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Consensus Statement

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Standardized Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus

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Key Words
Congenital diaphragmatic hernia · Consensus guidelines · Ventilation · High-frequency oscillatory ventilation · Extracorporeal membrane oxygenation · Pulmonary hypertension · Hemodynamic management · Surgical repair

Abstract
Congenital diaphragmatic hernia (CDH) is associated with high mortality and morbidity. To date, there are no standardized protocols for the treatment of infants with this anomaly. However, protocols based on the literature and expert opinion might improve outcome. This paper is a consensus statement from the CDH EURO Consortium prepared with the aim of achieving standardized postnatal treatment in European countries. During a consensus meeting between high-volume centers with expertise in the treatment of CDH in Europe (CDH EURO Consortium), the most recent literature on CDH was discussed. Thereafter, 5 experts graded the studies according to the Scottish Intercollegiate Guidelines Network (SIGN) Criteria. Differences in opinion were discussed until full consensus was reached. The final consensus statement, therefore, represents the opinion of all consortium members. Multicenter randomized controlled trials on CDH are lacking. Use of a standardized protocol, however, may contribute to more valid comparisons of patient data in multicenter studies and identification of areas for further research.

Introduction

Congenital diaphragmatic hernia (CDH) is a congenital anomaly which affects 1 in 3,000 live births [1]. Despite advances in neonatal care, CDH is associated with a high risk of mortality and morbidity [2]. The combination of pulmonary hypoplasia and abnormal morphology of the pulmonary vasculature leads to severe respiratory insufficiency in over 90% of cases in the first hours after birth. Infants with CDH are at increased risk of developing persistent pulmonary hypertension of the newborn (PPHN) due to a pathological development of the pulmonary vasculature. Several triggers such as hypoxemia, acidosis and pulmonary vascular damage caused by me-

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Table 1. Levels of evidence

Level	Description of evidence
1++	High quality meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews or randomized controlled trials, or randomized controlled trials with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies, or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal
3	Nonanalytic studies, e.g. case reports, case series
4	Expert opinion

Table 2. Grades of recommendation

Grade	Description of grade
A	At least 1 meta-analysis, systematic review, or randomized controlled trial rated as 1++ and directly applicable to the target population, or a systematic review of randomized controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or extrapolated evidence from studies rated as 2+

chanical ventilation sustain PPHN through reactive vasoconstriction and vascular remodeling. Therefore, it would seem best to achieve optimal management of elevated pulmonary arterial pressure and prevent further damage to the lung before undertaking surgical repair of the diaphragmatic defect.

Single center experience may not be representative as they often include a small number of patients [3]. A literature review by Logan et al. [4] revealed a limited number of clinical trials examining interventions to improve survival of infants with CDH. Recently, Deprest et al. [5] published a manuscript, together with some experts of the CDH EURO Consortium, on the perinatal management of isolated CDH. However, there are no extensive standardized protocols for the postnatal management of CDH. As a consequence, members of the CDH EURO Consortium, a collaboration of specialized CDH centers in Western Europe, have developed a consensus statement for the postnatal treatment of patients with CDH based on the recent literature and expert opinion.

Members of the CDH EURO Consortium from centers in which more than 10 infants with CDH are treated per year held a consensus meeting. It covered all aspects of the treatment of infants with CDH and was based on a summary of recent relevant literature. The studies were graded according to the Scottish Intercollegiate Guidelines Network (SIGN) Criteria [6]. This grading system is based on study design and methodological quality of individual studies. Five experts individually determined the levels of evidence of the literature on the guidance of a SIGN-checklist. Four of these have clinical experience with CDH and all 5 have scientific schooling and experience. Differences in opinion were discussed until full consensus was reached. The final consensus statement, therefore, represents the opinion of all consortium members. The levels of evidence and grades of recommendation according to the SIGN criteria are presented in tables 1 and 2, respectively.

Prenatal Diagnosis and Delivery

With the increased use of prenatal ultrasound, many cases of CDH are now detected before birth. After diagnosis, a more detailed evaluation should be performed to determine the location of the defect, the absolute and observed/expected lung-to-head ratio (O/E LHR), the position of the liver and the presence or absence of other associated congenital anomalies or syndromes [7, 8].

