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Neonatology (T Thorkelsson, Section Editor)

Initial Management of the Extremely Low-Birth-Weight Infant

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Opinion statement

This review focuses on latest developments in the care of extremely preterm infants during birth and the first hours of life. Improvements in obstetric management of pregnancies complicated by imminent preterm delivery include timely transfer to tertiary-care hospital, prenatal administration of steroid, and magnesium sulfate for neonatal neuroprotection. Placing the newborn infant in a plastic bag or wrapping immediately after birth has improved temperature control. The use of noninvasive respiratory support and caffeine and using lung protective measures during mechanical ventilation have improved long-term pulmonary outcome. Early feeding has improved growth and decreased gastrointestinal complications. Over the last decade, survival of extremely low-birth-weight infants, i.e., infants with birth weight <1000 g, has improved considerably, but with the price of high risk for long-term complications. Focus on future research should mainly aim at improving long-term outcome of this group of patients.

Introduction

There has been a marked improvement in the survival of preterm infants over the past few decades, especially the most immature ones [1, 2]. This is due to advances is obstetric and neonatal intensive care, including the use of prenatal steroids, administration of pulmonary surfactant, and advances in respiratory management. However, extreme prematurity is still associated with considerable mortality and morbidity, including adverse developmental

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outcome [3]. Therefore, optimal care is paramount for these infants, especially around the time of birth, in order to optimize their short- and long-term outcome.

The purpose of this article is to provide an overview of initial management of extremely low-birth-weight infants, traditionally defined as infants with birth weight less than 1000 g. We will discuss obstetric care, initial stabilization of the infant, and management in the intensive care unit in the first several hours after birth.

Prenatal care

The limit of viability is defined as the gestational age at which the infant has a reasonable chance of survival outside the womb. Survival rates in the extremely preterm population have improved greatly during the last few decades [3, 4, 5•, 6] with current survival rates of 80–95% among infants born at 26–28 weeks gestation, and survival rates among infants born between 23 and 24 weeks gestation are reported as high as 40–60% [4, 6]. However, a significant proportion of the infants in the earliest gestational ages survive with some degree of impairment. A recent meta-analysis revealed that the risk for moderate or severe impairments at school age varied between 43% at 23 weeks to 24% at 25 weeks of gestation [7].

There is a broad international consensus that infants born at > 25 weeks of gestation should be resuscitated and receive full intensive care, but there is an ongoing debate in both regional and national policies whether infants at 22–25 weeks of gestation should receive intensive care. Due to the complexity of the ethical and medical decisions when facing delivery near the limit of viability, it is very important that each institution sets up guidelines regarding management of these pregnancies. Decision-making ideally requires discussion at senior level among obstetricians and neonatologists with parental involvement at every step. Recent guidelines from the American College of Obstetricians and Gynecologists recommend that pro-active prenatal care as well as neonatal resuscitation from 24 weeks of gestation should be considered from 22 weeks of gestation [8].

Studies have shown that a pro-active prenatal approach increases survival in the extremely preterm population without the cost of higher morbidity [9, 10, 11••]. Prenatal transfer to a hospital where advanced maternal and neonatal intensive care is available should be advised for all pregnancies where early preterm delivery is imminent, preferably from 22 weeks of gestation [10, 12]. It is important that gestational age is accurately determined by a dating scan as survival rates increase by 2–3% per day in the 22 to 25 weeks of gestation.

Antenatal steroids have been shown to increase survival and decrease the risk for several serious complications of preterm birth [4, 13, 14•]. It is therefore recommended that a course of steroids should be given to pregnant women at gestations above limits of viability where preterm delivery is imminent, preferably given 48 h prior to delivery.

There is evidence of neuroprotective effects of prenatal maternal magnesium sulfate administration. A recent Cochrane review concluded that the prophylactic use of magnesium sulfate for maximum 48 h prior to delivery reduced the incidence of cerebral palsy as well as gross motor dysfunction at 18–30 months [15] with the number needed to treat set at 63. However, these results have not been confirmed in school-aged children [16]. Therefore, it is sufficient evidence to consider treatment with magnesium sulfate to mothers at risk for imminent preterm delivery.

