Current guidelines on management of congenital diaphragmatic hernia

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Abstract
The treatment of congenital diaphragmatic hernia (CDH) still represents a challenge, even for the specialised multidisciplinary teams in centres that provide treatment for CDH. Despite significant progress in the fields of pathophysiology, prenatal diagnosis, surgical techniques and intensive care, CDH is a disease still burdened with a high mortality. Due to the paucity of randomised studies, there are no standard guidelines for treatment. The present review looks at existing diagnostic and therapeutic principles based on the available literature.

Key words: congenital diaphragmatic hernia, persistent pulmonary hypertension, prenatal diagnosis, extracorporeal membrane oxygenation


Congenital diaphragmatic hernia (CDH) is characterised by pulmonary hypoplasia and a developmental defect of the diaphragm that allows abdominal viscera to herniate into the thorax. Newborns affected by CDH present with the symptoms of respiratory and circulatory insufficiency in the first hours of life [1, 2, 3]. Pulmonary hypoplasia occurs bilaterally, being more severe on the affected side. Underdevelopment of the pulmonary tissue and pulmonary vascular defects result in morphologically and functionally conditioned susceptibility to persistent pulmonary hypertension. Hypoxia, acidosis and mechanical ventilation, which trigger the reflex pulmonary vasoconstriction, lead to the development of vascular wall structural changes.

The incidence of CDH is found to be 1:2000–5000 of life births and CDH-related mortality is high [4, 5, 6, 7]. According to the Extracorporeal Life Support Organization Registry, the estimated overall survival of infants with CDH is about 60%. In the centres with long-term experience in the treatment of CDH patients, which provide optimal care and diagnostic procedures in the pre- and postnatal period, the survival rates reach 90%. The data presented above regard only the selected groups of patients and do not take into account the “hidden mortality”, i.e. cases of intrauterine foetal deaths, deaths in delivery rooms and obstetric departments, departments of lower referential levels lacking suitable clinical experience or possibilities to perform appropriate prenatal diagnostic procedures [1–7]. Almost half of CDH cases are associated with other coexisting congenital defects, some of which are lethal [8].

The lack of uniform guidelines results from insufficient data from multi-centre randomised clinical trials concerning the management of patients with CDH. The data gathered by the study group of the CDH EURO Consortium consisting of 13 European centres are worth stressing; the centres treat annually more than 10 children affected by CDH [9, 10]. Based on their findings, the protocols of management in specialist American medical centres have recently been published [11, 12].

MANAGEMENT IN THE PRENATAL PERIOD

The popularisation of prenatal ultrasound diagnostic procedures increased the number of early diagnoses of
CDH, which reached 50–60% in various specialist centres of Western Europe and in the United States [13].

The prenatal prediction of survival in CDH is based on: detection of the presence of the liver in the thorax, evaluation of the lung-to-head circumference ratio (LHR), assessment of the size of a diaphragmatic defect as well as the lung-to-thorax transverse area ratio (L/T ratio), foetal MRI, lung volume calculations, determination of the heart axis, position of the stomach, and presence of pleural or pericardial effusions [14, 15, 16]. The parameters that reliably determine the prognosis are LHR and the position of the liver [1]. The L/T ratio is used to assess the extent of pulmonary hypoplasia. Although the lung volume (LV) can be precisely measured using MRI or 3D ultrasound, its value to predict mortality, respiratory distress or necessity to perform post-delivery extracorporeal membrane oxygenation (ECMO) is lower compared to LHR [1, 14, 15, 16].

Additional developmental abnormalities detected in 40-60% of live-born neonates with CDH are independent factors increasing the mortality even to 90% [2, 8]. The most common additional abnormalities include chromosomal anomalies, defects of the heart, central nervous system (CNS), kidneys and the gastrointestinal tract [17]. In cases of intrauterine foetal deaths, the CNS defects predominate. In live-born babies with CDH, the cardiovascular defects are most commonly found and constitute 50% of all morphological defects. Although the precise cause of the majority of CDH cases is unknown, the genetic factors are considered to be always involved. CDH was demonstrated to be associated with more than 50 genetic syndromes [17].

TREATMENT IN THE PRENATAL PERIOD

Inspired by the coexistence of congenital laryngeal atresia and pulmonary tissue hyperplasia, Wilson and co-workers [18] suggested that the development of hypoplastic lungs could be stimulated by the foetal tracheal occlusion. Prenatal surgical interventions carried out in CDH cases included four types of procedures: open repair, open tracheal occlusion, endoscopic external tracheal occlusion and endoscopic foetal endoluminal tracheal occlusion (FETO) using a special balloon [19]. This last intervention is performed at gestational week 21–29; the occlusive balloon is punctured and removed at gestational week 34. By stimulating the growth of alveoli and capillaries as well as remodelling of pulmonary arterioles, FETO accelerates the growth of foetal lungs [19]. The procedure is considered to significantly improve the survival rates [20].