In infants with CDH, other associated congenital anomalies are present in 10–40% of the cases [9, 10]. Cardiac anomalies are present in about 25% of the infants with CDH [9, 11].

If CDH is diagnosed prenatally, an experienced tertiary center with a high case volume may be the optimal environment for the delivery and further treatment of an infant with CDH. A recent study by Grushka et al. [12] has shown that survival was higher in infants born in centers that have more than 6 cases a year admitted to their ward. There were, however, no differences in the need for extracorporeal membrane oxygenation (ECMO) treatment or duration of ventilation between centers that admitted more than 6 and centers that admitted less than 6 cases per year [4, 12].

There is still some doubt about the preferred mode of delivery and the timing of delivery in case of a CDH pregnancy. Recent studies from the CDH study group reported no significant differences in overall survival between patients with CDH born by spontaneous vaginal delivery, induced vaginal delivery and elective caesarean section [13, 14]. Survival without the use of ECMO, however, was higher for patients born by elective caesarean section according to one study [13]. With regards to the timing of delivery, a recent paper by Stevens et al. [14] reported that infants with CDH born at a gestational age of 37–38 weeks with a birth weight above 3.1 kg had a higher survival rate, less need for ECMO and a greater rate of survival if ECMO was used than infants with CDH born at a gestational age of 39–41 weeks. The reason for this difference in outcome is not clear, but case selection, differences among centers and an increase in pulmonary vascular abnormalities in later gestational ages have been proposed as possible explanations [14]. Earlier data of the ELSO Registry reported higher survival rates and a shorter duration of ECMO treatment in infants born at a gestational age of 40–42 weeks compared to infants with CDH born at a gestational age of 38–39 weeks who were treated with ECMO [15]. The best mode and timing of delivery in infants with CDH is still unclear and, therefore, deserves further study.

If there is premature labor or a risk of preterm delivery between 24 and 34 weeks gestational age, antenatal steroid therapy should be given according to the guidelines of the NIH [16]. Although there are no studies specifically focusing on this issue in premature infants with CDH, the consortium sees no reason to defer from this policy as prenatal steroid therapy has been shown to be of benefit in babies born prematurely without CDH. Prenatal steroid therapy given after a gestational age of 34 weeks has shown no benefit with regard to survival and respiratory outcome in infants with CDH [17].

Recommendations

- Following prenatal diagnosis, the absolute and O/E LHR and the position of the liver should be evaluated (grade of recommendation = D).
- Planned vaginal delivery or cesarean section after a gestational age of 37 weeks in a designated tertiary center should be pursued (grade of recommendation = D).
- In case of preterm labor prior to 34 weeks of gestation, antenatal steroids should be given (grade of recommendation = D).

Initial Treatment and Procedures in the Delivery Room

Initial treatment and procedures in the delivery room are based on the Guidelines of the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations [18].

Monitoring and Goal of Treatment

Measurements of heart rate, pre- and postductal saturations, and, if necessary, invasive or noninvasive blood pressure are recommended.

The key principles of successful delivery room resuscitation and stabilization are the avoidance of high airway pressures and the establishment of an adequate preductal arterial saturation. Previous studies advised keeping preductal arterial saturations between 85% and 95% as higher levels may lead to administration of a high oxygen concentration, more aggressive ventilation and a subsequent risk of oxygen toxicity and ventilator-induced lung injury [19–21]. However, some members of the consortium agreed on preductal saturation boundaries in the delivery room of 80–95% in infants with CDH based on expert opinion.

Intubation and Ventilation

Although there is no specific evidence, the consortium recommends intubating infants with CDH immediately after birth. This is done to reduce a possible risk of pulmonary hypertension due to prolonged acidosis and hypoxia which might be caused by delayed intubation. Ventilation by bag and mask may cause distension of the stomach and must be avoided as it may limit expansion

of the hypoplastic lung. Low peak pressures, preferably below 25 cm H_2O, are given to avoid lung damage to the hypoplastic and contralateral lung [22]. FiO_2 (fraction of the oxygen concentration) should be started at 1.0 and adjusted downwards to achieve preductal saturations between 80 and 95%.