There is conflicting evidence regarding antibiotic use in preterm labour. Current evidence suggests that the routine use of broad-spectrum antibiotics does not prolong pregnancy or improve outcome and should therefore not be recommended [17]. However, if there is evidence of rupture of membranes and amniotic fluid leakage antibiotics should be administered as it has been shown to prolong pregnancy and provide time for the administration of steroids [18].

Theoretically, tocolysis to prolong pregnancy could improve outcome. However, no current data support this notion even though tocolysis is routinely administered to women in preterm labor [19, 20]. If there is no sign of chorioamnionitis, it probably is prudent to administer tocolysis to delay preterm birth until corticosteroids have been administered for 48 h. However, studies have shown that prenatal inflammation in combination with ischemia increases the infant's risk for unfavorable neurodevelopmental outcome, and therefore, the decision to deliver the infant might be a better option in cases of suspected chorioamnionitis [21].

Cesarean delivery can be life saving for the preterm infant but carries increased risk of morbidity for the mother [22]. Current evidence suggests that a cesarean section increases survival and improves neurodevelopmental outcome of extremely preterm infants in cases of malpresentation or fetal growth restriction [4, 6, 23]. However, the significant increase in risk for the mother must be considered when deciding upon the mode of delivery.

Delivery room management

Preparation

Good preparation prior to delivery of the ELBW infant is important for successful resuscitation and good outcome of the infant. The team attending the birth should ideally be led by a neonatologist and include an experienced neonatal nurse. Prior to the delivery, it should be decided which team member is responsible for each component of the resuscitation. What needs to be prepared beforehand is shown in Table 1.

Cord clamping

Studies on term and moderately preterm infants have indicated that delaying clamping of the umbilical cord for more than 30 s is associated with less need for transfusions after birth, higher blood pressures, less intraventricular hemorrhage (IVH) of any grade, and less necrotizing enterocolitis [24••]. Studies on ELBW infants are scarce but suggest that the same holds true for this group of patients [25, 26]. However, cord clamping should not be delayed for more than 30 s, and great care should be taken to minimize the infant's heat loss.

Table 1. Preparation prior to arrival of the infant

Delivery room
Preheating of the delivery room/surgical suite
Radiant warmer
Warm towel
Plastic bag/wrap and a head cap
Pulse oximeter
ECG-monotor
Suction catheter
Gastric tube
T-piece device with a mask
Bag and mask
Laryngoscope, blade size 0
Endotracheal tubes, sizes 2.0, 2.5, and 3.0 mm ID
Cut tapes
Carbon dioxide detector
Surfactant
Umbilical catheter setup
Epinephrine
Normal saline
NICU
Incubator preheated to 36–37 °C with humidified air
Umbilical catheter setup
10% glucose infusion
Normal saline for arterial catheter infusion
CPAP
Respirator

It has been suggested that cord “milking” might accomplish goals similar to delayed cord clamping, but there is insufficient evidence on the safety and efficacy of this practice to recommend its routine use in the management of the ELBW infant.

Prevention of heat loss

The ELBW infant is especially prone to heat loss due to high body surface area-to-body weight ratio, decreased brown fat stores, thin subcutaneous fat layer, immature skin, and decreased glycogen stores. Hypothermia has been associated with increased mortality and morbidities, such as increased risk of IVH, apnea, hypoglycemia, and metabolic acidosis [27]. It is recommended that the temperature of newly born infants is maintained between 36.5 and 37.5 °C after birth through admission and stabilization [24••].

To prevent hypothermia, the delivery room or the surgical suite should be preheated to 24–26 °C prior to the delivery of the ELBW infant [28••]. Upon delivery, the infant should be wrapped in a warm blanket and placed under a radiant warmer. The practice of placing the newborn ELBW infant in a plastic bag or a wrap without drying and placing a cap on its head has been shown to significantly reduce the risk of hypothermia [29].