THE METHOD AND TIMING OF DELIVERY

The study results did not show significant differences in overall survival between CDH patients delivered through natural passages and by Caesarean sections [21, 22]. However, the survival rates without ECMO were found higher in the group of newborns delivered by planned (elective) Caesarean sections [21]. As far as the timing of delivery is concerned, higher survival rates were observed in CDH newborns delivered at gestational week 37–38 with the birth weight exceeding 3.1 kg; moreover, in such cases, ECMO was less often required [22]. According to the same study, in the ECMO group higher survival rates were noted amongst children born at gestational week 39–41. The data gathered in the Registry of the Extracorporeal Life Support Organisation demonstrated higher survival rates and shorter times of ECMO in babies born at gestational week 40–42 compared to those delivered at gestational week 38–39 [23].

In cases at risk of preterm delivery between the gestational week 24 and 34, prenatal steroid therapy should be used according to the recommendations of the National Institute of Health [9, 24]. Prenatal steroid therapy administered after the gestational week 34 does not result in higher survival rates and improved respiratory efficiency of newborns with CDH [24].

MANAGEMENT IN THE POSTNATAL PERIOD

INITIAL MANAGEMENT IN THE DELIVERY ROOM

According to the guidelines of the study group of CDH EURO Consortium [9]:

— after delivery, the newborn trachea should be intubated without initial ventilation with positive pressures through a facial mask,

— the goal in the delivery room is to achieve pre-ductal SaO2 between 80% and 95%,

— during mechanical ventilation, a peak inspiratory pressure should not exceed 25 cm H2O,

— a gastric tube with continuous or intermittent suction should be inserted,

— arterial blood pressure has to be maintained at the level appropriate for the gestational age.

— In cases of hypotension and/or features of organ hypoperfusion, a crystalloid should be administered, 10–20 mL kg b.w. [1] 1–2 times; moreover, pressor amines should be considered.

— sedation and analgesia are obligatory and should be continued during the further stages of neonatal care. The child’s state should be assessed using one of the scales of pain and sedation (e.g. the COMFORT scale) [19, 26],

— routine use of surfactant is not recommended as the surfactant therapy was demonstrated to reduce the survival of both full-term and premature infants with CDH [27, 28].

MANAGEMENT IN THE INTENSIVE THERAPY UNIT

MECHANICAL VENTILATION

The available literature data indicate that mechanical ventilation-induced lung injury may have a significant ne-
ngative impact on the treatment outcome in newborns with CDH [29, 30]. Permissive hypercapnia and “lung-sparing ventilation” used in newborns with CDH have been demonstrated to increase their survival rates [31, 32].

Over 90% of centres participating in the International CDH Registry programme report that the peak airway pressure should be limited and find permissive hypercapnia advisable; low values of PaCO₂ — management reducing the pulmonary vascular resistance, are not considered necessary [1, 4].

At present the CDH EURO Consortium group is carrying out a multi-centre, prospective, randomized clinical study to assess the usefulness of various modes of mechanical ventilation in neonates with CDH (www.vicitrial.com) [9].

According to two prospective studies, higher survival was observed in the group of patients in whom spontaneous respiration was maintained [31, 33]. Therefore, the use of muscle relaxants is not beneficial [7, 9]. The objective of effective treatment with mechanical ventilation is to achieve pre-ductal SaO₂ within the range of 85–95% and post-ductal SaO₂ above 70% as well as PaCO₂ between 45–60 mm Hg (permissive hypercapnia) [9]. During the first two hours after delivery, pre-ductal SaO₂ of 70% is acceptable, if the next measurements show an increasing tendency without the necessity to change the ventilation parameters, at proper organ perfusion, pH > 7.2 and PaCO₂ < 65 mm Hg [9, 29].

In the next period, pre-ductal SaO₂ should be maintained between 85-95%. However, in some cases, the minimum level of 80% is acceptable at pH above 7.2, concentration of lactates < 5 mmol L⁻¹, diuresis above 1 mL kg b.w.⁻¹ h⁻¹, which are assumed to be indicative of proper organ perfusion.

The toxic effect of oxygen should be minimized by a reduction in FiO₂ under control of SaO₂ to the values ensuring its expected value [9, 31]. Therefore, after stabilizing the general condition of the patient, the inspiratory concentration of oxygen in the respiratory mixture should be reduced, if pre-ductal SaO₂ exceeds 95% [9].