Nasogastric Tube

Immediate placement of an oro- or nasogastric tube with continuous or intermittent suction will help to prevent bowel distension and any further lung compression. Until surgical repair, continuous suctioning is the recommended procedure to decompress the abdomen.

Vascular Access

A central or peripheral venous line should be inserted to allow the administration of fluids and, if necessary, inotropic vasopressor drugs. An arterial line should be inserted for blood sampling and monitoring the arterial blood pressure; preferably, this should be done in the labor ward. As preductal PaO_2 measurements reflect the cerebral oxygenation, the arterial line should be inserted into the right radial artery if possible. An umbilical arterial line may be placed, but as this reflects the postductal situation, it is less desirable than a right radial artery line.

Blood Pressure Support

In infants with CDH, pulmonary vascular resistance remains elevated after birth, resulting in right-to-left shunting of blood through the ductus arteriosus and/or foramen ovale. This can lead to hypoxemia and acidosis, which in turn can perpetuate pulmonary hypertension. Measures to increase systemic blood pressure may minimize right-to-left shunting. However, there is no need to increase blood pressure levels to supranormal values if preductal saturations are between 80 and 95%. Thus, the consortium advises to maintain arterial blood pressures at normal levels for gestational age [23]. Only if preductal saturations fall below the target values, higher blood pressures should be pursued. If there is hypotension and/or poor perfusion, 10–20 ml/kg NaCl 0.9% should be administered once or twice. If perfusion and blood pressure do not improve, inotropic and vasopressor agents should be considered according to the local practice of the hospital.

Sedation and Analgesia

There is no specific evidence on sedation and analgesia in infants with CDH. However, several investigators have studied physiological responses of neonates to awake intubation and reported significant rises in systemic arterial blood pressure and intracranial pressure, as well as significant decreases in heart rate and transcutaneous oxygen saturations [24]. As soon as venous access is established, sedation and analgesia should be started without delay. Careful monitoring of the blood pressure is warranted in these situations. There is debate whether infants with CDH should receive a neuromuscular blocking agent. Indeed, many of the consortium members do not routinely paralyze CDH infants.

Enema

Some centers give enemas to infants with CDH with the goal to decompress the bowel by inducing defecation. There is no evidence that this procedure improves outcome.

Surfactant

Preliminary data indicated that surfactant therapy may be associated with a higher mortality rate, greater use of ECMO therapy and more chronic lung disease in infants with CDH [25]. In preterm infants with CDH, surfactant administration was also associated with lower survival rate [26]. Therefore, the routine use of surfactant replacement in infants with CDH should be avoided.

Recommendations

- After delivery, the infant should be intubated immediately without bag and mask ventilation (grade of recommendation = D).
- The goal of treatment in the delivery room is achieving acceptable preductal saturation levels between 80 and 95% (grade of recommendation = D).
- Ventilation in the delivery room may be done by conventional ventilator or ventilation bag with a peak pressure as low as possible, preferably below 25 cm H_2O (grade of recommendation = D).
- An oro-or nasogastric tube with continuous or intermittent suction should be placed (grade of recommendation = D).
- Arterial blood pressure has to be maintained at a normal level for gestational age. In case of hypotension and/or poor perfusion, 10–20 ml/kg NaCl 0.9% should be administered 1–2 times and inotropic agents should be considered (grade of recommendation = D).
- Sedatives and analgesics should be given (grade of recommendation = D).
- No routine use of surfactant in either term or preterm infants with CDH (grade of recommendation = D).

