Chapter 9

Non-Pulmonary Management of Newborns with Respiratory Distress

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Additional information is available at the end of the chapter

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Abstract

Due to the developmental immaturity of the lungs and other organs, the premature newborns are more prone to develop respiratory distress syndrome (RDS) and other problems of prematurity. The prevention of heat and water loses improves survival. Intolerance to excessive fluids and electrolytes in the transitional period may affect urine and sodium excretion together with maladaptation of cardiovascular system, the development of heart failure, and deterioration of RDS due to patent ductus arteriosus (PDA) and further development of bronchopulmonary dysplasia (BPD). Closure of PDA is frequently needed. The "trophic feeding" and intensive nutrition as soon as possible prevent weight loss and further growth restriction. Greater sensitivity to pain, short- and long-term effects of inappropriately treated pain, use of opioids and sedatives are of concern in the short- and long-term outcomes. Cardiovascular stability and adequate perfusion of the brain both affect the neurological outcome. Delayed cord clamping and erythropoietin help maintaining adequate levels of circulating hemoglobin which might affect later cognitive outcomes. In the following sections, detailed descriptions of non-pulmonary management will be presented. We conducted electronic searches of articles on supportive (non-pulmonary) management of newborns with RDS. Consensus guidelines on newborns with respiratory distress have been reviewed.

Keywords: newborns, evidence-based therapy, antenatal steroids, transport in utero, regionalization of maternity hospitals and neonatal intensive care units, thermoregulation, fluid, nutrition, antibiotics, pain, blood pressure, perfusion, patent ductus arteriosus

1. Introduction

Non-pulmonary management of newborns with respiratory distress syndrome (RDS) is neither the last nor the least important part of the management, but it is supposed to be involved and intertwined in the whole necessary work-up integrated for the well-being of the tinny newborn. Each momentum from the prenatal care, pregnancy, and finally to the birth of the newborn should be considered when we are aiming to improve the final outcome, that is, delivery of a healthy newborn. Pulmonary management of newborns with RDS is only one, though very important and lifesaving, but not sufficient and adequate part of the whole care management of the newborns with RDS.

2. Methods

This chapter will look at the importance of prenatal care, temperature control, control of hypoglycemia, fluid and nutritional intake, the impact of perinatal infection and the use and misuse of antibiotics, frequency of unnecessary procedures, proper pain management, the impact of excessive use of opiates on ventilation duration in the management of newborns with RDS. The impact of optimal blood pressure, tissue perfusion, and patent ductus arteriosus (PDA) with hemodynamic management in newborns with RDS is going to be reviewed. Also, the short- and long-term outcomes in respect of supportive management of newborns in the intensive care unit will be addressed. We conducted electronic searches of articles on supportive (non-pulmonary) management and reviewed the consensus guidelines on management of newborns with RDS [1].

3. Prenatal care

Every newborn can develop RDS, but the likelihood among the premature infants to be affected with the RDS is the highest [2, 3]. Therefore, as neonatal RDS is a disease predominantly affecting the preterm newborns, all the measures to decrease preterm delivery encompass its management. Preconception advice starting in teenage youth to prevent pregnancy in too young teenage girls is important, and social programs should be developed and delivered among the youths. This is not only the problem in poor countries in the world but is even more problematic in wealthy countries with high-gross domestic product but also extreme social inequalities. This preconception advice is closely related to proper protection from the sexually transmitted diseases which may also affect the fetal and later newborn's life. Both, youth pregnancy and sexually transmitted diseases together with under- or malnutrition, strongly affect the development of the fetus and premature delivery. Publically available access to the proper maternity care, at least in well-developed countries, should be offered to every pregnant woman: adequate number of visits at the obstetrician's, appropriate number of obstetric ultrasounds, teaching programs and screening for infections, developmental malformations, etc. Special problems are unwanted pregnancies because any termination of unwanted pregnancy brings different problems to the mother and future wanted pregnancies, but it

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is worth mentioning that illegal and criminal or nonprofessional abortion endangers the health and lives of the women [4].

