkih bolnica ili udaljenih područja Hrvatske u prvom tjednu života tijekom 2013. i 2017. god. Kontinuirane varijable prikazane su kao aritmetička sredina i standardna devijacija ili medijan (najmanja-najveća vrijednost), a kategorijske varijable kao postotak. Za usporedbu karakteristika bolesnika u dva perioda korišten je *t*-test na temelju dvaju uzoraka, X^2-test a po potrebi i Fisherov egzaktni test. U svim slučajevima *P* vrijednosti <0.05 smatrale su se statistički značajnima. ***Rezultati:*** Primjena nCPAP-a kao primarne respiratorne potpore porasla je s 25% tijekom 2013. god. na 72% u 2017. god. (*P*<0.001) uz istodobno smanjenje supstitucije surfaktanta s 69% na 33% (*P*=0.002) . Incidencija komorbiditeta je bila manja u 2017. god. nego u 2013. god.; stopa teških oblika BPD-a (3 *v.* 42%, *P*<0.001), teškog ROP-a (0% *v.* 14%, *P*=0.025), IVH ≥ 3 (11% *v.* 33%, *P*=0.023). Trajanje mehaničke ventilacije je skraćeno s 31 dan u 2013. god. na 6 dana u 2017. god. (*P*<0.001), kao i duljina hospitalizacije (sa 74 na 57 dana; *P*=0.001). Značajno je smanjena i količina gubitaka krvi zbog laboratorijskog uzorkovanja (od 1128 ml u 2013. god. na 564 ml u 2017. god.; *P*=0.004) te ukupan broj primijenjenih transfuzija koncentrata eritrocita (s 92 na 36; *P*=0.009). Incidencija NEK-a koji je zahtijevao kiruršku intervenciju, vrijeme do uspostave potpunog enteralnog unosa i učestalost dojenja se nisu značajno mijenjali. ***Zaključak:*** Promjene prakse poboljšale su ishode liječene nedonoščadi tijekom vremena, što se ogleda u značajno manjem pobolijevanju u gotovo svim morbiditetnim kategorijama. Primjena nCPAP-a kao primarne respiratorne potpore i bolja kontrola gubitaka krvi zbog laboratorijskog uzorkovanja smanjile su incidenciju komorbiditeta i skratile vrijeme liječenja.

Ključne riječi: nedonoščad vrlo male rodne mase, respiratorna potpora, transfuzija eritrocita, bronhopulmonalna displazija, intraventrikularno krvarenje, retinopatija nedonoščadi.

1. Preface

Infants born very preterm (<32 weeks' gestation) and very low birth weight (birth weight <1500 g) are at an increased risk of mortality and multiple morbidities (1). In high-income countries, complications resulting from preterm birth are the leading cause of mortality in children younger than 5 (2). Globally, over a million of those prematurely born will die, either as a direct result of their prematurity or because preterm birth places them at higher risk of developing severe complications like intracranial haemorrhage or sepsis (3). Many of those surviving will face long-term disability throughout their lives caused by complications of premature birth such as bronchopulmonary dysplasia, learning difficulties and cerebral palsy (3).

Since mortality and the degree of disabilities can be decreased, practices in the neonatology field are always advancing and improving. From prenatal administration of steroids to incubators to maintain body temperature, neonatologists are always trying to develop new ways to prevent comorbidities that could develop in a premature newborn and improve life quality, a trend that represents itself with increasing survival rates of premature newborns (4–6).

In this scientific paper I will analyse these changes and advancements in the Neonatal intensive care unit (NICU) at University Hospital Centre Zagreb and discuss their impact on the outcome of prematurely born infants, with the aim to show if they have improved the outcome, not only by decreasing comorbidities but also by shortening the patient's stay at the NICU.

1.1. The premature infant

A normal pregnancy usually lasts around 40 weeks. This period, however, is sometimes shortened due complications that put the life of the fetus, the mother, or both of them at risk. If an infant is born before the 37th gestational week, they are considered a premature neonate. The degree of their prematurity depends on their gestational age (GA), which can be calculated from the mother's first day of their last menstruation, or with the help of ultrasound imaging (7,8). Depending on the GA, they can be classified as extremely preterm (born earlier than 28 weeks), very preterm (born after 28 weeks but before 32 weeks) and late preterm (born after 32 weeks but before 37 weeks) (3,7).

Prematurity can also be defined by the infant's birth weight (BW), which may classify them as low birth weight (LBW) if their BW is less than 2500 g, very low birth weight (VLBW) if their BW is less than 1500 g, and extremely low birth weight (ELBW) if their BW is less than 1000 g (7).

Morbidity and mortality depends greatly on GA and BW and are inversely proportional to them; the lower the GA and BW, the higher the morbidity and mortality are (7,9).

1.2. **Short-term complications**

Short-term complications are comorbidities that arise during the neonatal period of an premature infant and typically occur during their stay at the NICU. They pose an increased risk for mortality and contribute to the development of lifelong disabilities (10). The most frequent short-term complications are mentioned below.

1.2.1. **Bronchopulmonary Dysplasia**

Bronchopulmonary Dysplasia (BPD) is a chronic lung disease characterised by lung inflammation, abnormal lung growth, and abnormal development of the alveoli and pulmonary vasculature in premature infants. The ethology is multifactorial, combining several risk factors including lung immaturity, prolonged use of assisted ventilation and high oxygen concentrations (oxidative stress), and inflammation (11). Clinically, the disease will manifest by chronic dependance on respiratory devices, increased need for oxygen at 36 weeks' postmenstrual age (PMA) and radiographic changes of the lungs (8,12–14). The reported incidence of BPD varies broadly, but the National Institute of Child Health and Human Development (NICHD) Neonatal Network reports that BPD is diagnosed at the time of discharge from the NICU in 25% to 35% of VLBW infants; with infants born at 22 to 26 weeks at higher risk (15). Discrepancy in the literature regarding the incidence of BPD might be related to the definition of the disease, the different protocols for the use of oxygen at 36 weeks PMA, to variations in the use of postnatal steroids, and to a plateau in survival that may have been reached among extremely preterm infants. Although clear diagnostic criteria have yet to be determined, BPD is currently defined as the oxygen dependency for longer than 28 days with further assessment of the severity based on the oxygen concentration and degree of support needed at 36 weeks PMA or discharge home, whichever comes first (Table 1) (16).

Diminishing the time on mechanical ventilation (MV) and early introduction of nasal continuous positive airway pressure (nCPAP) has decreased the severity of BPD and increased survival. However, it is still a major comorbidity in premature infants since it increases the likelihood of long-term impairment of pulmonary function, persisting into adolescence and early adulthood (12,15,17,18). Furthermore, BPD is an independent risk factor for adverse neurodevelopmental outcome. Premature infants with BPD have lower head circumferences, moderate to severe cerebral paralysis, and reduced cognitive and language scores compared to those without BPD (19).

Table 1. Definition of Bronchopulmonary Dysplasia from the NICHD Workshop on BPD

Gestational Age	**<32 weeks**	**≥32 weeks**

Time point of assessment	36 weeks' PMA or discharge to home, whichever comes first	>28 days, but <56 days' postnatal age or discharge home, whichever comes first
	Treatment with oxygen >21% for at least 28 days **PLUS**	
Mild BPD	Breathing room air at 36 weeks' PMA or discharge, whichever comes first	Breathing room air by 56 days' postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 weeks' PMA or discharge, whichever comes first	Need for <30% oxygen at 56 days' postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen and/or PPV/nCPAP at 36 weeks' PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or PPV/nCPAP at 56 days' postnatal age or discharge, whichever comes first

Abbreviations: BPD, Bronchopulmonary dysplasia; nCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation; PMA, postmenstrual age.

1.2.2. **Intraventricular Hemorrhage**

Intraventricular hemorrhage (IVH) is one of the common serious complications of very preterm birth and an important cause of brain injury and subsequent neurodevelopmental impairment (8,20). In the Vermont-Oxford Network, 6.2% of infants with birth weights 500 to 1500 g had a serious (grade III of IV) IVH in 2000 to 2001 and in 2008 to 2009 (21).

The bleeding almost always starts from the fragile vessels located in the infant's germinal matrix. Hemorrhage may be restricted to the subependymal germinal matrix, but large hemorrhages are often followed by progressive ventricular enlargement and/or parenchymal hemorrhagic infarction in the adjacent periventricular white matter through the mechanism of obstruction to the terminal vein. The amount of blood lost may be large enough to result in hypotension, hypovolemia, and death (14,17,20).