Ventilation Management in the Intensive Care Unit

A ventilation strategy aiming for preductal saturations between 85 and 95%, postductal saturation levels above 70% and arterial CO_2 levels between 45–60 mm Hg (permissive hypercapnia) is well accepted. In the first 2 h, preductal saturation levels as low as 70% may be accepted if they are slowly improving without ventilator changes and organ perfusion is acceptable, indicated by a pH greater than 7.2 and $PaCO_2$ <65 mm Hg [27, 28]. Thereafter, preductal saturation levels are preferably kept between 85 and 95%. In individual cases, however, levels down to 80% may be accepted, providing organs are well perfused as indicated by a pH above 7.2, lactate levels <5 mmol/l and urinary output above 1 ml/kg/h. Oxygen toxicity can be avoided by decreasing FiO_2 guided by the saturation levels described above [29].

The optimal initial ventilation mode for newborns with CDH is not clear. Nevertheless, there is accumulating evidence that ventilator-induced lung injury may have a significant negative impact on outcome in newborns with CDH [30–33]. Permissive hypercapnia and 'gentle ventilation' in neonates with CDH has been reported to increase survival [29, 34–36].

Conventional Ventilation

Until now, the most experience exists with pressure-controlled ventilation as conventional ventilation mode in infants with CDH.

Based on retrospective studies [27–29, 35–37] and clinical experience, the consortium recommends limitation of peak pressures to 25 cm H_2O or less, a PEEP (positive end-expiratory pressure) of 2–5 cm H_2O and adjustment of the ventilator rate to obtain $PaCO_2$ levels between 45 and 60 mm Hg. If a PIP (positive inspiratory pressure) of over 28 cm H_2O is necessary to achieve pCO_2 and saturation levels within the target range, other treatment modalities should be considered. Weaning from ventilation should preferentially be by means of decreasing PIP; frequency and/or the PIP-PEEP should be modified to achieve $PaCO_2$ levels above 45 mm Hg.

High-Frequency Oscillatory Ventilation

The physiological rationale for use of high-frequency oscillatory ventilation (HFOV) derives from its ability to preserve end-expiratory lung volume while avoiding overdistension, and therefore lung injury, at end-inspiration. Retrospective studies have demonstrated effective CO_2 reduction and increased survival in neonates with CDH [38, 39]. However, a prospective randomized controlled trial on the use of HFOV as an initial ventilation mode in infants with CDH is still lacking.

The indications for HFOV are not clearly defined. Mostly it is used as rescue therapy in severe and persisting hypoxemia and hypercapnia on conventional ventilation. In some centers it is the standard initial ventilation mode. There is no evidence for the initial settings of HFOV in infants with CDH. The mean airway pressure, however, should be adjusted to have an adequate expansion of the lungs. A chest radiograph should be performed to confirm that the lungs are not overinflated, as defined by a contralateral lung expansion such that more than 8 ribs are visible above the diaphragm [40].

Chest Radiograph

In all patients, a chest radiograph should be made as soon as possible to assess the initial condition. Chest radiographs should be repeated guided by the patient's clinical condition and mode of ventilation.

Recommendations

- Adapt treatment to reach a preductal saturation between 85 and 95% and a postductal saturation above 70% (grade of recommendation = D).
- In individual cases, preductal saturation above 80% might be acceptable, as long as organs are well perfused (grade of recommendation = D).
- The target $PaCO_2$ range should be between 45 and 60 mm Hg (grade of recommendation = D).
- Pressure-controlled ventilation: initial settings are a PIP of 20–25 cm H_2O and a PEEP of 2–5 cm H_2O; ventilator rate of 40–60/min (grade of recommendation = D).
- HFOV: initial setting mean airway pressure 13–17 cm H_2O, frequency 10 Hz, Δp 30–50 cm H_2O depending on chest wall vibration (grade of recommendation = D).
- After stabilization, the FiO_2 should be decreased if preductal saturation is above 95% (grade of recommendation = D).

Further Management in the Intensive Care Unit

Monitoring

Heart rate, invasive blood pressure and pre- and postductal saturation should be monitored routinely.

Hemodynamic Management

Hemodynamic management should be aimed at achieving appropriate end-organ perfusion determined

by heart rate, capillary refill, urine output and lactate levels. If the heart rate is within the normal range, capillary refill is below 3 s, urine output is over 1.0 ml/kg/h, lactate concentration is below 3 mmol/l and there are no symptoms of poor perfusion, no inotropic support is required.