In well-organized health systems, ultrasound measurement of cervical length in midtrimester enables prediction of preterm labor and women with short cervix (<25 mm) should be offered vaginal progesterone treatment [5]. Women with threatening preterm labor should be transferred by "in utero" transport to tertiary level medical centers where better outcomes in regards to mothers and newborns can be provided [6]. In the case of preterm premature rupture of membranes (PPROM), after reassuring maternal and fetal wellbeing threatened preterm delivery can be delayed by antibiotics treatment for 7 days to mothers from about 23 weeks up to 34 weeks of gestation [7]. Antibiotics reduce the rate of chorioamnionitis, preterm birth, infection, and respiratory insufficiency [8]. On the contrary, antibiotics have not been proved beneficial for mothers with preterm labor and intact membranes [9]. Delaying the preterm delivery has been also proved for magnesium sulfate which also has beneficial effects for the brain of the preterm newborn [10]. Preterm labor is efficaciously postponed by tocolytics [11]. Antenatal steroids given to mothers from about 23 weeks up to 34 weeks of gestation decrease the risk of neonatal death, RDS, intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC) [12]. Moreover, antenatal steroids given more than 24 h and <7 days before elective cesarean section at term also influence the RDS in the late-preterm or term newborn [13]. Until further studies are done, one repeated dose of antenatal steroids given a week after the first dose is recommended [14].

Chorioamnionitis describes intrauterine inflammation of maternal and fetal tissues and endangers both, the mother and the newborn. It has been recognized as the major risk factor for preterm birth, prematurity-associated mortality in morbidity of newborns: the neonatal sepsis, RDS, cystic periventricular leukomalacia (PVL), IVH, and cerebral palsy [15, 16]. Since guidelines for the prevention of perinatal group B streptococcal (GBS) disease have been published, the incidence of early-onset GBS disease in newborns has dramatically decreased. The mayor prevention key is universal antenatal GBS screening of pregnant women and intrapartum antibiotic prophylaxis (IAP) for women with high-risk of infection with penicillin, ampicillin, or cefazolin. Adequate IAP is achieved by infusion of antibiotics at least 4 h before delivery [17].

4. Interhospital, "in utero" transport, and regionalization

Interhospital air and ground transportation of critically ill neonates, regionalization, organization of "in utero" transportations, and new tertiary perinatal centers, which care for the most at risk premature newborns, have greatly decreased the perinatal mortality rate over the last 30 years all over the world [6]. As an example, we present the results from the Republic of Slovenia where we have greatly decreased the perinatal mortality rate over the last 30 years to a rate of 3.5% for neonates weighing at least 1000 g in 2006. We have organized transportation since 1976, and we have transport "in utero" in two Slovenian perinatal centers since 1985 [18].

5. Temperature management

From the neonatal history, we learned that misunderstanding the adverse effects of low body temperature in the premature infants was related to higher mortality rate in hypothermic infants. With understanding the importance of normal body temperature later together with the invention of heated air incubators, the mortality rate dropped as much as twice immediately [19–21]. After birth, the newborn baby is exposed to extrauterine environment with temperature changes in relation to the environmental temperatures which are usually lower than the body temperature. Newborns and especially preterms have increased proportion of body surface in relation to body volume, their body has low-temperature capacity, and their skin is immature with increased water permeability. They also have low supplies of skin fat. Since oxygen and energy consumption are lowest in the range of thermal neutrality, it is important to keep newborns in those limited ambient temperature ranges to enable them to have their body temperature ranging from 36.5 to 37.5°C. By acknowledging the importance of thermal neutrality, this is one of the most manageable problems of non-pulmonary management of newborns with RDS [22].

Temperature regulation enables optimal efficiency of the metabolic processes and enzyme activities with the lowest oxygen and calorie consumption. Newborns are unable to produce sufficient heat by metabolic reactions, by muscle activity during motion, and by nonshivering thermogenesis in the brown fat, which starts to evolve between 26th and 30th weeks of gestation. Loosing heath from the body is modulated by changing the vascular tone of peripheral vessels and by sweating, which is not fully developed by the 36th week of gestation.

There are four ways newborns may lose heat to the environment. Immediately after birth, they are wet from the amniotic fluid and evaporation decreases their body temperature fast so all the measures to dry their body have to be taken. Recently, to decrease evaporation from the immature water permeable skin, very premature newborns, still wet, are immediately wrapped into plastic wraps or bags and caps [23–27]. To lessen the evaporation, the air in the incubators for all the preterms beyond 31 weeks of gestation should be humidified (60–80%) and preterm newborns should not be bathed until they can maintain their body temperature. The humidity should be decreased by 5% every day if they can maintain stable body temperature, and stopped when preterms can maintain their body temperature in 40% humidity [28]. Every object radiates—it gives or receives the heat in relation to the temperature difference. Therefore, it is important to keep the air temperature in a defined range and also to take into account the external temperatures, the room walls and windows and the isolation walls of the incubators [29]. Objects can lose heat by losing or gaining heat from the object in contact by conduction. Placing the newborn baby to the mother's abdomen allows skin to skin contact besides parental bonding and enables conduction of the heat from the mother to the child [22, 30–32]. Resuscitation on wet basis can cause a huge heat loss from the newborn and should be avoided. Infusing cold fluids also causes conduction loss of heat. Moving air causes heat loss by convection.