According to Papile, IVH is classified by severity into four grades (Table 2) (17). IVH can be assessed with imaging technology like US and MRI (8,14,20).

Table 2. Papile Grading of Intraventricular Hemorrhage

Grade	Description
Grade I	Hemorrhage confined to the subependymal germinal matrix in the caudothalamic groove
Grade II	Hemorrhage in germinal matrix and a small amount within ventricular lumen, with the clot occupying less than 50% of the ventricular lumen and not distending the ventricular system
Grade III	Germinal matrix hemorrhage with a large amount of clot (>50% of ventricular lumen) distending the ventricular system
Grade IV	Germinal matrix and intraventricular hemorrhage in apparent continuity with hemorrhage into the periventricular white matter

Preventive methods have been studied. Antenatal corticosteroids before preterm delivery have shown a very consistent reduction in IVH, including severe IVH in many randomized trials (14,20). Other preventive measures include delayed cord clamping, allowing transfusion of blood from the placenta (22), and avoiding postnatal swings in intracranial pressure (14). Antenatal vitamin K has been investigated in seven randomized clinical trials, but a meta-analysis did not show a significant benefit (23).

Treatment is mostly supportive with the aim to maintain adequate blood perfusion (14,24) and current goal is early diagnosis through regular ultrasound screenings followed by immediate treatment (20).

In general, grade I and II hemorrhages carry good prognosis, but serious complications are associated with grade III and IV, respectively (17). Bleeding into the parenchyma can lead to the formation of cystic lesions called cystic periventricular leukomalacia (cPVL), which result in long-term disabilities, including neurologic deficits (14,25).

1.2.3. **Necrotizing Enterocolitis**

Necrotizing enterocolitis (NEC) is a devastating gastrointestinal disease that affects predominantly premature newborns. The prevalence of this disease is about 7% among infants born at less than 32 weeks' gestation with BW between 500 and 1500 g (26). It is characterized by ischemic intestinal necrosis and is considered a medical emergency and one of the major causes of mortality in the NICU. The mortality of NEC is 20% to 30%, with the greatest mortality among infants who require surgery (27). Little is known of the pathophysiology behind NEC, other than it is multifactorial. However, gut immaturity, aggressive initiation of enteral feeding (formula), decreased blood flow, and infections have all been identified as key players (8,17,28).

Feeding intolerance and abdominal distention are typical signs of NEC. In addition, clinical signs also include temperature instability, vomiting, bloody stool, diarrhea, and abdominal tenderness. Within hours after onset of initial symptoms, it can progress rapidly to necrosis of the intestines, intestinal perforation, peritonitis, septic shock, and death. Time of presentation depends on the degree of prematurity of the neonate, occurring sooner in less premature patients (8,17,28,29).

Diagnosis is made based on clinical signs and confirmed by plain abdominal radiograph, which illustrates air in the bowel. Furthermore, organisms may be cultured from blood samples in cases of septicemia (17,28,29). Treatments include stomach decompression by nasogastric suction, fluid replacement and switching from enteral feeding to parenteral nutrition until resolution of symptoms. The use of empirical antibiotics is also recommended to limit progression.

Finally, surgery is the treatment for infants with intestinal perforation or gangrene (17,30).

Many approaches have been proposed for the prevention of NEC. Gradual increase of trophic feeding (nonaggressive enteral feeding) as well as feeding maternal breast milk (31) have been proven to offer protection. Although several trials suggest that administration of probiotics may provide some degree of protection and decrease the incidence of NEC (17), it would be wise to exert caution in their use in preterm infants because probiotics have not been shown to decrease NEC-related mortality definitively and may increase the incidence of sepsis in infants with BW less than 750 g (32).

1.2.4. **Retinopathy of Prematurity**

Retinopathy of prematurity (ROP) refers to changes on the retina that can be found in the immature retina of preterm infants and it is strongly related to blindness, myopia and strabismus (33–35).

In the past, it was believed that ROP was merely associated with hyperoxia. Nowadays, it is thought that multiple causes, including assisted ventilation, intracranial hemorrhage (ICH), hyperglycemia, vitamin deficiencies among others, are involved in the pathogenesis since any of these processes can injure the developing vessels and cause an abnormal retinal vascularization (8,14,17,34).

Diagnosis and grading are done by looking directly at the retina with a lens or indirectly with an ophthalmoscope. Grading is done on stages that go from I to V and it depends on the development of vessels on specific zones and the damage this growth causes to the retina (8,14,29,36).

Prevention is encouraged by avoiding oscillations of blood pressure and oxygen saturation (14). Breast milk is considered to be a protective factor against ROP (35). Routine screening is the key for early detection and treatment and follow-up with an ophthalmologist is recommended until the abnormalities resolve. Possible treatment options available for advanced stages of the disease are laser photocoagulation, which is the prefered treatment, cryotherapy and anti-vascular endothelial growth factor (8,14,33).

1.3. **Common practices in the NICU**

Because preterm neonates are prone to numerous pathologies, some of them mentioned above, they need to receive different care protocols during their stay at the NICU. These practices are discussed below.

1.3.1. **Phlebotomy and Blood Transfusion.**

Phlebotomy is necessary to assess the neonate's development and wellbeing through different laboratory values. However, blood loss due to blood sampling is the most common cause of iatrogenic anemia and one of the most common causes of anemia of prematurity. Therefore, every instance of blood

drawing should be recorded and tighter control on blood sampling and testing should be imposed (8,14,37).

To treat anemia, newborns receive blood transfusions. However, recent publications show that transfusions might be more harmful than beneficial since frequent blood transfusions appear to increase the risk for comorbidities like BPD and NEC (38–40).

1.3.2. **Respiratory Support**

Respiratory care is considered one of the interventions that greatly improved the survival rate of premature neonates. Mechanical ventilation (MV) was first introduced to prevent neonates to go into cardiorespiratory failure. However, with the introduction of MV, pathologies like BPD started to appear. Nasal CPAP (nCPAP) was introduced as a non-invasive alternative to MV and allowed for continuous spontaneous respiration with a diminished need for intubation. Later, several trials proved that the use of nCPAP prophylactically or as a mode of primary ventilation lowered the need for intubation and decreased the incidence of BPD, even without treatment with surfactant (18,41–43).

2. **Hypothesis**

Preterm infants who are exposed to newer medical protocols will have less severe short-term comorbidities and better outcomes than preterm infants which were treated according to older protocols.

3. **Objective**

The aim of the study was to evaluate the impact of changes in neonatal intensive care practices on short term outcomes and length of hospital stay of VLBW infants admitted to the NICU of the University Hospital Centre (UHC) Zagreb in 2013, and to compare that data with data from 2017 at the same Unit.

4. **Material and Methods**

Ethical approval

The data was collected without identification. Due to the study design (non-interventional, retrospective cohort study) the written consent was waived.

Inclusion and exclusion criteria

This study retrospectively reviewed the medical records of all premature infants born at a PMA ≤32 weeks and/or a BW ≤1500 g who were subsequently admitted to the NICU of a tertiary medical center. The UHC Zagreb lacks a maternity ward, thus all neonates in this study are outborns, either transferred from local Zagreb hospitals or remote areas in Croatia.

We compared the outcomes of VLBW infants between 2 epochs, before and after the changes in neonatal intensive care practices. The first epoch encompassed the patients admitted between January 1, 2013 and December 31, 2013 and the second epoch

between January 1, 2017 and December 31, 2017.

Newborns with major congenital and chromosomal anomalies, hydrops fetalis, those admitted moribund or after the age of 7 days, newborns who died in the first week of life, as well as those transferred to other NICU's before the age of 7 days were excluded.

Data collection

Patient variables that were abstracted included demographic information (date of birth, sex, place of birth), birth information (delivery hospital, antenatal steroids, GA assessed by menstrual age, BW, Apgar scores), physiological variables obtained early during hospitalization (SNAP-II, SNAPPE-II, body temperature on admission), exogenous surfactant administration, initial respiratory support in the NICU, and duration of respiratory support. The amount of phlebotomy blood loss, the number of infants transfused and the number of transfusions per infant were retrieved for the period from the day of admission to the day of discharge from hospital. All infants were divided into 2 groups according to type of feeding they received at discharge: exclusively breast milk and mixed feeding (Group 1) or exclusively artificial formula (Group 2). Frequencies of each group were calculated. Intrauterine growth restriction (IUGR) was defined as a birth weight below 10th percentile for GA on Fenton's fetal growth charts. The percentiles were calculated on Ped(z), an online pediatric calculator using Fenton data (44). The SNAP-II and SNAPPE-II scores were obtained with the help of an online calculator developed by the French Society of Anesthesia and Resuscitation (45).