Assessment of heart rate and oxygenation

An increase in the newborn's heart rate is considered the most sensitive indicator of a successful response to intervention during resuscitation. Therefore, a rapid and accurate method to measure the newborn's heart rate is critically important. Auscultation of the precordium has traditionally been the preferred method for heart rate assessment during newborn resuscitation, and palpation of a pulse in the umbilical artery has also been used for this purpose. However, studies have shown that auscultation tends to underestimate the heart rate and palpation of a pulse in the umbilical stump may be difficult and unreliable [30]. Recently, pulse oximetry has been used as a tool for evaluating heart rate during resuscitation, but it tends to underestimate the heart rate during the first few minutes of life [31], which may potentially lead to unnecessary interventions. Electrocardiography (ECG) has been shown to be more accurate method of heart rate evaluation than clinical assessment or pulse oximetry [32, 33]. Therefore, we suggest placement of three-lead ECG as soon as the infant arrives at the resuscitation table for the monitoring of the infant's heart rate.

The use of pulse oximetry has been shown to be of value for the assessment of oxygenation during newborn resuscitation [24••]. Preferably, preductal saturation should be measured, which is performed by placing the oximeter probe on the right hand or arm of the infant.

Respiratory management

Most ELBW infants need respiratory support immediately after birth in order to achieve adequate alveolar-capillary gas exchange. However, the immature lungs of ELBW infants are vulnerable, and ventilation with high inflation pressures immediately after birth has been shown to induce lung injury in immature animals [34]. Therefore, inflation pressures should not exceed what is required to achieve improvement in heart rate or chest expansion [24••]. Usually, this is achieved with pressures not higher than 20–25 cm H2O. For this purpose, pressure-regulated T-piece mechanical devices are commonly used, by which inflation pressures can be accurately monitored and adjusted. These devices can also been used to provide the spontaneously breathing infant with continuous positive airway pressure (CPAP), which has been shown to reduce the need for mechanical ventilation in infants born at 25–28-week gestation [35]. Blend of air and oxygen should be used, and initial oxygen concentration of 21–30% is recommended [24••] which should subsequently be adjusted according to oxygen saturations. Hyperoxia should be prevented as it may increase the risk of retinopathy of prematurity (ROP). Preductal oxygen saturation targeting depends on the age of the infant. The following oxygen targeting during initial stabilization and resuscitation have been suggested [24••]:

1 min	60–65%
2 min	65–70%
3 min	70–75%
4 min	75–80%
5 min	80–85%
10 min	85–95%

Although these data are based on studies on term infants [36], they can be used as a guideline in the care of the ELBW infant.

Infants who have inadequate respiratory drive and those who do not reach adequate oxygen saturations with noninvasive respiratory support need to be intubated. Appropriate size of the endotracheal tube and its location are shown in Table 2. Carbon dioxide detectors can be used to determine whether the endotracheal tube is in the trachea [37]. Surfactant should subsequently be given, preferably prior to transfer to the nursery.

Transport to the NICU

A preheated incubator (36–37 °C) is a convenient way for transporting the ELBW infant from the delivery room to the nursery. Respiratory support should preferably be provided by a T-piece device. Oxygen supply should be provided with an oxygen-air blender, the infant's oxygenation monitored with a pulse oximeter, and both hypoxia and hyperoxia avoided.

Initial NICU management

The initial management in the NICU should aim at preventing rather than correcting physiological imbalances in these extremely fragile patients. When arriving in the nursery, it is important and facilitates the initial treatment of the infant that preparation for its arrival has already been done. It is prudent to have

Table 2. Size and location of the endotracheal tube

Gestation (weeks)	Estimated birth weight (g)	ETT size	Location at lip (cm)
23	587	2.0–2.5	5.5
24	686	2.5	5.5
25	789	2.5	6.0
26	896	2.5	6.0
27	1000	2.5–3.0	6.5

ETT Endotracheal tube

a checklist for what should be prepared beforehand to ensure that nothing is forgotten and to minimize the risk for unnecessary delay and to allow full attention on the care of the infant (Table 1).

Thermal environment

Hypothermia should be prevented as studies have shown a correlation between hypothermia at arrival in the NICU and early neonatal mortality in extremely preterm infants [38, 39•, 40]. This is especially important while stabilizing the infant, inserting catheters, and during intubation. For that purpose, the infant should remain inside the plastic bag or wrapping until all initial interventions are complete. If necessary, radiant heaters or warm blankets should be used during procedures. All extremely preterm infants should be nursed in a closed incubator with constant temperature and humidification since their immature skin is highly permeable and insensible water loss is much higher than in term infants [41, 42]. Either servo-control or frequent manual temperature measurements should be used to maintain constant skin temperature of 36.5–37.5 °C [43].