According to the CDH-EURO Consortium, the following initially set parameters are recommended:

— pressure-controlled ventilation: PIP = 20–25 cm H₂O, PEEP = 2–5 cm H₂O; f = 40–60 min⁻¹,
— HFOV: mean airway pressure = 13–17 cm H₂O, f=10 Hz, Δp= 30–50 cm H₂O.

Whenever during pressure-controlled ventilation PIP above 28 cm H₂O has to be used to maintain proper saturation and PaCO₂, some other methods of therapy should be considered (HFOV, ECMO).

HFOV is most commonly used as a second-line therapy in severe and persistent hypoxaemia and hypercapnia, despite the use of conventional mechanical ventilation.

The mean airway pressures during HFOV should by contrasted under control of thoracic X-ray. The lung border on the contralateral side should not reach above the 8th rib [9].

**CIRCULATORY SUPPORT**

To support the circulatory functions, ECG-monitored proper organ perfusion, time of capillary refill, diuresis and concentrations of lactates should be provided [9]. The heart rate within normal limits, capillary refill time < 3 s, diuresis > 1.0 mL kg b.w.⁻¹ h⁻¹, lactate concentration < 3 mmol L⁻¹ and lack of organ hypoperfusion symptoms evidence that inotropic agents are not indicated [9].

The presence of symptoms of insufficient organ perfusion or decreased arterial blood pressure below the value normal for the gestational age and decreased values of pre-ductal SaO₂ below 80% are indications for echocardiography, which should determine whether the cause of disturbances is pulmonary hypertensive crisis, cardiogenic or hypovolaemic shock [9].

If the probable cause is hypovolaemia, fluid therapy should be initiated (10–20 mL kg b.w.⁻¹ 0.9% NaCl — up to three times within the first 1–2 hours) [9]. If hypotension is resistant to fluid therapy and the left and/or right ventricular dysfunction induced by impaired myocardial contractility is observed, inotropic agents should be administered [9]. To date, no type or dose of a catecholamine of choice has been determined for newborns with CDH. Some authors recommend avoiding noradrenaline and dopamine administered alone due to increases in pulmonary vascular resistance [3, 34]. Thus, some protocols suggest low doses of dopamine (2–3 µg kg b.w.⁻¹ min⁻¹) combined with dobutamine (10–15 µg kg b.w.⁻¹ min⁻¹); if no effects are observed the “third-line catecholamine is recommended, i.e. adrenaline in a dose of 0.005–0.1 µg kg b.w.⁻¹ min⁻¹ or more [34].

According to the American guidelines, the safe zone is the use of dopamine up to 20 µg kg b.w.⁻¹ min⁻¹ and adrenaline up to 0.1 µg kg b.w.⁻¹ min⁻¹ [11, 12]. The results of one study demonstrated beneficial noradrenaline-induced effects of increased systemic pressure with simultaneously decreased pulmonary artery/systemic arterial pressure ratio, improved pulmonary flow and increased cardiac output in newborns with persistent pulmonary hypertension of newborn [35].

Hydrocortisone can be used for hypotension resistant to conventional treatment [9, 36]. In premature babies with low birth weight, the symptoms of shock were observed to subside after 72 hours of steroid therapy. The efficacy of treatment is attributable to increased systemic peripheral resistance resulting from inhibited activity of inducible nitric oxide synthase (iNOS) and increased sensitivity and density of adrenergic receptors.

**TREATMENT OF PULMONARY HYPERTENSION**

Echocardiography performed within the first 24 hours after delivery is one of the best methods to assess the diameters of the pulmonary trunk and right ventricular function in real time [9, 37]. Echocardiographic monitoring is recom-
mended throughout the PPHN therapy [9]. The PAP/SAP ratio is considered an objective indicator of the severity of PPHT and prognosis [38]. At PAP/SAP ≥ 1.0, 100% mortality was noted. The pre-ductal values of SaO2 below 85% and symptoms of organ hypoperfusion are indications for treatment of pulmonary hypertension by optimisation of systemic arterial blood pressure [9]. If pulmonary hypertension persists, inhaled nitric oxide (iNO) therapy should be applied. In newborns with PPHN, iNO improves oxygenation and decreases the need for ECMO [39].

The largest randomized, controlled study concerning iNO therapy in newborns with CDH did not demonstrate its beneficial effects [40]. The protocol of iNO dosage has not been designed to date [9].

In cases when iNO therapy fails and the right-to-left shunt through the foramen ovale is observed, prostaglandin E1 is recommended to re-open the persistent arterial duct and to protect the right ventricle against excessive strain [9].