Patient care protocols

In UHC-NICU, routine MV mode was patient-triggered modality using a Babylog 8000+ (Drager, Lubeck, Germany) PSV+VG (pressure support ventilation + volume guarantee) and non invasive ventilation was performed with Infant Flow nCPAP (Care Fusion, USA) with nasal prongs or mask with an initial mean airway pressure value of 5-7 cmH_2O in both epochs.

Epoch I

Standard approach to neonates with RDS was tracheal intubation immediately upon admission with surfactant administration and ongoing (prolonged) MV. Neonates were extubated and switched to nCPAP-Biphasic mode when complete lung recovery was achieved according to ventilatory parameters (PIP<15 cmH_2O, FiO_2<30% with SpO_2 90-95%), and blood gas analysis (permitting hypercapnia ≤65 mmHg). In neonates intubated prior to admission in the NICU, MV was continued until the above-mentioned extubation criteria were met.

Laboratory tests were ordered as a matter of routine and there was no monitoring of the accumulative blood loss volume. Infants were fed mainly with bovine milk-based preterm formula.

Epoch II

Not intubated neonates with RDS were placed on nCPAP-Biphasic mode immediately

upon arrival. If the infant's FiO_2 requirement increased to >60% on non-invasive respiratory support to maintain an saturation of peripheral oxygen (SpO_2) at or above 88%, with signs that respiratory support with a ventilator will be needed (pCO_2 >65 mmHg) or hemodynamic instability defined as a blood pressure that was low for GA, poor perfusion, or both; early administration of surfactant followed by rapid extubation to nCPAP was preferable to prolonged ventilation. Neonates who were intubated prior to admission in the NICU, were switched to nCPAP as early as possible, depending on their respiratory condition and criteria mentioned above (pCO_2 <65 mmHg with a pH >7,2; SpO_2 >88% with an FiO_2 <50%, MAP <15 cm H_2O, hemodynamic stability). Criteria for reintubation were the same as those for initial intubation.

In order to prevent laboratory blood loss, we have implemented a policy of conservative blood management. Laboratory diagnostic tests were decided on a day-to-day basis rather than scheduled automatically, and careful monitoring of the cumulative volume of blood samples acquired from each patient was done.

In epoch II, process of family-centered care in NICU was started. Unrestricted parental presence in the NICU, parental involvement in infant caregiving, breastfeeding, and kangaroo care were promoted to enhance mother-infant bonding.

Outcomes

The main outcomes were the degree of severe morbidity among infants discharged alive. Severe neonatal morbidity comprised severe grades of NEC (assessed by surgery or peritoneal drainage), ROP (laser treatment, intravitreal bevacizumab), IVH (grades III or IV; classified according to Papile et al. (46)) or cPVL, and BPD (as defined by Jobe and Bancalari (16)). The secondary measured outcome was the LOS, and transfusion rates.

Statistical analysis

Data are presented using mean ± standard deviation (SD) or median (minimum-maximum) values for continuous variables, and frequency percentages for categorical variables. Characteristics were compared between groups using the 2- sample *t*-test, Chi square test, or Fisher's exact test. In all cases 2-tailed *P* values <0.05 were considered statistically significant.

5. Results

The basic data and clinical information of 120 VLBW infants admitted to a NICU in 2013 and 2017 were extracted from the hospital's database: 63 and 57 patients in 2013 and 2017, respectively. Forty eight patients were excluded (27 and 21 in first and second epoch, respectively) because they were either admitted after the 7th day of life (n=23), had fetal hydrops (n=1), congenital malformation or chromosomal anomalies (n=5), were transferred from NICU to other facility before the age of 7 days (n=2), or died in the first

week of life (n=17). Of the remaining 72 patients, 36 were treated in the first, and 36 in the second epoch (Figure 1). Characteristics of excluded infants are summarized in Table 3.

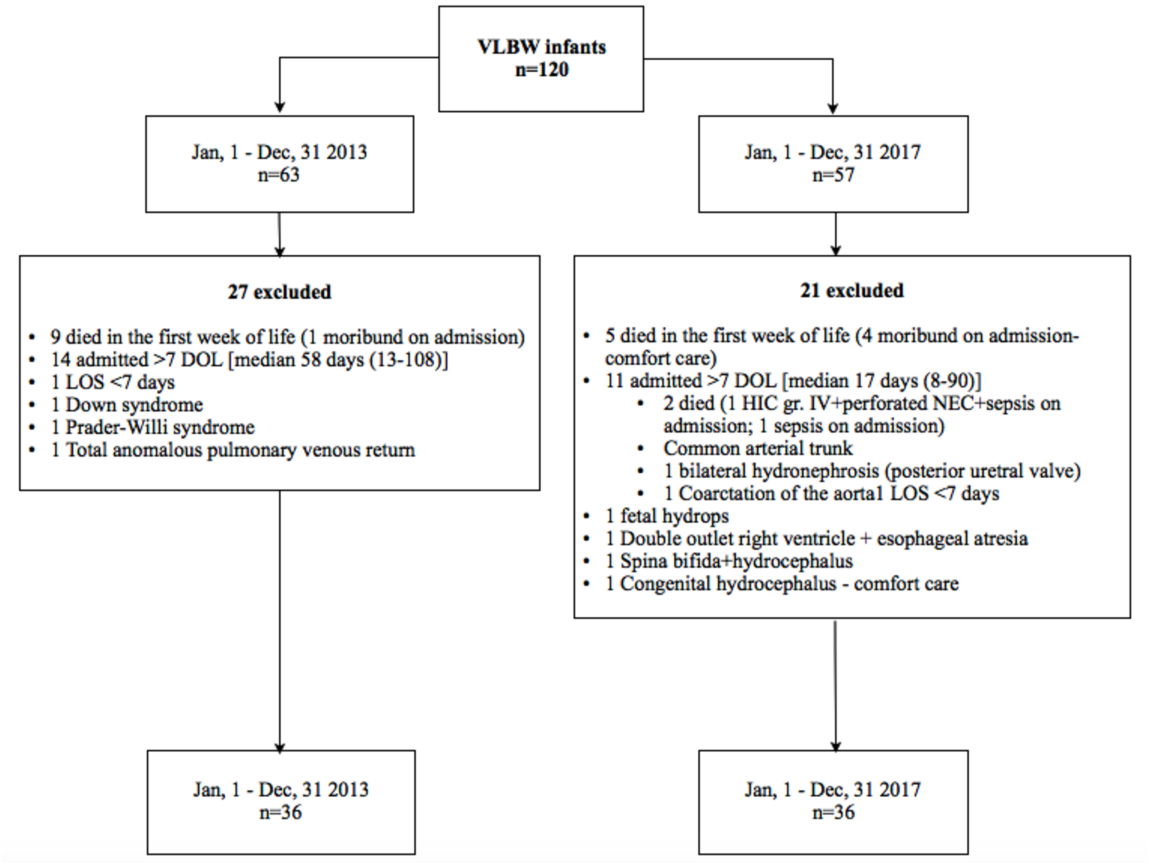

Figure 1. Flow chart of VLBW infants included in this study

Table 3. Characteristics of deceased VLBW infants admitted in the first week of life

	1st Epoch - 2013 (n=9)	2nd Epoch - 2017 (n=6)	*P*
Gestational age, wk	25±3	24.6±1	0,092
Age on admission, h	2±1.4	1.3±4.5	0,674
Birth weight, g	660±305	595±159	0,409
LOS, d	1.6±3	1.3±3.8	0,088

Abbreviation: LOS, length of stay.

The number of VLBW infants who were admitted in the first week of life did not differ between the study years. Patients' characteristics in two birth cohorts (2013 and 2017) are compared in Table 4. There was a small increase in overall median BW and GA in 2017, but it didn't reach statistical significance. The median BW for infants born in 2013 was 1,085 g and 1,295 g in 2017. The median GA in 2013 was 28 weeks (±2.4) compared to 29.3 weeks (±1.9) in 2017.