Hypothermia may lead to hypoglycemia or acidosis and has been associated with increased mortality, increased risk of late-onset sepsis, IVH, pulmonary insufficiency, and hemorrhage

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[20, 21]. The vicious cycle of cooling causes norepinephrine release with pulmonary and peripheral vasoconstriction with increased right-to-left shunting of blood and maintenance of fetal circulation postnatally. To enable thermal neutrality, preterm newborns should be nursed in preheated and humidified incubators, and in heated beds after 32nd week of gestation or >1500 g. We provide them heated and humidified gases and clothe newborns with clothes and caps [33, 34].

6. Perinatal infection management

After the initial care of the newborn in the delivery room with drying the newborn's skin, providing warmth, positioning the head, and clearing the airway, the evaluation of respiration, and consequently oxygenation of peripheral organs follows. In case transitional period is prolonged and the signs of RDS persist, we have to obtain chest radiograph, blood gas analysis and perform sepsis work-up with complete blood count and cultures and start empirical antibiotic treatment with ampicillin or penicillin and gentamicin, especially if risk factors for early-onset sepsis are present. Early-onset infection with GBS typically imitates the RDS in preterm newborns with the clinical presentation and also radiographically so usually it is difficult to differentiate pneumonia from RDS without infection. Besides GBS congenital pneumonia can be caused by *Escherichia coli* and other microorganisms [35]. A well appearing newborn to a mother with chorioamnionitis should have a limited diagnostic evaluation and receive empirical antibiotic therapy. Well-appearing term newborns, born to mothers with appropriate IAP or inappropriate IAP with rupture of membranes for <18 h, need routine care and observation. Those term newborns whose mothers had inappropriate IAP and rupture of membranes for more than 18 h and all preterm newborns with inadequate IAP need clinical and laboratory evaluation and observation [17, 36]. There is no evidence to support routine antibiotic treatment of newborns with RDS and without risk factors for early-onset sepsis [37, 38]. In those newborns with RDS which do not have laboratory signs of sepsis and have negative cultures, the antibiotics should be discontinued as early as feasible [37, 39].

Late-onset sepsis occurs in one-fifth of premature newborns and is associated with increased mortality, prolonged hospitalization, and prolonged artificial ventilation, PDA, NEC, and BPD [40]. Newborns that were treated for neonatal sepsis later are at risk of poor weight gain and adverse neurodevelopmental outcome [41].

7. Fluid and electrolyte management

After birth, water and electrolyte balance is influenced by transitional and developmental adaptations of the newborn. More preterm newborns have more total body water, and extracellular fluid volume constitutes a greater part of total body water in comparison with term newborns. Furthermore, after birth, renal function of preterm newborns is reduced in comparison with term newborns and they lose more weight with diuresis which results from

an isotonic reduction of extracellular fluid. Newborns, especially more preterm ones loose water insensibly through the skin and respiratory system, especially in RDS, when respiratory rate is increased [42, 43]. Insensible water loss is increased by radiant heaters, phototherapeutic lights, and inappropriate water content of inspired air. Antenatal steroids besides the already mentioned effect on lung maturation also accelerate skin and kidney maturation. Preterm newborns whose mothers have received antenatal steroids had lower insensible water loss, less hypernatremia, earlier diuresis and natriuresis, and less nonoliguric hyperkalemia [44, 45]. In the first postnatal days, water balance is kept in a slightly negative state. Excessive fluid administration is associated with increased risk of PDA, NEC, and BPD [46]. Fluid balance and volume status can be evaluated by physical examination with signs of hydration, edema, and hemodynamic stability, body weight loss or gain, balance of fluid intake and output, and biochemistry evaluation of electrolyte concentration in plasma of the newborns. Fluid requirements therefore account for maintenance requirements, obligatory losses, and possible deficits and are gestational and postnatal age, ambient temperature and humidity, renal and respiratory function dependent. The electrolyte requirements for sodium, potassium, and chloride are approximately 1–2 mEq/kg/day except for the first day when isotonic reduction of extracellular fluid ensues. Diuretics cause electrolyte disturbances due to urinary loss of sodium and potassium and loop diuretics are associated with nephrocalcinosis so we prefer not to use them routinely [47].

8. Nutritional management

The newborn's nutritional status is influenced by his past history with genetic background, maternal body composition, and nutrition before and during pregnancy [48]. Many preterm newborns are born growth restricted because of inadequate intrauterine nutrient supply. Postnatal nutrition and metabolic capacity impact postnatal growth and development and have long-term consequences on the lung, brain, and other organ development and cognitive function [49]. The newborn’s brain consumes half of all the energy provided, and too little calories mean less brain volume and worse neurocognitive outcome. Adequate volume of fluids, the protein content, and energy balance in the newborn’s, and especially preterm’s nutrition should cover metabolic expenditure and growth requirements, thus setting the ground for optimal outcomes.