If there are signs of poor perfusion or if the blood pressure is below the normal level for gestational age with a preductal saturation below 80%, echocardiography should be performed to determine whether the poor perfusion is due to hypovolemic or cardiogenic shock. If there is hypovolemia, saline fluid therapy should be started (10–20 ml/kg NaCl 0.9% up to 3 times during the first 1–2 h). If necessary, this should be followed by inotropic therapy. Hydrocortisone may be used for treatment of hypotension after conventional treatment has failed [41]. In case of poor perfusion, vasopressor therapy should be started. In case of cardiogenic shock, as demonstrated by dysfunction of the left and/or right ventricle, inotropic agents should be considered [42].

Recommendations

- If symptoms of poor perfusion and/or blood pressure below the normal level for gestational age occur and are associated with preductal saturation below 80%, echocardiographic assessment should be performed (grade of recommendation = D).
- In case of hypovolemia, isotonic fluid therapy 10–20 ml/kg NaCl 0.9% up to 3 times during the first 2 h may be given and inotropics should be considered (grade of recommendation = D).

Pulmonary Hypertension Management

The physiological basis of pulmonary hypertension in infants with CDH is a decreased number of pulmonary arterial structures associated with significant adventitial and medial wall thickening due to an increased amount of smooth muscle cells in pulmonary arteries of all sizes, with abnormal intra-acinar arterioles. As a result, elevated pulmonary vascular resistance may lead to right-to-left shunting after birth. This may result in hypoxemia and a difference in pre- and postductal oxygen saturation. However, absence of a pre- and postductal gradient in oxygenation does not exclude the diagnosis of pulmonary hypertension in the newborn since the right-to-left shunting may occur predominantly through the foramen ovale rather than through the ductus arteriosus. Therefore, 2-dimensional echocardiography performed within the first 24 h after birth remains one of the best modalities for the real-time assessment of pulmonary arterial diameter and right heart function [43–45]. Especially in severe cases of pulmonary hypertension, a cardiac ultrasound may help to evaluate right ventricular dysfunction and/or right ventricular overload, which can also lead to left ventricular dysfunction. In patients with CDH, left ventricular dysfunction, either caused by right ventricular overload or a relative underdevelopment of the left ventricle, is associated with a poor prognosis [46].

If preductal saturations fall below 85% and there are signs of poor organ perfusion, treatment of pulmonary hypertension should be initiated by optimizing blood pressure. Adequate intravascular volume should be maintained with intravenous fluids as described above. Transfusion of packed red blood cells may be required to optimize tissue oxygen delivery. No studies show evidence of increasing systemic vascular resistance to treat right-to-left shunting, but a number of centers advise using inotropics such as dopamine, dobutamine and epinephrine to maintain blood pressure at the normal levels for gestational age. Most recent publications advise to keep the systemic blood pressure over 40 mm Hg [47]. One study successfully used norepinephrine to increase systemic blood pressure in neonates with PPHN [48].

If pulmonary hypertension persists, pulmonary vasodilator therapy should be given, with inhaled nitric oxide (iNO) as the first therapeutic choice. Endogenous nitric oxide regulates vascular tone by relaxation of vascular smooth muscle cells. In several studies, iNO produces potent and selective pulmonary vasodilation. In neonates with PPHN, iNO improves oxygenation and decreases the need for ECMO. The largest randomized controlled trial of early iNO therapy in infants with PPHN due to CDH did not demonstrate a beneficial effect for iNO [49]. The immediate short-term improvements in oxygenation seen in some treated infants may be of benefit, however, for transport or the bridging period to ECMO. At an oxygenation index of 20 or higher and/or a pre- and postductal saturation difference of 10% or more, iNO may be given for at least 1 h [50]. Studies to date have not reported a consistent effect according to iNO dose [51, 52]. Therefore, this needs further prospective study.

If there is no or an insufficient response to iNO, intravenous prostacyclin or prostaglandin E1 should be considered. In recent case reports, these agents have been used successfully in treating pulmonary hypertension in neonates with and without CDH [53–57]. The effects of

treatment for pulmonary hypertension may be best addressed by repeated cardiac evaluation [46]. A 10–20% reduction in the pre- and postductal saturation difference or a 10–20% increase in PaO_2, however, may be used as guidance in evaluating the course of pulmonary hypertension [58].