The use of MV, surfactant, and oxygen therapy decreased significantly over time. In 2013, 26 (72%) infants who survived received assisted ventilation for a median duration of

30.7 days, compared to 7 infants (20%, *P*<0.001) supported for a median of 5.6 days (*P*<0.001) in 2017. In 2013, only 25% of infants were treated with nCPAP as primary respiratory support or in an attempt to extubate and switch to nCPAP upon arrival, compared with 72% in 2017. These results are illustrated in Figure 2, where the difference on both MV and oxygen therapy can be easily compared.

Table 4 describes the rates of short-term morbidities in the two cohorts. All complications occurred less frequently in the second epoch. The incidence of BPD was significantly lower in 2017 than in 2013 (44 *v.* 78%, *P*<0.001), especially in the severe spectrum of the disease (3 *v.* 42%). The incidence of severe ROP was also reduced in 2017 compared to the 2013 cohort (0% *v.* 14%). No infant was treated for ROP in 2017. In 2013 five infants, who were all BW <1100 g, were treated for ROP using laser or intravitreal bevacizumab. In 2017, there was also a significant reduction in the proportion of IVH grades III and IV (11% *v.* 33%).

The overall median of LOS for surviving infants was reduced from 74.4 days (25.1-358.4 days) in 2013 to 56.5 days (13.5-110.2 days) in 2017. There were no differences in median PMA on hospital discharge between the two cohorts (40 *v.* 37.7 in 2013 and 2017, respectively).

Table 4. Demographics and clinical data[a]

	1st Epoch - 2013 (n=36)	**2nd Epoch - 2017 (n=36)**	***P***
Male sex	20 (56)	20 (56)	1.000
Gestational age, wk	28 (2.4)	29.3 (1.9)	0,844
Birth weight, g	1,085 (560-1,860)	1,295 (780-1,840)	0,072
Intrauterine growth restriction	4 (11)	4 (11)	1.000
Birth weight <1000 g	8 (22)	4 (11)	0,206
Antenatal steroids	NA	23 (64)	-
Apgar score			
1st min	*(n=35)*	*(n=35)*	0.329
≤6	23 (66)	19 (54)	
≥7	12 (34)	16 (46)	
5th min	*(n=34)*	*(n=35)*	0.925
≤6	13 (38)	13 (37)	
≥7	21 (62)	22 (63)	
Age at admission, h	2.1 (0.8-143.4)	3 (0.5-130)	0,818
Respiratory support			

SNAPPE-II	*(n=30)* 32 (0-133)	23 (0-84)	0,068
Primary mode of ventilation			
invasive mechanical ventilation	26 (72)	7 (20)	**<0,001**
nCPAP/extubation to nCPAP	9 (25)	26 (72)	
none/HFNC	1 (3)	3 (8)	
Primary nCPAP failure	3 (33)	7 (27)	0,787
Total duration of invasive mechanical ventilation, d	*(n=29)* 30.7 (0.5-105)	*(n=19)* 5.6 (0.1-23)	**<0,001**
Surfactant administration	25 (69)	12 (33)	**0,002**
Pneumothorax after admission	0 (0)	3 (8)	0,239
Oxygen, DOL	50 (4-359)[1]	27 (4-89)	**0,004**
Length of stay			
NICU stay, d	73 (15-235)	54 (14-104)	**<0,001**
Hospital stay, d	74 (25-358)	57 (14-110)	**0,001**
Discharge to home (from NICU)	21 (58)	22 (61)	0,810
PMA on hospital discharge, wk	40 (34.4-76.7)	37.7 (33.1-46)	0,508
Morbidity			
Bronchopulmonary dysplasia			
none	8 (22)	20 (56)	**<0,001**
mild	11 (30)	10 (27)	
moderate	2 (6)	5 (14)	
severe	15 (42)	1 (3)	
IVH ≥3	12 (33)[2]	4 (11)	**0,023**
ROP, laser therapy/intravitreal bevacizumab	5 (14)	0 (0)	**0,025**
Surgical NEC	2 (6)	2 (6)	1.000
Time to full enteral feed, d	*(n=33)* 36 (12-117)	*(n=35)* 34 (9-95)	0,330
Feeding on discharge			
breast milk/mixed	10	16	0,141
formula	26	20	

Abbreviations: DOL, day of life; HFNC, high-flow nasal cannula; IVH, intraventricular hemorrhage; NA, non available; NEC, necrotizing enterocolitis; PMA, postmenstrual age; ROP, retinopathy of prematurity.

[a] Values are number of patients (%), mean (standard deviation), or median (minimum-maximum).

[1] 2 patients discharged on supplemental oxygen; [2]1 ventriculoperitoneal shunt.

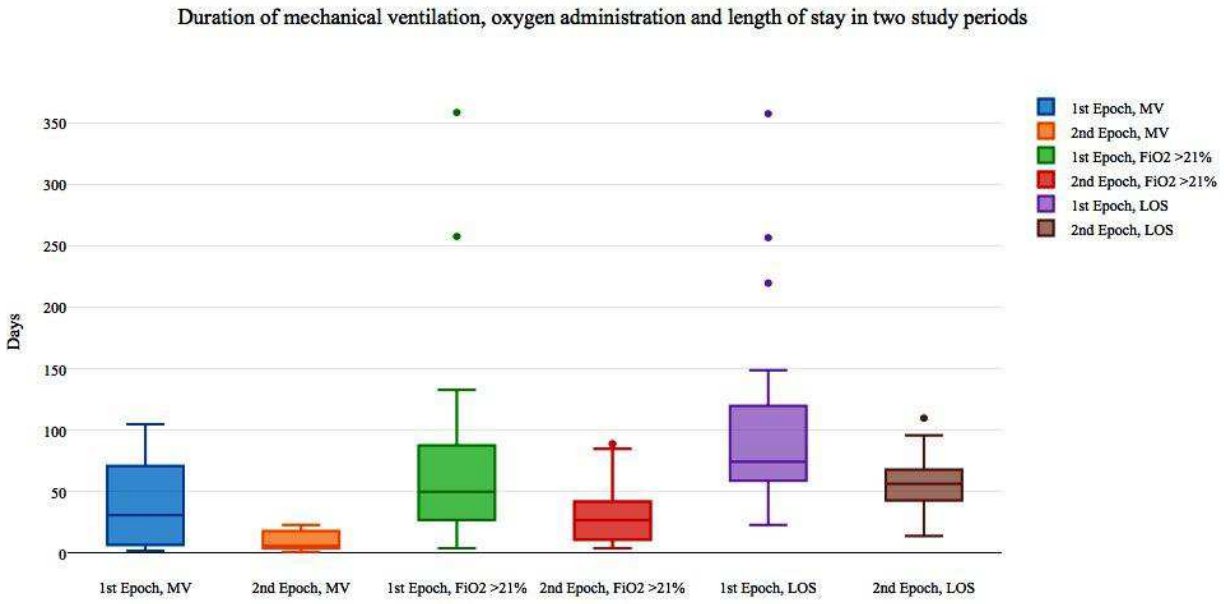

Figure 2. Duration of mechanical ventilation, oxygen administration and length of stay during two time periods

Figures 3 and 4 show the percentage of VLBW infants, grouped by weight, who were placed on either MV or nCPAP as primary ventilation of mode. A statistically significant difference was found in the subgroup of infants with BW <1000 g (*P*=0.002) and BW 1000-1500 g (*P*=0.006); in 2013 all infants <1000 g (n=8) were placed on MV. This approach completely changed in 2017 as all infants with BW <1000 g (n=4) received nCPAP support. Although there were more infants supported with nCPAP in the BW >1500 g subgroup in the second epoch, it did not reach statistical significance (*P*=0.109).