The pulmonary hypertension therapy is found effective when the pre- and post-ductal SaO2 gradient is reduced by 10–20%, PaO2 increased by 10–20% and the PAP/SAP ratio reduced below 0.5 [9, 39].

The data describing newborns with CDH indicate some improvement in oxygenation and cardiac output following the use of sildenafil, both in monotherapy and combined with iNO [41]. The beneficial effects of other vasodilators used in patients with CDH to treat pulmonary hypertension have not been demonstrated (e.g. endothelin antagonists, inhibitors of tyrosine kinase, inhibitors of phosphodiesterase III, magnesium sulphate, prostacyclin or terlipressin) [9, 42, 43].

**EXTRACORPOREAL OXYGENATION OF BLOOD**

Meta-analyses involving retrospective studies revealed that the introduction of ECMO improved the survival of newborns with CDH [44, 45]. The reports demonstrating haemodynamic stabilization in the perioperative period using ECMO highlight the benefits of delaying surgeries; it is emphasised, however, that the surgery should be performed after and not during ECMO therapy, especially in high-risk newborns [46].

ECMO criteria according to the CDH EURO Consortium (9):

- inability to maintain pre-ductal SaO2 > 85% or post-ductal SaO2 > 70%,
- increased PaCO2 and development of respiratory acidosis (pH < 7.15) despite optimisation of mechanical ventilation,
- necessity to use the peak inspiratory pressure > 28 cm H2O or mean airway pressure > 17 cm H2O to achieve saturation > 85%,
- hypoxia with coexisting metabolic acidosis (lactate concentration ≥ 5 mmol L⁻¹, pH < 7.15),
- hypotension resistant to fluid therapy and inotropic agents with decreased diuresis (< 0.5 mL kg b.w.⁻¹ h⁻¹ for at least 12–24 h),
- the oxygenation index (Oi) — mean airway pressure x FiO2 x 100/PaO2 at the level ≥ 40.

According to the American guidelines, the ECMO therapy should be initiated when Oi is: > 35 for 30 min, > 30 for 2 h, or > 25 for 4 h [12, 13].

**TIMING OF SURGICAL REPAIR AND POST-OPERATIVE MANAGEMENT**

It is believed that the postponement of surgical repair until vital functions are stabilized significantly improves survival [31, 33, 45, 47]. According to the CDH-EURO Consortium recommendations, surgical repair of a diaphragmatic defect should be carried out when the following criteria have been met:

- mean arterial blood pressure normal for the gestational age,
- pre-ductal saturation within the limits of 85 to 95% at FiO2 < 0.5,
- lactate concentration below 3 mmol L⁻¹,
- diuresis above 2 mL kg⁻¹ h⁻¹.

Despite the increased risk, surgical repair on ECMO is acceptable [9, 45].

At present, routine drainage of the pleural cavity is abandoned due to a high risk of rupture or infection of the hypoplastic pulmonary tissue [3, 9, 33]. Moreover, accumulation of fluid in the pleural cavity prevents excessive extension of lungs on the opposite side [3].

The hopes to improve treatment outcomes are placed in increasingly popular thoracoscopic techniques, which were earlier used only in cases of small hernias [48].

**LONG-TERM TREATMENT AND ITS COMPLICATIONS**

The problems of long-term care are associated with surgical re-repairs of recurrent hernias, chronic lung disease (CLD), nutritional disorders, total intravenous or gastric tube nutrition, or percutaneous gastrostomy, gastro-oesophageal reflux, musculoskeletal deformities and retarded psychomotor development [2, 49].

Obstructive-restrictive disturbances of ventilation cause chronic respiratory failure requiring long-term oxygen and ventilator therapy. The mortality due to recurrent pneumomias among patients with CDH discharged from intensive therapy units reaches 39% [2].

**SUMMARY**

Despite the lack of multi-centre, controlled, randomised clinical trials evaluating individual elements of therapy of newborns with CDH, the usefulness of standardised treat-
ment was demonstrated. A significant improvement in survival after institution of uniform therapeutic management was noted [9, 10, 11, 12]. The analysis of data regarding long-term care of children with CDH is equally important as about 87% of patients who survived CDH have chronic diseases of the lungs, gastrointestinal tract or nervous system [6]. The Committee on Fetus and Newborn of the surgical division of the American Academy of Paediatrics published a comprehensive plan for detection and management of CDH-associated morbidities [49]. Furthermore, improved survival rates in patients with CDH are also connected with high expenditures. In the United States, the annual hospitalization costs alone (without the costs of long-term care) are estimated at 250 mln dollars [50].

References:


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