In newborns with RDS, early enteral feeding is frequently delayed because of concomitant medical problems and fear of complications as the feeding intolerance and NEC. Therefore, the parenteral nutrition is commenced as early as possible to correct prenatal, to prevent postnatal growth failure and to improve outcomes [50, 51]. The parenteral nutrition has to provide enough calories for energy and growth, which are met by carbohydrates, proteins, and lipids. Carbohydrates provide glucose, proteins provide essential amino acids and nitrogen, and lipids provide essential fatty acids. Essential nutrients needed for growth are electrolytes, vitamins, minerals, and trace elements [52–54].

The premature newborn needs parenterally about 100 kcal/kg/day of nonprotein energy for growing, 3/5 in the form of carbohydrates and 2/5 in the form of lipids. Glucose is the form of

carbohydrates that we give parenterally, and it is the primary energy supply for the newborn's brain. We start with 7 g/kg/day of glucose, which provides 4.8 mg/kg/min of glucose, and we increase the amount by 1.5–2 g/kg/day, up to 15 g/kg/day and maximum of 18 g/kg/day (12.5 mg/kg/min). Preterm newborns are prone to hypoglycemia because of higher glucose needs, decreased fat stores, and higher-energy consumption. On the other hand, for many metabolic and nutritional reasons, they are also prone to hyperglycemia. As early as feasible, we start with 2 g/kg/day of proteins and increase the amount by 0.5–1 to 3.5–4 g/kg/day of proteins, which is needed to attain the intrauterine growth rate [55, 56]. It is also important to provide the preterm 25 nonprotein kcal/1 g of proteins. Low blood urea nitrogen (BUN) is a sign of inadequate protein intake, but a high BUN does not correlate well with a high protein intake [57]. A preterm newborn daily loses 1 g of proteins through the kidneys, and a good caloric input with appropriately balanced diet accumulates 2 g of proteins. Thus, improperly balanced nutrition of a newborn can lead to a loss of 15% of protein mass in 2 days [58]. There are eight essential amino acids in parenteral nutrition and six more for the preterm newborn. Adding cysteine to the parenteral nutrition improved nitrogen balance [59], but the addition of glutamine had no clinical impact [60]. Concomitantly with proteins, we administer 20% of intravenous lipids, including essential fatty acids and long-chain n–3 polyunsaturated fatty acids and start with 1 g/kg/day and increase by 0.5 g/kg/day to a maximum of 3–4 g/kg/day [61–63]. Already 0.5 g/kg/day may provide prevention of essential fatty acid deficiency, and the tolerance is guided by triglyceride level of <200 mg/dL. The tolerance is better achieved with the use of continuous infusion of intravenous lipids over 24 h rather than intermittent dosing [64].

To maintain bone health, the newborns need 1.5–2 mmol/kg/day of calcium and the same amount of phosphorus, and 0.18–0.3 mmol/kg/day of magnesium. The optimal weight ratio of calcium and phosphorus is 1.3–1.7:1. Pediatric vitamin formulations of water- and fat-soluble vitamins and trace elements are in use, but they do not provide enough amounts of vitamin A, D and E so we add them enterally if feasible. Vitamin A affects normal eye and lung development, immunity, and cell differentiation. Supplementation of vitamin A in preterm newborns was associated with reduced risk of oxygen requirement [65]. Selenium supplementation prevented short-term morbidity in preterm newborns [66]. Although carnitine supplementation was not associated with weight gain or apnea reduction [67, 68] there are recommendations to add parenteral carnitine to preterm newborns needing parenteral nutrition for more than 2 weeks [69]. Nutritional status can be evaluated by anthropometry, body composition and biochemistry, clinical assessment and quantity, and quality dietary evaluation. Adverse effects of parenteral nutrition include line infection and sepsis, extravasation of parenteral fluid, cholestasis, and bone disease.