Figure 3. Mechanical ventilation by birth weight in VLBW infants during two times periods

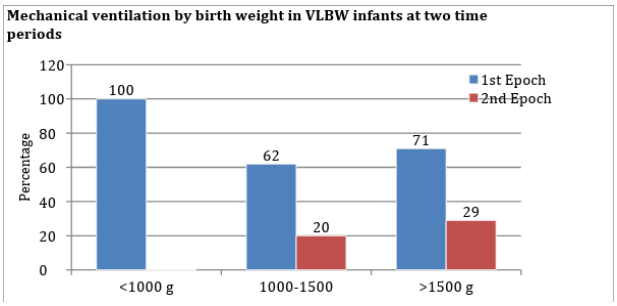

Figure 4. nCPAP by birth weight in VLBW infants during two times periods

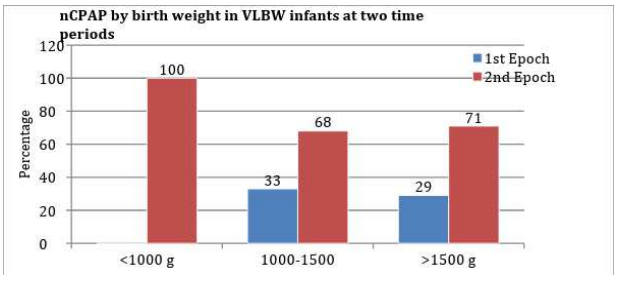

Figure 5 compares the incidence and severity of BPD in Epoch 1 and 2, showing a decrease between 2013 and 2017. Improvements **n=2** on lessening the degree of disease can also seen, the most striking is the change in the

percentages of patients with severe BPD, which decreased from 42% (n=15) to 3% (n=1).

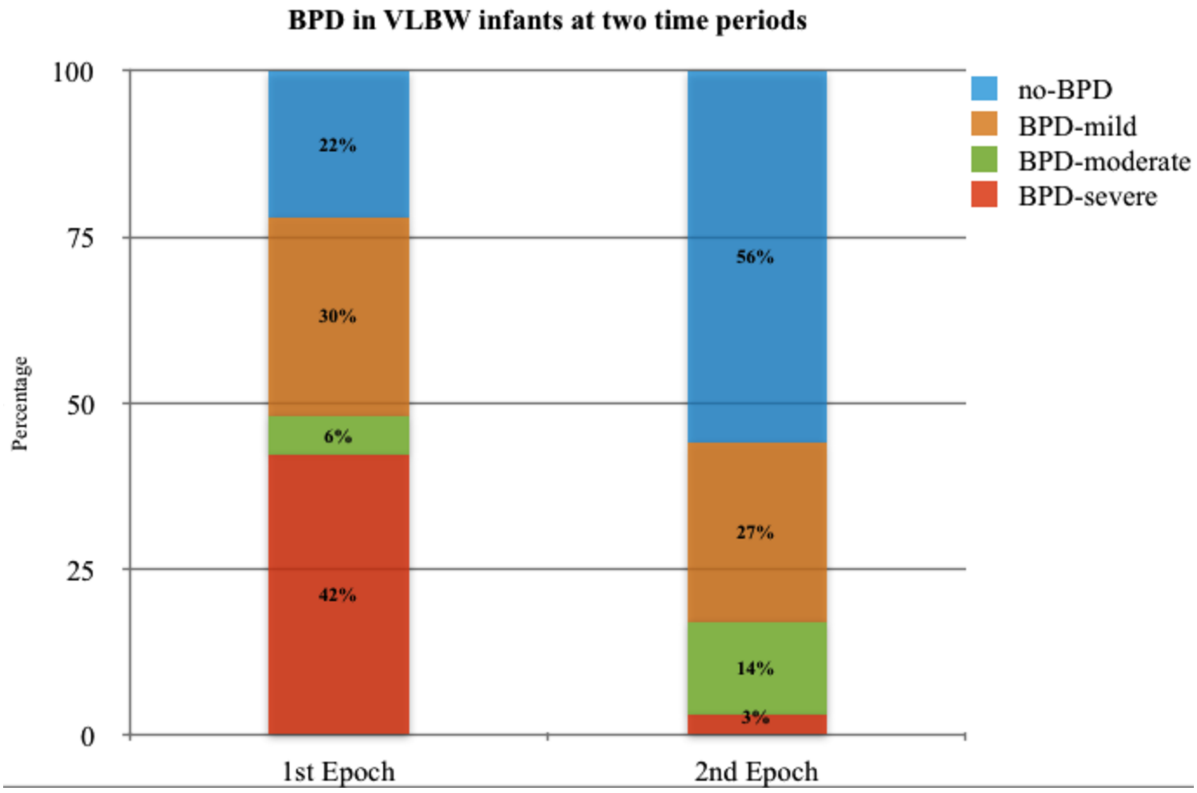

Figure 5. Incidence and severity of of BPD at two time periods

Demographic and clinical characteristics of VLBW infants from epoch 1 stratified by 'BPD none/mild' and 'BPD moderate/severe' were compared in Table 5. Patients' characteristics are compared with no statistical significance in GA, IUGR and SNAPPE-II scores. There was a marked difference in BW between both groups, i.e. patients that had 'none/mild BPD' had a median BW of 1220 g (880-1,680), while patients who had 'moderate/severe BPD' had a median BW of 1,010 g (560-1,530). Percentage of neonates mechanically ventilated and duration of MV and oxygen therapy was significantly higher in the 'moderate/severe BPD' group compared to the 'none/mild BPD group' (88% *v.* 58%; 70 *v.* 5 days; 91 *v.* 32 days, respectively). Infants who developed moderate or severe BPD required more blood transfusions (88% *v.* 58%). There was a significant increase in comorbidities in 'moderate/severe' BPD group: IVH grade ≥3 (53% *v.* 16%) and severe ROP (29% *v.* 0%). Furthermore, in comparison with 'none/mild BPD' group, neonates with 'moderate/severe' BPD reached full enteral feedings later (63 *v.* 31 days), were fed more often with formula (88% *v.* 58%), and had longer hospital stays (117 v. 62 days).

Table 5. Demographic and clinical characteristics of the 36 surviving infants in first Epoch (2013) according to BPD

	BPD none/mild (n=19)	**BPD moderate/severe (n=17)**	***P***
Gestational age, wk	30.1 (25-32.7)	26.7 (24-31)	0,736
Birth weight, g	1,220 (880-1,860)	1,010 (560-1,530)	**0,001**
Intrauterine growth restriction	2 (11)	2 (12)	0,906
Birth weight <1000 g	1 (5)	7 (41)	**0,01**
SNAPPE-II	*(n=17)* 26 (0-95)	*(n=13)* 57 (13-133)	0,132
Primary mode of ventilation			
Invasive mechanical ventilation	11 (58)	15 (88)	**0,042**
nCPAP/extubation to nCPAP/	8 (42)	2 (12)	
None			
Invasive mechanical ventilation, d	5 (0-32)	70 (0.5-105)	**<0,001**
Oxygen, DOL	32 (5-54)	*(n=14)* 91 (43-359)	**<0,001**
NICU stay, d	62 (15-139)	117 (65-235)	**<0,001**
Hospital stay, d	62 (23-139)	117 (65-358)	**<0,001**
Discharge to home (from NICU)	11	10	0,955
IVH ≥3	3 (16)	9 (53)	**0,018**
ROP - laser therapy/intravitreal bevacizumab	0 (0)	5 (29)	**0,016**
Surgical NEC	0 (0)	2 (12)	0,216
Time to full enteral feed, day	31 (12-50)	*(n=14)* 63 (14-117)	**<0,001**
Feeding on discharge			
breast milk/mixed	8 (42)	2 (12)	**0,042**
formula	11 (58)	15 (88)	
PRBCT, n of patients	11 (58)	15 (88)	**0,042**

Abbreviations: DOL, day of life; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PRBCT, packed red blood cell transfusion; ROP, retinopathy of prematurity

[a] Values are number of patients (%), mean (standard deviation), or median (minimum-maximum).

Table 6 compares phlebotomy blood loss and packed red blood cell transfusion (PRBCT) between the two epochs. The amount of phlebotomy blood loss was greatly reduced from a median of 29 ml (10-97 ml) in 2013 to 15 ml (5-58 ml) in 2017. The number of patients who received PRBC are lower in 2017 (n=19) than in 2013 (n=26). Additionally, the number of PRBC per patient (3.5 *v.* 2) and ml of PRBC per patient (57 *v.* 35 ml) also decreased in 2017, in comparison to 2013.