In the presence of systemic or suprasystemic pulmonary artery pressure, the right ventricle might be overloaded, as demonstrated by enlargement of the right ventricle and a leftward shift of the interventricular septum. This can lead to insufficient filling of the left ventricle and poor systemic perfusion. To protect the right ventricle from excessive overload due to increased afterload, re-opening of the ductus arteriosus might be performed [46].

Sildenafil, a phosphodiesterase 5 inhibitor, has been used in the treatment of pulmonary hypertension in adults and in the management of postoperative pulmonary hypertension in children with CDH [59, 60]. Case reports in newborns with CDH suggest some improvement in oxygenation and cardiac output from sildenafil alone or in combination with iNO [60]. Currently, there are no randomized controlled trials studying the use of phosphodiesterase inhibition in infants with CDH, although a recent open-label study reported on pharmacokinetics in neonates treated with sildenafil [61]. Other pulmonary vasodilators that have been used in pulmonary hypertension in infants include endothelin antagonists and tyrosine kinase inhibitors [62–67]. The consortium recommends that sildenafil and other pulmonary vasodilators should only be used in the chronic phase of pulmonary hypertension in CDH because there is no evidence that this helps in the acute phase in infants with CDH.

Recommendations

- Perform echocardiography within the first 24 h after birth (grade of recommendation = D).
- Blood pressure support should be given to maintain arterial blood pressure levels at normal levels for gestational age (grade of recommendation = D).
- iNO should be considered if there is evidence of extrapulmonary right-to-left shunting and the oxygenation index is above 20 and/or the saturation difference is more than 10% (grade of recommendation = D).
- In case of suprasystemic pulmonary artery pressure and right-to-left shunting through the foramen ovale, i.v. prostaglandin E1 has to be considered (grade of recommendation = D).

Extracorporeal Membrane Oxygenation

The role of ECMO in the treatment of infants with CDH is still unclear [68]. In nonrandomized trials, ECMO has been reported to improve survival in infants with CDH [69, 70]. In some reports, oxygenation index, alveolar-arterial O_2 difference or a combination of both is used as a selection criterion for ECMO. In other reports, ECMO is considered if there is poor systemic perfusion with sustained hypoxemia with inadequate oxygen delivery and persistent metabolic acidosis. Some centers only consider ECMO in infants with CDH if they show an adequate amount of lung parenchyma suggested by a period of adequate preductal oxygenation and/or ventilation [71]. The use of ECMO has decreased [22], and is now more often used in preoperative stabilization [72]. Reports of stabilization and subsequent repair on ECMO have highlighted the benefit of delaying surgery and doing it after ECMO rather than on ECMO, particularly among high-risk infants [73]. A meta-analysis of retrospective studies suggests that the introduction of ECMO has improved survival in infants with CDH [74]. A meta-analysis of randomized controlled trials with small sample sizes indicated a reduction in early mortality with ECMO, but no long-term benefit [74].

Criteria for ECMO (Grade of Recommendation = D):

- Inability to maintain preductal saturations >85% or postductal saturations >70%.
- Increased $PaCO_2$ and respiratory acidosis with pH <7.15 despite optimalization of ventilatory management.
- Peak inspiratory pressure >28 cm H_2O or mean airway pressure >17 cm H_2O is required to achieve saturation >85%.
- Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥5 mmol/l and pH <7.15.
- Systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output <0.5 ml/kg/h for at least 12–24 h.
- Oxygenation index (mean airway pressure × FiO_2 × 100/PaO_2) ≥40 consistently present.