To correct the intrauterine growth restriction and achieve appropriate postnatal weight gain, the enteral feeding is also of great significance [70]. It is important to start enteral feeding as early as feasible; in very low birth weight (VLBW) newborns 10–20 mL/kg/day is started in the first 2–5 days, in low birth weight (LBW) newborns in first days [71]. Colostrum acts as the immune therapy for the newborn's intestine. Feeding newborns with minimal volumes of milk is known as trophic feeding, which has many beneficial effects for further feeding, increased

hormone secretion, motility, and decreased permeability of the gastrointestinal tract [72]. After a few days of gastrointestinal priming, feedings are increased by 10–20 mL/kg/day. Human milk in comparison with formula resulted in earlier adequate energy intake [73, 74]. Fast advancement of milk volume has no adverse outcome in comparison with slow advancement [71]. Feeding every two hours was superior to feeding every three hours in regards to the time to reach full enteral feeds and better weight gain [75]. Tube feeding can be bolus or continuous and neither is superior [76]. Feeding intolerance can be determined by emesis, gastric residuals, distended, and tender abdomen with changed bowel sounds and stool output, but most of them have little prognostic value [77–80]. The prokinetic erythromycin has not been shown to be effective [81–83]. When the newborn tolerates 100 mL/kg/day or has been consuming mother's milk for 1 week, formula or mother's milk is fortified. The goal of enteral feeding of the preterm newborn is to gain more than 15 g/kg/day.

9. Pain management

Critically ill newborn is confronted with different, more or less painful procedures every day in the NICU. Not every procedure is painful, but the usual response from the newborn is typical —removal of the affected part of the body and crying. The more severe the pain, the more distressful situation is for the newborn. Brain not yet fully developed may receive too many painful stimulations per day, and the tinny newborn may overreact even if the next stimulus is less or even not painful. Newborn Individualized Developmental Care and Assessment Program (NIDCAP) is a method of ensuring an adequate physical environment, reducing overwhelming sensory stimulations, and increasing sensitive parent caregiving, for proper brain growth and development of preterm newborns. Despite non-convincing evidence that NIDCAP improves long-term neurodevelopmental or short-term medical outcome, there is a need for high-quality researches using different techniques to diminish high environmental stress on the premature infants during their treatment in the NICU [84].

Newborns with RDS experience different kinds of pain depending on their morbidities: skin breaking procedures and tissue injury provoke acute or physiological pain, surgery, localized inflammation, and birth trauma cause established pain and diseases like NEC, meningitis, and scalded skin syndrome give rise to prolonged or chronic pain [85]. It has been estimated that sick newborns experience 12–16 procedures each day which are increasingly painful:

1. Routine procedures (physical examination, diaper changes, nasogastric or orogastric insertion, bladder catheterization) [86];
2. Moderately invasive procedures (endotracheal suction, heel lance, venipuncture, arterial puncture, peripherally inserted central catheter placement); and
3. Severely invasive procedures (central venous line placement, chest tube insertion) [87].

Management of pain in newborns with RDS encompasses prevention with first awareness of causing pain with different painful procedures and reduction of painful management of the newborn. The second line includes objective assessment for the detection of pain in each

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neonate. Thirdly, controlling the pain includes cooperation with parents to diminish pain experience, delivering proper analgesia before expected painful medical care and combining nonpharmacological interventions and pharmacological therapy [88–90].

An important issue in caring for a newborn with RDS is minimal handling or "do not touch" approach. This also enables us to take in mind the possible pain we are going to cause to the newborn with our intended handling and executed procedures. On the other hand, we have to carefully plan the management not to compromise the well-being of the newborn by not performing vital examinations and investigations. By planning the handling of the newborn in limited number of sessions per day, it is possible to disrupt the newborns less times and perform the examinations, nursing care, and blood withdrawal at the same time. We should use laboratory equipment that enables us to analyze several different chemical substances from one small blood sample to reduce the volume of blood taken from the child and avoid iatrogenic anemia. All sick newborns with RDS need intravenous line for fluid, nutritional, antimicrobial, blood pressure, and pain management so a central venous line as soon as possible and for newborns who need several blood investigations per day an artery line should be placed both with appropriate analgesia. With minimally invasive approach, we can gain many data on the well-being of the newborn by noninvasive monitoring with the use of transcutaneous measuring of the oxygen saturation in peripheral arteries and in different organs by the use of near-infrared spectroscopy (NIRS), partial pressures of oxygen, and carbon dioxide in skin capillaries or bilirubin concentrations [85, 89, 91].

For the assessment of pain, different observational scales designed for special newborn population are in use, which encompass many physiological and behavioral variables. Especially with observation of behavior, there is much subjectivity in the assessment procedure. The available assessment scales have proved usable in acute pain, but there is limited applicability of the assessment scales for assessing prolonged pain, pain in extremely low birth weight (ELBW) newborns and in those receiving paralytic agents [85].