Table 6. Phlebotomy blood loss and packed red blood cell transfusion

	1st Epoch - 2013 (n=36)	**2nd Epoch - 2017 (n=36)**	***P***
Amount of phlebotomy blood loss, ml			
total	1128*	564	**0,004**
median (min-max)	29 (10-97)	15 (5-58)	
No. of patients who received PRBC transfusion	26 (72.2)	19 (52.8)	0,088
PRBCT, n			
	n=26	n=19	
total	92	36	**0,009**
per patient, average	3.5	2	
per patient, median (min-max)	3 (1-9)	2 (1-4)	
PRBCT, ml			
	n=26	n=19	
total	2212	882	**0,047**
per patient, average	85	46	
per patient, median (min-max)	57 (15-310)	35 (10-141)	

Abbreviation: PRBCT, packed red blood cell transfusion
* missing data for 5 infants (3 of them received multiple PRBC transfusions)

Table 7 compares infants who received and those who did not receive PRBCT in both epochs. BW was lower in the group of patients who received PRBCT, and this trend could be observed in both epoch 1 (1,050 g *v.* 1,360 g) and epoch 2 (1,250 g *v.* 1,460 g), as illustrated in Figure 6. Represented in figure 7, the groups of patients that received PRBCT had larger phlebotomy blood loss than patients who did not receive PRBCT (36 *v.* 15 ml and 19 *v.* 9 ml; in 2013 and 2017, respectively). The incidence of BPD was higher in patients who had received PRBCT on both 2013 (92% *v.* 30%) and 2017 (68% *v.* 24%).

Table 7. Comparison between infants who received and those who did not receive PRBCT in two Epochs

	1st Epoch - 2013			2nd Epoch - 2017		
	PRBCT+ (n=26)	**PRBCT - (n=10)**	***P***	**PRBCT+ (n=19)**	**PRBCT - (n=17)**	***P***
GA, wk	27.7 (24-32)	31 (28-32.7)	0,639	29 (26-31)	30 (27.9-34)	0,943
BW, g	1,050 (560-1,740)	1,360 (1,000-1,860)	**0,002**	1,250 (780-1,840)	1,460 (990-1,760)	**0,016**
SNAPPE-II	*(n=21)* 37 (5-133)	*(n=9)* 23 (0-58)	0,074	35 (5-84)	*(n=16)* 17 (0-60)	**0,012**
Phlebotomy blood loss, ml	*(n=21)* 36 (19-97)	15 (10-26)	**0,006**	19 (8-58)	*(n=16)* 9 (4-22)	**0,045**
BPD, n (mild, moderate, severe)	24 (92)	3 (30)	**<0,001**	13 (68)	4 (24)	**0,007**

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; SNAPPE-II, score for neonatal acute physiology with perinatal extension-II

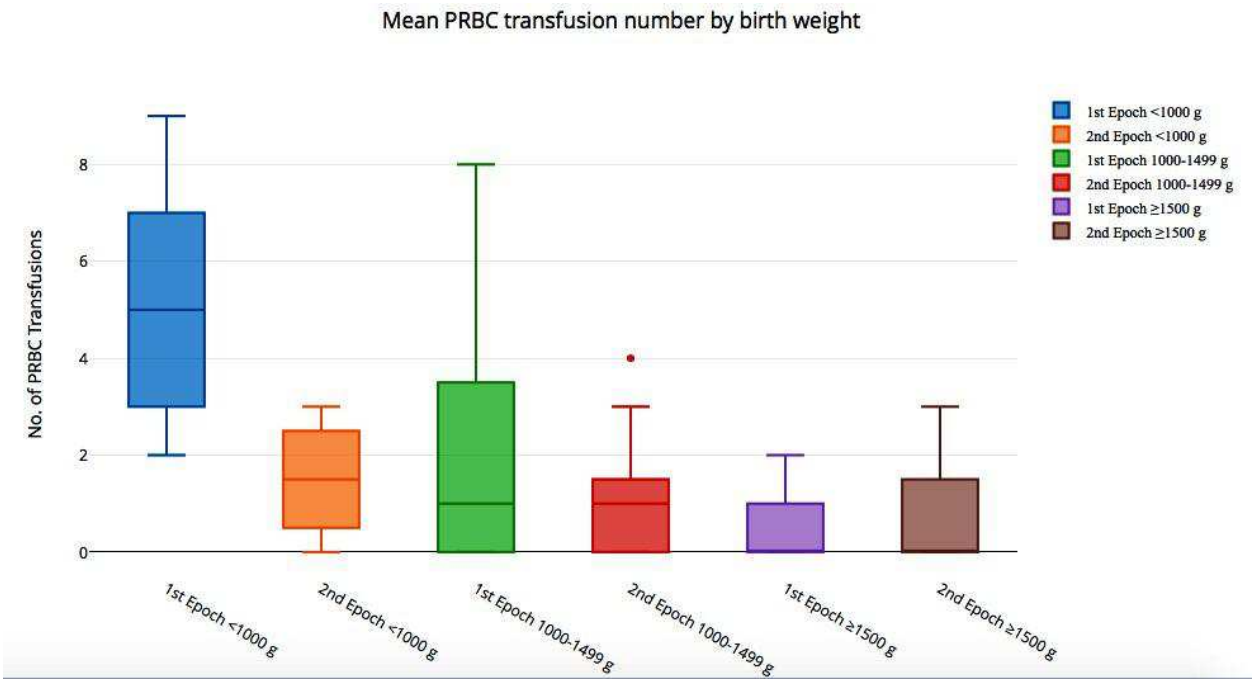

Figure 6. Mean PRBCT number by birth weight at the two periods

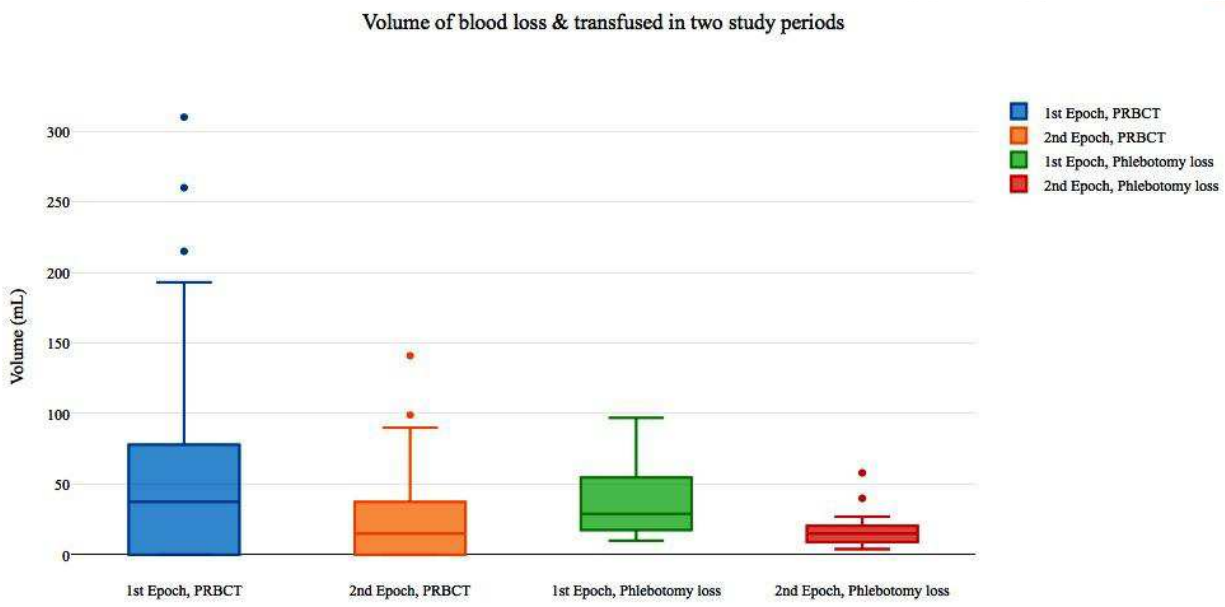

Figure 7. Volume of blood loss and transfusion at two time periods

8. Discussion

This study summarized the short-term outcomes of VLBW infants who were admitted and treated at the NICU of the UHC Zagreb during the year 2013 and the year 2017. These two years were chosen deliberately because some protocols changed during that period of time. The most prominent was the designation of nCPAP as the primary method of respiratory support. Other changes involved stricter control on blood draws and family-centered care practices such as unrestricted parental visits, and family presence and participation in care in the NICU.

Comparison of outcomes before and after the introduction of nCPAP as primary method of respiratory support

Between the years 2013 and 2017, the NICU at the UHC Zagreb switched their primary mode of ventilation from MV to nCPAP. This change has notably decreased the need of MV and oxygen therapy.

In different published papers, the prolonged use of MV and oxygen therapy has been linked with a higher risk of developing different comorbidities when compared to the use of nCPAP (42,43,47,48). In our study these results could be repeated since the overall incidence of BPD decreased from 78% to 44%. More impressively, severe BDP diminished from 42% to 3% after the introduction of nCPAP as first choice for respiratory support.