Timing of Surgical Repair and Postoperative Management

Survival rates in infants with CDH undergoing surgical repair after preoperative stabilization range from 79 to 92% [4, 34, 35, 75]. There are controversies about the timing of the surgical repair in patients who require

ECMO therapy. Early studies reported a high rate of hemorrhagic complications and high mortality when bleeding developed [73, 76]. A retrospective study from the CDH registry showed increased survival among patients who undergo repair of CDH after ECMO therapy relative to those who undergo repair while on ECMO [77]. The routine use of a chest tube postoperatively has been abandoned, as an effusion usually quickly fills the pleural cavity after repair. Moreover, this promotes infectious contamination of the pleural space without any benefits, such as acceleration of ipsilateral lung expansion, postoperatively. In individual cases, a pleural effusion after repair may compromise pulmonary function and ventilation, necessitating chest tube insertion [78].

Recommendations

- Surgical repair of the defect in the diaphragm should be performed after physiological stabilization, defined as follows (grade of recommendation = D):
  - mean arterial blood pressure normal for gestational age;
  - preductal saturation levels of 85 to 95% SaO_2 on fractional inspired oxygen below 50%;
  - lactate below 3 mmol/l; and
  - urine output more than 2 ml/kg/h.
- No routine chest tube placement (grade of recommendation = D).
- Repair on ECMO may also be considered (grade of recommendation = D).

Sedation and Analgesia

A wide range of sedation and analgesia practices has been described. Most centers use opioid analgesics such as morphine sulfate or fentanyl. Neuromuscular blocking is sometimes used in cases of asynchronous breathing. Although there is no specific evidence in infants with CDH, neuromuscular blocking is associated with several major side-effects and should be avoided [79]. The infant's condition using validated analgesia and sedation scoring systems, such as the COMFORT behavior score [80], should be regularly assessed.

Recommendations

- Infants should remain sedated and monitored using validated analgesia and sedation scoring systems (grade of recommendation = D).
- Neuromuscular blocking agents should be avoided if possible (grade of recommendation = D).

Fluid Management and Parenteral Feeding

Restrictive fluid management in the first 24 h consists of 40 ml/kg/day of fluids, including medication, with additional saline fluid therapy for intravascular filling. Thereafter, fluid and caloric intake should be increased based on clinical condition. Glucose, lipids and proteins should be given according the ESPGHAN/ESPEN guidelines [81]. Diuretics should be given in case of a positive fluid balance, aiming for diuresis of 1–2 ml/kg/h.

Recommendations

- 40 ml/kg/day including medication for the first 24 h, intake increases thereafter (grade of recommendation = D).
- Diuretics should be considered in case of a positive fluid balance, aim for diuresis of 1–2 ml/kg/h (grade of recommendation = D).

Enteral Feeding and Gastroesophageal Reflux

Nutritional morbidity remains a problem in survivors of CDH during infancy and early childhood, particularly gastroesophageal reflux ranging from 20 to 84% during the first year of life [82]. In survivors of CDH, gastroesophageal reflux may be treated both by antireflux medication and by surgical intervention. No prospective studies are available on the specific type of antireflux medication. Other common sequelae are oral aversion and need for tube enteral feeding. No prospective studies are available on the type of antireflux mediation.

Recommendation

- Enteral feeding should be started postoperatively combined with antireflux medication (grade of recommendation = D).

Conclusion

The European task force for CDH (CDH EURO Consortium) has agreed on a protocol of standardized postnatal treatment guidelines. This protocol was a prerequisite for a multicenter randomized trial of ventilation modes in infants with CDH (VICI-trial, www.vicitrial.com). At present, this protocol cannot be more than a consensus document because data from multicenter randomized controlled trials are lacking. The consortium prepared these consensus guidelines with the aim

of providing neonatologists and pediatric intensive care physicians with a protocolized European treatment strategy. Use of this protocol will also contribute to more valid comparisons of patient data in multicenter studies and to the identification of areas for further research. It was beyond the scope of these consensus guidelines to describe long-term follow-up in infants with CDH. However, long-term follow-up in children with CDH is highly important because approximately 87% of survivors of CDH have longer lasting associated morbidities, such as pulmonary, gastrointestinal and neurological problems [83]. The American Academy of Pediatrics Section on Surgery and the Committee on Fetus and Newborn published a comprehensive plan for the detection and management of these associated morbidities [84].

Members of the CDH Euro Consortium Group

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