Fluids and electrolytes

Early venous and arterial accesses should be established. The insertion of umbilical catheters is to be preferred over peripheral catheters as they provide easy pain-free central access without breaking the skin barrier. Extremely preterm infants are prone to hypoglycemia, which should be avoided at all costs. Therefore, the provision of glucose containing solution should be commenced as soon as possible. Initially, 10% dextrose without electrolytes can be used to prevent hypoglycemia but early administration of amino acids (2–2.5 g/kg/24 h) and lipids (0.5–1 g/kg/24 h) seems to improve protein balance and blood glucose control as well as improve post-natal growth [44, 45]. Early enteral feeding has been shown to lower the rate of necrotizing enterocolitis and improve post-natal growth and should be initiated as soon as possible, starting at 0.5 ml every other hour [46], preferably the infant's own mother's milk but otherwise donor breast milk [47–49]. Therefore, mothers should be encouraged to start pumping breast milk as soon as possible.

Reasonable initial fluid administrations are 80–100 ml/kg/24 h. However, due to high insensible water loss of extremely preterm infants, their fluid requirement can be significantly higher. Subsequent fluid administration should be adjusted by plasma sodium levels, which should be monitored every 4–6 h and the amount of fluids given adjusted accordingly, without adding sodium unless serum sodium level is below 130 mmol/L [50]. Potassium should not be provided unless the infant has documented hypokalemia, as ELBW are at risk of hyperkalemia the first 24–48 h after birth.

Respiratory management

All extremely preterm infants are in variable degree of respiratory distress and need respiratory support. The need for intubation and positive pressure ventilation increases with decreasing gestational length, but those infants who do not require intubation fare best only with nasal CPAP [51]. For infants in need of surfactant, rapid intubation and extubation should be strived as mechanical ventilation increases the risk for bronchopulmonary dysplasia (BPD) [52, 53]. Surfactant should be administered to infants requiring FiO2 >0.40 [53] using rapid sequence induction for intubation if the infant does not require intubation in the delivery room [54]. If the infant does not require mechanical ventilation following surfactant administration, extubation and subsequent provision of nasal CPAP and caffeine have been shown to decrease apnea of prematurity and BPD, as well as to improve neurodevelopmental outcome [55, 56]. If the infant requires further mechanical ventilation, an approach to limit lung injury should be adopted. This includes avoiding baro-/volutrauma due to high tidal volumes and avoiding excessive exposure to supplemental oxygen [57••, 58•]. The infants should be ventilated with as low inspiratory volumes as possible and preferably utilizing volume-targeted ventilatory modes [58•]. Excessive supplemental oxygen should be avoided to reduce the risks of complications such as BPD and ROP, but insufficient oxygen supplementation is associated with increased mortality [59, 60•]. Thus, targeted oxygen saturations should be set at 91–95% [59, 60•, 61]. PaCO2 levels should be closely monitored and targeted at 45–55 mmHg to avoid both hypo- and hypercapnia [62]. Hypocapnia indicates excessively large tidal volumes which can predispose to BPD and has also been associated with periventricular leukomalacia (PVL) and poor neurodevelopmental outcome [63–65]. Severe hypercapnia on the other hand leads to acidosis and has been associated with IVH and poor neurodevelopmental outcome [66, 67]. Thus, close monitoring and regulation of PaCO2 is important. This can be accomplished by frequent blood gas measurements, volume-targeted ventilation, and transcutaneous monitoring of carbon dioxide (tcPCO2) or, preferably, a combination of all of the above. Great care must be taken when applying transcutaneous probes on the immature skin due to the risk of burns and it may not be feasible in the lowest gestational ages the first few days of life. Electrode temperature of 40 °C decreases the risk for skin burns but produces a measurement bias where tcPCO2 tends to overestimate arterial PCO2, but the correlation between tcPCO2 and arterial PCO2 is sufficient for its clinical use under these circumstances [68, 69].