Our study is also in concordance with papers reporting that the use of nCPAP diminishes the duration of ventilation (42,43). In 2013, the mean duration of ventilation was 31 days (0.5-105 days), which significantly dropped to 6 days (0.1-23 days) in 2017.

A decrease in incidence and severity of comorbidities have also been reported with the

increased use of nCPAP (49). This trend can also be observed in our results: a decline in incidence of IVH ≥3 (33% *v.* 11%) and severe ROP (14% *v.* 0%) were noted since the replacement of MV with nCPAP as primary method of ventilation.

Importance of regulation of laboratory diagnostics

The volume of blood drawn is significantly increased by unnecessary testing, and without monitoring quantity of blood taken it is easy for a neonate to become anemic. In fact, Fanaroff et al. (8) stated that a neonate on MV therapy might lose over 5 ml of blood per day for laboratory diagnostics, which is a substantial amount for an infant who weighs less than 1,500 g.

Between 2013 and 2017, a strategy of conservative blood management was implemented at the NICU of the UHC Zagreb. Before the introduction of newer protocols, blood tests were routinely made without adequate monitoring. Now, the decision on what tests are necessary is made on a daily basis rather than scheduled automatically. This has resulted in a decrease in the phlebotomy blood loss from a median of 29 ml (10 - 97 ml) in 2013 to 15 ml (5 - 58 ml) in 2017.

Decrease in blood loss has also led to a decreased the need for blood transfusions. In 2013, 26 patients received transfusions, compared to only 19 patients in 2017. Furthermore, the amount of blood transfused also decreased, from an average of 85 ml per patient in 2013 to an average of 46 ml in 2017.

Different researchers have claimed that blood transfusions increase the risk of BPD (38,39) and our analysis showed similar results. Out of 26 patients who received PRBCT in 2013, 92% (n=24) developed BPD. In contrast, among the patients who did not receive PRBCT (n=10), only 3 patients developed BDP (P <0.001). Results were similar in 2017, where out of the 19 patients who received PRBCT, 68% (n=13) were diagnosed with BPD, while of the 17 patients who did not receive transfusion, only 4 developed BPD (P=0.007).

Kangaroo care, breastfeeding and encouraging parental participation.

The new worldwide tendency is to allow parents to spend as much time as they want with their newborn while hospitalized in the NICU. Parents are allowed touch, talk and are encouraged to help with certain basic care activities.

Feeding with breast milk is advocated and prefered over the use of formula because it offers passive immunity, is rich in nutrients, and is easier to digest. Furthermore, it provides protection to comorbidities that might appear in a preterm newborn such as NEC (50,51).

Kangaroo care is a relatively new technique where the neonate is placed on the parent's naked chest. It has shown to regulate the infant's body temperature, heart rate and

breathing pattern. It also reduces stress and pain and it is easier for breastfeeding (52,53).

In 2013, infants were fed mainly with bovine milk-based preterm formula and visits were regulated. Currently, breast milk is encouraged, as well as parental involvement in infant caregiving. In the analysis of patients who developed BPD, it was noted that a group of patients who developed BPD were less fed with their mother's milk than those who did not develop BPD (Table 3, p.16).

And while there is no specific variable that could prove this theory, infants in 2017 did had better outcome than in 2013. Median length of stay for surviving infants was reduced and complications occurred less frequently in the second epoch.

Limitations

It is important to note that due to its retrospective nature, our study was limited by missing information. This was more evident for the record from the year 2013. Usage of antenatal corticosteroids had to be excluded from analysis due to incomplete or inaccurate data from most files dating from 2013. This variable would have provided a better insight in the decrease of comorbidities, like IVH and NEC, since studies have proven links between the antenatal corticosteroids and better short term outcomes (54–56).

9. Conclusion

When compared, newer protocols have improved short-term outcomes in hospitalized premature neonates. Usage of nCPAP, better policies on blood diagnostic procedures, and family-centred care procedures seems to have decreased the incidence and severity of short-term comorbidities and decreased the LOS. This study supports the use of nCPAP as primary ventilation or prophylactically and a strict control on blood tests in order to improve the prognosis of VLBW neonates.

10. Acknowledgments

First, I would like to thank the people who helped me make this thesis possible. My mentor, docent Ruža Grizelj for her guidance, patience and trust; Dr. Tomislav Ćaleta for his enormous help, and everyone at the NICU at the University Hospital Centre Zagreb. Special thanks to Mrs. Nevenka and Mrs. Aida for their assistance with the paperwork and the countless patient histories and Mrs. Ksenija Matacun for helping with the English to Croatian translations.

Second, I'd also like to take this opportunity to thank the neonatologists at the Children's Clinical University Hospital in Riga; Dr. Daiga Kviluna for allowing me to join her team, my two times mentor Dr. Renate Zarina for her advice, assistance and encouragement and my friend Dr. Jekaterina Homenko. Without them I wouldn't have found my true passion.

Above all, I'd like to thank my family; my amazing parents, brothers, sister in law and niece who have been my rock and emotional support through the good and the bad days that all medical student has. My grandparents, aunts, uncles and cousins who have cheered for me since day one. And my friends and future colleagues, who have survived all this craziness with me. I would have never been able to do it without you all. *Gracias, paldies, hvala*!

11. References

1. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med. 2015 Jan 22;372(4):331–40.

2. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015 Jan 31;385(9966):430–40.

3. WHO | Born too soon [Internet]. World Health Organization; 2014 [cited 2018 May 12]. Available from: http://www.who.int/maternal_child_adolescent/documents/born_too_soon/en/

4. Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. BMJ. 2008 May 31;336(7655):1221–3.

5. Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics. 2012 Jun; 129(6):1019–26.

6. Bode MM, D'Eugenio DB, Forsyth N, Coleman J, Gross CR, Gross SJ. Outcome of extreme prematurity: a prospective comparison of 2 regional cohorts born 20 years apart. Pediatrics. 2009 Sep;124(3):866–74.

7. Mandy GT. Incidence and mortality of the preterm infant [Internet]. UpToDate. 2018 [cited 2018 May 17]. Available from: https://www.uptodate.com/contents/incidence-and-mortality-of-the-preterm-infant?search=neonatology%20&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

8. Fanaroff AA, Fanaroff. JM. Klaus & Fanaroff's care of the high-risk neonate. 6th ed. Fanaroff AA, Fanaroff. JM, editors. Elsevier Saunders;

9. Matthews TJ, MacDorman MF, Thoma ME. Infant Mortality Statistics From the 2013 Period Linked Birth/Infant Death Data Set. Natl Vital Stat Rep. 2015 Aug 6;64(9):1–30.

10. Mandy GT. Short-term complications of the preterm infant. In: Weisman LE, Kim MS, editors. UpToDate. Waltham, MA: UpToDate; 2018.

11. Sosenko IRS BE. New developments in the pathogenesis and prevention of bronchopulmonary dysplasia. Bancalari E PRA, editor. Philadelphia, PA: Saunders; 2012. (The newborn lung: neonatology questions and controversies).

12. Eichenwald EC. Pathogenesis and clinical features of bronchopulmonary dysplasia. In: Redding G, Kim MS, editors. UpToDate. Waltham, MA: UpToDate; 2017.

13. Bhandari A, Bhandari V. Bronchopulmonary dysplasia: an update. Indian J Pediatr. 2007 Jan; 74(1):73–7.

14. Debbie Fraser Askin And. Chapter 10: The High-Risk Newborn and Family. In: Marilyn J. Hockenberry, PhD, RN-CS, PNP, FAAN, David Wilson Ms, editors. Evolve Resources for Wong's Nursing Care of Infants and Children. 10th. Elsevier; 2015.

15. Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004 Nov;114(5):1305–11.

16. Jobe AH, Bancalari E. Bronchopulmonary Dysplasia. Am J Respir Crit Care Med. 2001 Jun; 163(7):1723–9.

17. Thilo EH, Rosenberg AA. Chapter 1: The Newborn Infant. In: Hay WW Jr, Levin MJ, Sondheimer JM, Deterding RR, editors. CURRENT Diagnosis & Treatment Pediatrics. 19th ed. McGraw-Hill; 2009.

18. Roberts CL, Badgery-Parker T, Algert CS, Bowen JR, Nassar N. Trends in use of neonatal CPAP: a population-based study. BMC Pediatr. 2011 Oct 17;11:89.