First step on the ladder of pain management constitutes the nonpharmacological measures which include sweet peroral solutions, breastfeeding, sucking, skin-to-skin contact, and swaddling with facilitated tucking and sensorial saturation [92]. Combined use of nonpharmacological measures act synergistically [93–95]. Furthermore, when used with pharmacological measures, the pharmacologic use is lesser in frequency and dosage [88, 96]. Sucrose and glucose used before skin-breaking procedures reduced total crying time, lessened changes of physiological variables, and facial expressions and pain scores of multidimensional pain assessment scales [97, 98]. Currently, it is not entirely clear how sweet solutions suppress the responses to painful stimulation; do they only diminish the response to pain or they really influence the pain perception. With repeated dosing, there is a concern on neurodevelopmental outcome in the preterm newborns [99]. Sucrose alone is used for minor procedures, and combined with other analgesics for moderately painful procedures [97]. In cases when physically possible, breastfeeding or mother's milk is at least as effective as sweet solutions [100]. Further on, engaging different body sensors with sensations, like non-nutritive sucking, swaddling, facilitated tucking, rocking, holding, kangaroo care and sensorial saturation, gives the brain other stimuli and therefore the brain has closed door for pain reception [88, 92].

Topical analgesia with the use of Eutectic Mixture of Local Anesthetics (EMLA) or lidocaine alone are used with effect in venous, arterial, and lumbar punctures and also venous, arterial catheter placement, and circumcision. With reasonable dosing, methemoglobinemia is not a significant problem [101].

Systemic analgesia can be provided by nonopioid, nonsteroidal anti-inflammatory agents, opioid analgesics, and sedatives. Paracetamol (acetaminophen) does not diminish pain perception after assisted vaginal birth, heel lance, or eye examination. Paracetamol may diminish the need for morphine after surgical procedures in newborns [102]. We use nonsteroidal anti-inflammatory agents for closing PDA in preterm newborns, but because of their serious adverse effects, like gastrointestinal bleeding, platelet dysfunction and decreased glomerular filtration rate, we do not use them as analgesics in newborns. The most powerful analgesics are opioids, and morphine is the most frequently used, either intermittently for acute pain with invasive procedures or continuously for established pain during artificial ventilation or after surgery. Morphine reduces acute pain after some invasive procedures: central line, tracheal, and chest tube insertion [103, 104], but not heelstick [105] or tracheal suctioning [106, 107]. The NEOPAIN study showed no difference in mortality rate, severe IVH and PVL between ventilated preterm newborns receiving continuous morphine or placebo. The preterm newborns treated with morphine had less pain, but more hypotension, longer duration of artificial ventilation and longer time to full volume feeds [103]. Morphine is safe and effective for treating established pain after surgery in newborns [108, 109]. In extremely preterm newborns, opioid analgesics should be used cautiously [110, 111].

More rapid analgesia with fewer hemodynamic adverse effects is achieved by fentanyl and shorter-acting derivatives, which is suitable for acute invasive procedures in controlled clinical setting like tracheal tube and central line placement [112, 113]. There was no favorable effect on established pain during artificial ventilation of premature newborns using fentanyl [114]. Furthermore, premature newborns treated with continuous fentanyl had prolonged time of artificial ventilation and of meconium passage. Fentanyl is used for treating established pain after surgery and in newborns with pulmonary hypertension.

Ketamine causes analgesia with sedation and amnesia with no effect on respiration and increasing blood pressure and heart rate [115]. It is used in newborns with hemodynamic instability for acute pain with invasive procedures and for established pain during and after surgery [116]. Among sedatives midazolam which can cause prolonged sedation in sick preterm newborns is not recommended for use in preterm newborns [117].

Painful experiences in early childhood may have unfavorable consequences for neurodevelopment [118, 119]. Although there are some data indicating that prolonged use of analgesics in newborns does not influence long-term neurodevelopmental and behavioral outcome [120–122], more recent studies have shown some adverse long-term effects on growth, neurological, and behavioral outcome [123]. A positive autonomic nervous system's stability to pain in neonates with kangaroo care or skin to skin care can be proved by measuring heart rate variability [124, 125].

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10. Blood pressure and perfusion management

Systemic blood pressure is dependent on systemic blood flow with cardiac output and systemic vascular resistance. Hypotension ensues in cases of decreased cardiac output as a result of cardiac dysfunction or hypovolemia with inadequate compensation with vasomotor tone, or, decreased vasomotor tone with inadequate compensatory increase in cardiac output. Hypotension, especially in preterms, is difficult to define unequivocally; population-based normative blood pressure data show the increment of blood pressure with increasing gestational and postnatal age, but normal gestational and postnatal age dependent blood pressure range is not known [126]. The physiological principles of blood pressure define autoregulatory threshold where there is loss of autoregulation of blood flow to vital organs, functional threshold where there is loss of cellular function, and ischemic threshold where there is loss of functional integrity [127]. Blood pressure correlates poorly with systemic and cerebral blood flow; therefore, different measurement approaches combined with clinical assessment of adequate perfusion have been investigated for the purpose of better hemodynamic monitoring. Systemic blood flow can be measured by clinician performed ultrasound of the heart and blood vessels with the pressure wave-form analysis and by magnetic resonance imaging (MRI) [128, 129]. Systemic resistance is evaluated by Laser-Doppler technique and by NIRS [130]. Noninvasively, NIRS gives us information about oxygenation of organs, inferring about oxygen delivery, and oxygen demand of certain tissues. The brain activity can continuously be monitored by concomitant use of NIRS and amplitude integrated electroencephalography (EEG) [131, 132].