Cardiovascular management

Cardiovascular instability is common in the extremely preterm infant and is associated with IVH and unfavorable neurodevelopmental outcome [70]. However, to recognize and treat hypotension in the preterm infant pose a clinical challenge. Curves for normal blood pressures in extremely preterm infants are lacking, but it has been recommended to use the infant's gestational week as a reference to mean arterial blood pressure [71]. Currently, there is no consensus on how to define hypotension and when to initiate treatment [72, 73] and treatment has not been shown to improve outcome [74••]. The clinician must make an overall assessment of the infant to decide when to initiate treatment for cardiovascular instability, and there is increasing evidence that "permissive hypotension" to a certain degree in the clinically well perfused infant may be acceptable [72, 75]. The assessment includes, in addition to mean arterial blood pressure, clinical evaluation of end-organ perfusion and cardiac ECHO to determine cardiac output [76]. Measurement of superior vena cava flow can also be helpful, but it is highly operator dependent. Cephalic nearinfrared spectroscopy (NIRS) has been used to assess cerebral blood flow and can be of value in units experienced in the use of this device [77].

If the infant needs treatment for cardiovascular instability, the clinician should aim at choosing the optimal treatment depending on its cause. Most preterm infants with low blood pressures have normal intravascular volume [72, 78], and it is a common observation that fluid boluses have little change in the blood pressure and any changes which may be noted are transient [72]. Furthermore, volume boluses have been associated with increased mortality and unfavorable neurodevelopmental outcome [79, 80]. Therefore, volume expansion should not be provided unless there is evidence of hypovolemia [81], instead inotropes should be commenced, either dobutamine or dopamine [75]. If there are clinical and/or echographical signs of poor cardiac output, dobutamine should be the inotrope of choice. In sepsis and other conditions where peripheral vascular resistance is low with normal or high cardiac output, treatment with dopamine should the drug of choice, as it increases peripheral vascular resistance in addition to its inotropic effects [82]. Epinephrine can also be used for this purpose [83], but data on the use of norepinephrine in ELBW infants are sparse. Treatment with hydrocortisone in physiological stress doses (1 mg/kg × 4) may be considered if aforementioned treatments are unsuccessful in the very sick infant [84].

Antimicrobiotics

Extremely preterm infants are at increased risk of developing bacterial infections but are also vulnerable to the adverse effects of indiscriminate use of antibiotics. Current evidence suggests that antibiotics are only warranted if there is a clinical suspicion of infection and should be discontinued if blood culture is negative, unless there are clinical or laboratory signs of infection [85]. Prophylactic use of antibiotics should be discouraged. Each unit should set a policy for empirical choice of antibiotics [85]. On the other hand, studies have shown that antifungal prophylactic treatment in ELBS infants decreases the risk of invasive antifungal infections and should therefore be recommended [86•].

Conclusions

ELBW infants are a vulnerable group of patients, and good initial management is paramount for their short- and long-term outcome. This includes good monitoring of the fetus and early interventions if fetal stress occurs. Timely preparation prior to arrival of the infant and good coordination of the medical and nursing staff during initial stabilization are important. Hypothermia should be prevented. Lung protective measures should be provided during respiratory support, mainly by avoiding high inflation pressures. Three-lead ECG is the most reliable way of heart rate monitoring during resuscitation, and pulse oximetry is a convenient way of monitoring oxygenation. Hypoglycemia should be prevented by early administration of glucose-containing solution, and early provision of other nutrients is also important. Noninvasive respiratory support should be preferred over invasive ventilation. Both hypo- and hypercapnea should be prevented, and oxygen saturation should be targeted at 91–95%. Cardiovascular instability of the ELBW infant is common, but unfortunately consensus on when and how to provide cardiovascular support is lacking. Research in this and other areas in the management of ELBW infants are needed in order to further improve the outcome of these delicate patients.

Compliance with Ethical Standards

Conflict of Interest

Snjolaug Sveinsdottir declares no conflict of interest. Matthildur Sigurdardottir declares no conflict of interest. Thordur Thorkelsson declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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