19. Natarajan G, Pappas A, Shankaran S, Kendrick DE, Das A, Higgins RD, et al. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. Early Hum Dev. 2012 Jul;88(7):509–15.

20. de Vries LS. Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) in the newborn: Pathogenesis, clinical presentation, and diagnosis. In: Martin R, Kim MS, editors. UpToDate. Waltham, MA: UpToDate; 2018.

21. Horbar JD, Soll RF, Edwards WH. The Vermont Oxford Network: a community of practice. Clin Perinatol. 2010 Mar;37(1):29–47.

22. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping

and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev. 2012 Aug 15;(8):CD003248.

23. Crowther CA, Crosby DD, Henderson-Smart DJ. Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage. Cochrane Database Syst Rev. 2010 Jan 20; (1):CD000229.

24. de Vries LS. Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) in the newborn: Prevention, management, and complications. In: Martin R, Kim MS, editors. UpToDate. Waltham, MA: UpToDate; 2018.

25. Kenet G, Kuperman AA, Strauss T, Brenner B. Neonatal IVH--mechanisms and management. Thromb Res. 2011 Feb;127 Suppl 3:S120–2.

26. Holman RC, Stoll BJ, Curns AT, Yorita KL, Steiner CA, Schonberger LB. Necrotising enterocolitis hospitalisations among neonates in the United States. Paediatr Perinat Epidemiol. 2006 Nov;20(6):498–506.

27. Fitzgibbons SC, Ching Y, Yu D, Carpenter J, Kenny M, Weldon C, et al. Mortality of necrotizing enterocolitis expressed by birth weight categories. J Pediatr Surg. 2009 Jun;44(6): 1072–5; discussion 1075–6.

28. Kim JH. Neonatal necrotizing enterocolitis: Clinical features and diagnosis. In: Abrams SA, Kim MS, editors. UpToDate. Waltham, MA: UpToDate; 2018.

29. Davies MW, Cartwright DW, Inglis GDT. Pocket Notes on Neonatology. 2nd ed. Elsevier Australia; 2009.

30. Kim JH. Neonatal necrotizing enterocolitis: Management. In: Abrams SA, Kim MS, editors. UpToDate. Waltham, MA: UpToDate; 2018.

31. Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr. 2010 Apr;156(4):562–7.e1.

32. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011 Jan 20;364(3):255–64.

33. Fierson WM, American Academy of Pediatrics Section on Ophthalmology, American Academy

of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013 Jan;131(1):189–95.

34. Coats DK. Retinopathy of prematurity: Pathogenesis, epidemiology, classification, and screening. In: Garcia-Prats JA, Armsby C, editors. UpToDate. Waltham, MA: UpToDate; 2017.

35. Zhou J, Shukla VV, John D, Chen C. Human Milk Feeding as a Protective Factor for Retinopathy of Prematurity: A Meta-analysis. Pediatrics. 2015 Dec;136(6):e1576–86.

36. Retinopathy of Prematurity Causes, Signs & Symptoms, Diagnosis - Retinopathy of Prematurity - HealthCommunities.com [Internet]. [cited 2018 June 6]. Available from: http://www.healthcommunities.com/retinopathy-of-prematurity/children/causes-of-rop.shtml

37. Jakacka N, Snarski E, Mekuria S. Prevention of Iatrogenic Anemia in Critical and Neonatal Care. Adv Clin Exp Med. 2016 Jan;25(1):191–7.

38. Valieva OA, Strandjord TP, Mayock DE, Juul SE. Effects of transfusions in extremely low birth weight infants: a retrospective study. J Pediatr. 2009 Sep;155(3):331–7.e1.

39. Zhang Z, Huang X, Lu H. Association between red blood cell transfusion and bronchopulmonary dysplasia in preterm infants. Sci Rep. 2014 Mar 11;4:4340.

40. Cooke RW, Drury JA, Yoxall CW, James C. Blood transfusion and chronic lung disease in preterm infants. Eur J Pediatr. 1997 Jan;156(1):47–50.

41. Cummings JJ, Polin RA, Committee on Fetus and Newborn, American Academy of Pediatrics. Noninvasive Respiratory Support. Pediatrics [Internet]. 2016 Jan;137(1). Available from: http://dx.doi.org/10.1542/peds.2015-3758

42. Committee on Fetus and Newborn, American Academy of Pediatrics. Respiratory support in preterm infants at birth. Pediatrics. 2014 Jan;133(1):171–4.

43. Subramaniam P Ho Jj. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants (Review). Cochrane Database Syst Rev. 2016; (6):Art. No.: CD001243.

44. Gräfe D. Ped(z) - Pediatric Calculator [Internet]. 2016. Available from: https://www.pedz.de/

en/neo.html

45. French Society of Anesthesia and Intensive Care. Scoring systems for ICU and surgical patients: SNAP-II and SNAPPE II (Score for Neonatal Acute Physiology and SNAP Perinatal Extension) [Internet]. Available from: http://www.sfar.org/scores2/snap22.php#haut

46. L.A. Papile, N.J. Burstein, R.Burstein, and H. Koffler. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm,. J Pediatr. 1978;92(4):529–34,.

47. Torres-Castro C, Valle-Leal J, Martínez-Limón AJ, Lastra-Jiménez Z, Delgado-Bojórquez LC. Pulmonary complications associated with mechanical ventilation in neonates. Bol Med Hosp Infant Mex. 2016 Sep 1;73(5):318–24.

48. Bamat N, Fierro J, Wright CJ, Millar D, Kirpalani H. Nasal continuous positive airway pressure levels for the prevention of morbidity and mortality in very low birth weight infants. Cochrane Neonatal Group, editor. Cochrane Database Syst Rev. 2017 Sep 1;122:e1086.

49. Kann IC, Solevåg AL. Economic and health consequences of non-invasive respiratory support in newborn infants: a difference-in-difference analysis using data from the Norwegian patient registry. BMC Health Serv Res. 2014 Nov 1;14:494.

50. Choices N. Breastfeeding your premature baby - NHS.UK [Internet]. Department of Health. [cited 2018 Jun 14]. Available from: https://www.nhs.uk/conditions/pregnancy-and-baby/breastfeeding-premature-baby/

51. Schanler RJ. Infant benefits of breastfeeding. In: Abrams SA, Hoppin AG, editors. UpToDate. Waltham, MA: UpToDate; 2018.

52. Boundy EO, Dastjerdi R, Spiegelman D, Fawzi WW, Missmer SA, Lieberman E, et al. Kangaroo Mother Care and Neonatal Outcomes: A Meta-analysis. Pediatrics [Internet]. 2016 Jan;137(1). Available from: http://dx.doi.org/10.1542/peds.2015-2238

53. Care For The Premature Baby [Internet]. American Pregnancy Association. 2017 [cited 2017 June 10]. Available from: http://americanpregnancy.org/labor-and-birth/premature-care/

54. Lee M-J. Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery. In: Lockwood CJ, Barss VA, editors. UpToDate. Waltham, MA: UpToDate; 2018.

55. Bittar RE, Francisco RPV, Zugaib M. Antenatal Corticosteroid Administration for Reducing the Risk of Neonatal Morbidities from Prematurity. Rev Bras Ginecol Obstet. 2016 Mar;38(3): 117–9.

56. Bonanno C, Wapner RJ. Antenatal corticosteroids in the management of preterm birth: are we back where we started? Obstet Gynecol Clin North Am. 2012 Mar;39(1):47–63.

12. **Biography**

I was born on July, 24th of 1992 in Caracas, Venezuela. I finished my primary and secondary education at Colegio Canigua in Caracas, additionally I did a year in the international baccalaureate program at XV. Gimnazija in Zagreb. In 2010, I enrolled at the School of Medicine in University of Zagreb. Throughout my studies I was a student representative for eMed student council for the english program, an active member at CROMSIC and, for two consecutive years, I was a students' demonstrator for History Taking and Physical Examination. During the years of 2014 and 2015 I did a one-month internship at the Emergency and the Surgical Departments of Clinica Sanatrix in Caracas, Venezuela, where I learned about diagnosis and treatment of medical and surgical emergencies. In the years of 2016 and 2017 I was allowed to do a one-month internship at the Neonatology Department of the Children's Clinical University Hospital in Riga, Latvia, where I found my true calling. I will graduate in July 2018.