The blood flow is regulated by cardiac output, carbon dioxide tension, local neuronal and chemical activity, changes in cerebrospinal fluid hydrogen ion concentration, arterial oxygen content, hemoglobin, and blood glucose [133–135]. Accordingly, systemic blood flow can be improved by inotropes or volume, and systemic resistance can be improved by vasopressors and lusitropes. Treatment of neonatal hypotension improves blood pressure, cardiac output, organ blood flow, lactic acidosis, peripheral perfusion, and urine output. Neonatal hypotension endangers cerebral autoregulation and increases morbidity and mortality in preterm newborns [136, 137].

Low systemic blood pressure frequently occurs in the early stages of RDS. Therefore, blood pressure should frequently be measured, either noninvasively or invasively with intravascular line. For volume expansion, after hypovolemia crystalloid or colloid solutions are used [138, 139]. For decreased cardiac output because of cardiac dysfunction, the initial agent is dopamine, later dobutamine, and epinephrine are added [140, 141]. In newborns with refractory hypotension or high-dose inotropic therapy, glucocorticoid therapy increases blood pressure [142, 143]. Different developmental factors affect hemodynamic response to sympathomimetic amines in newborns [144]. Before deciding on a specific therapy of hypotension, potentially reversible causes have to be taken in mind and corrected if possible (measurement error, blood loss, pneumothorax, sepsis, adrenocortical insufficiency).

There is conflicting evidence on the management of hypotension improving clinically meaningful longer-term outcome measures in VLBW newborns, but there are many confounding

factors influencing the outcome of management of preterm newborns and studies are weak to show the impact [145–148].

Besides cardiac output, the oxygen supply to the tissues depends also on the content of oxygen in the arteries, which is in the biggest part a function of concentration of hemoglobin. Target values of hemoglobin or hematocrit differ with regards to the gestational and postnatal age of the newborn, the rate of evolution of anemia, the presence of clinical signs of anemia, and the degree of respiratory support [149]. Targeting to lower concentrations of hemoglobin in ELBW newborns might have no effect on short-term outcomes, but may have a negative impact on the longer-tem neurodevelopmental outcome [150, 151]. Anemia can be avoided or postponed by delayed cord clamping or cord milking and also by applications of erythropoietin. Delayed cord clamping and cord milking in preterm newborns was associated with higher hematocrit, fewer transfusions, less IVH, NEC, and no increased need for phototherapy because of jaundice [152–156]. Also, preterm newborns who were receiving erythropoietin received fewer transfusions and had higher cognitive scores at 18–22 months of corrected age [157, 158].

11. PDA management

Shunting blood from the aorta to the pulmonary artery means decreased blood flow in the systemic circulation and low perfusion of peripheral organs and increased blood flow in the pulmonary circulation with RDS, pulmonary edema, BPD, IVH, NEC, and heart failure. Newborns with PDA have higher mortality rate and increased risk of pulmonary edema, hemorrhage, and BPD. The field of management of the PDA is an area in neonatal practice which has, perhaps, changed the most in the last decades and many questions still remain unanswered. The uses of antenatal steroids, postnatal surfactant, and the gentler modes of ventilation with lower oxygen saturation targets may have lowered the incidence and the impact of clinically significant PDA shunt. In VLBV newborns with RDS, PDA is present in 30% [159, 160]. Current management of the PDA generally includes three approaches. Supportive care for newborns with PDA encompasses providing thermal neutrality, using PEEP, keeping hematocrit between 35 and 40%, fluid restriction of 110–130 ml/kg/day, permissive hypercapnia, low oxygen saturation targets and, in case of diuretic need, thiazide diuretics over loop diuretics. If the newborn has poor perfusion, a large left-to-right shunt and remains artificially ventilated for a longer time a course of cyclooxygenase (COX) inhibitors is administered, favoring ibuprofen over indomethacin, because the latter is reducing blood flow to the brain, gastrointestinal tract, and kidneys [161, 162]. Ibuprofen is efficacious for closing PDA given either intravenously or orally [163]. Newborns, who remain artificially ventilated and have failed to respond to COX inhibitor, are candidates for surgical ligation, which has been associated with adverse long-term outcomes [164].

The prophylactic therapy to reduce the incidence of PDA has not been proved to be of benefit. The prophylactic indomethacin has been shown to have no impact on mortality, neurologic impairment, BPD, or NEC although it was associated with reduction of hemodynamically important PDA and severe IVH [165]. The prophylactic ibuprofen has been linked with adverse effects [166, 167].

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12. Postnatal supplemental management of respiratory support

Apnea of prematurity is a developmental consequence of immature respiratory center in premature newborns. Besides mechanical ventilation with oxygen supplementation the management of apnea of prematurity encompasses supportive measures like assuring the temperature stability, proper positioning of the newborn's head and neck and ensuring the nasal patency. Methylxanthines stimulate the respiratory drive by increasing the responsiveness of respiratory center to carbon dioxide and decreasing its hypoxic depression. The medicines also have inotropic effects on respiratory muscles [168]. Caffeine is being preferred over theophylline and other agents [169]. Caffeine therapy has been proved to shorten the duration of mechanical ventilation and supplemental oxygen and also reducing the risk of BPD and PDA ligation [170, 171]. The same effects have been shown for prophylactic use of caffeine in very preterm newborns [172, 173]. There have been some positive neurodevelopmental effects of caffeine therapy proved during follow-up of children treated with caffeine during neonatal period [174–176].

The duration of mechanical ventilation can be shortened and the risk of BPD diminished by the use of postnatal tapering course of low- (<0.2 mg/kg/day) or even very low-dose dexamethasone (0.05 mg/kg/day) [177, 178]. Hydrocortisone has been proved to have the same beneficial effects on earlier extubating of mechanically ventilated preterm newborns [179].

13. Conclusion

For the best outcomes of newborns with RDS, besides optimal pulmonary management, it is of extreme importance to have optimal supportive care (**Table 1**) starting prenatally and aiming at newborns being delivered in highly specialized tertiary centers with timing of birth after completion of a course of prenatal steroids. Body temperature should be maintained between 36.5 and 37.5°C. Preterm newborns should be nursed in incubators with high relative humidity (60–80%) and started on intravenous fluids of 70–80 ml/kg/day, later managed individually, based on weight change and serum electrolyte concentrations. Both parenteral and minimal enteral nutrition should be started as early as possible—from day 1—and quickly increased to 3.5 g/kg/day of proteins and 3 g/kg/day of lipids. Proper infection control starts prenatally with administering antibiotics to women with preterm prelabor rupture of membranes, and before labor to those with risk factors for early-onset sepsis. Furthermore, antibiotics are given to newborns with RDS until early-onset sepsis is ruled out. Adequate treatment of pain may be associated with decreased complications and mortality. Sedatives do not provide pain relief and may mask newborn's response to pain. Additionally, proper management of the PDA and hemodynamic support of the circulation with good systemic perfusion and oxygenation are also of utmost importance for the best outcomes of newborns with RDS.

Prenatal care	All the measures to prevent preterm delivery should be taken (counseling, progesterone, antibiotic, magnesium sulfate, tocolysis) If possible, birth should be delayed to allow effect of antenatal steroid therapy to the mother Timely and safe transport of the expectant mother to specialized tertiary centers Appropriate intrapartum antibiotic prophylaxis
Delivery room stabilization	Delayed cord clamping or cord milking at birth Collecting cord blood for diagnostic purposes (hemogram, hemoculture, blood group, virology) Stabilization of the preterm newborn in a plastic bag under a radiant warmer Drying the newborn's skin, providing warmth, positioning the head and clearing the airway, evaluation of respiration and oxygenation of peripheral organs
Supportive care	Nursing the newborn in incubators with heated and humidified air In cases with risk factors for early-onset sepsis and/or clinical and laboratory signs of sepsis antibiotics should be started Insertion of central lines to enable blood withdrawal for diagnostic purposes and parenteral nutrition Careful fluid and electrolyte therapy Early parenteral nutrition and early trophic feeding Minimal handling with clustered care of examination, blood withdrawal and nursing care at the same time but not to overburden the neonate Regular use of appropriate pain assessment scales and proper analgesia before planned procedures Regular measurement of blood pressure and assessment of peripheral perfusion to decide on possible hemodynamic therapy Targeting hemoglobin or hematocrit values in regards to the gestational and postnatal age, the rate of evolution of anemia, the presence of clinical signs of anemia and the degree of respiratory support needed Consideration on the presence and clinical significance of patent ductus arteriosus to decide on possible therapies Caffeine therapy to minimize the need for and duration of ventilation Consideration on postnatal tapering course of low- or very low-dose dexamethasone or hydrocortisone

Adapted from Sweet et al. [1].

Table 1. Summary of recommendations for non-pulmonary management of newborns with respiratory distress.

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