Chapter 10

Congenital Diaphragmatic Hernia

Joanne Baerg, Arul Thirumoorthi and
Rajaie Hazboun

Additional information is available at the end of the chapter

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Abstract

Despite advances in neonatal and surgical care, the management of congenital diaphragmatic hernia (CDH) remains challenging with no definitive standard treatment guidelines. Several centers report mortality rates as low as 20%, but if extracorporeal membrane oxygenation (ECMO) support is required, the mortality rate rises to 50%. The disease severity is related to the degree of pulmonary hypoplasia and pulmonary hypertension that occurs with CDH. Both conditions decrease the infant's ability to ventilate and oxygenate adequately at delivery. These physiologic conditions that impair gas exchange are the important determinants of morbidity and mortality in CDH infants. Presently, delivery of infants with CDH is recommended close to term gestation. The focus of care includes gentle ventilation, hemodynamic monitoring, and treatment of pulmonary hypertension followed by surgery for the defect. Extracorporeal membrane oxygenation (ECMO) is considered after failure of conventional medical management for infants ≥ 34 weeks' gestation or with weight >2 kg and no associated major lethal anomalies. This chapter discusses long-term follow-up recommendations for survivors, which should involve a multidisciplinary approach, as there are many surgical and nonsurgical consequences to the disease process. Clinical strategies that address these multifaceted aspects of care, from prenatal to long-term follow-up, may further reduce the high mortality rate for these infants.

Keywords: respiratory failure, pulmonary hypertension, pulmonary hypoplasia, extracorporeal membrane oxygenation

1. Introduction

A congenital diaphragmatic hernia (CDH) is a developmental defect of the posterior lateral part of the diaphragm. The opening allows the abdominal organs to slide into the chest or

"herniate" which may lead to underdevelopment of the lungs. The lung on the ipsilateral side of the hernia is generally smaller.

CDH is six times more common on the left than the right. The incidence is reported between one in 2200 and one in 3500 live births. Rare bilateral defects are generally fatal. The differential diagnosis includes congenital pulmonary airway malformation (CPAM), bronchogenic cyst, and eventration [1].

Despite advances in neonatal and surgical care, the management of CDH remains challenging with no definitive standard treatment guidelines. The mortality rate is high, with little change over the past few decades, and is generally reported between 30 and 45%. Several centers report mortality rates as low as 20%. If extracorporeal membrane oxygenation (ECMO) support is required, the mortality rate rises to 50% [2].

The severity of the disease is related to the degree of pulmonary hypoplasia and pulmonary hypertension that occurs with CDH. Both conditions decrease the infant's ability to ventilate and oxygenate adequately at delivery. These physiologic conditions that impair gas exchange are the important determinants of morbidity and mortality in CDH infants.

2. Embryology

Incomplete fusion of embryologic elements that give rise to the diaphragm leads to the hernia defect. CDH occurs at distinct sites. Ninety percent are a posterolateral defect (Bochdalek hernia) and 9% are an anterolateral defect (Morgagni hernia). Total agenesis may occur.

3. Inheritance patterns

Congenital diaphragmatic hernia generally presents sporadically. The CDH risk in a sibling is less than 2%, due to multifactorial patterns of inheritance [3]. There are rare incidences of dominant and X-linked recessive inheritance for isolated defects [4]. Bilateral lesions tend to familial inheritance and bilateralism, and tend to have less severe associated anomalies. Familial diaphragmatic agenesis, however, is an autosomal recessive syndrome, is a distinct syndrome with a worse prognosis than posterolateral diaphragmatic hernia [5].

There are no firmly established teratogens associated with CDH. Diaphragmatic hernia is associated with Fryn's syndrome [6], Beckwith-Wiedemann syndrome [7], and Pierre Robin syndrome [8].

4. Associated anomalies

Most fetuses with severe associated anomalies die in utero. Therefore, the incidence of prenatal abnormalities is higher than that reported in the literature by pediatric surgeons and

lower than postmortem studies. In prenatal series, only about 50% of fetuses have an isolated diaphragmatic defect. In about 25% of cases, there is a chromosomal abnormality, usually Trisomy 21, trisomy 18 or 13, which is similar to omphalocele infants [9]. In another 25%, there is a major defect including cardiovascular defects atrial septal defect (ASD), ventricular septal defect (VSD), hypoplastic left heart, tetralogy of Fallot, transposition). The overall survival of infants with CDH and a chromosomal anomaly is poor.

4.1. Prenatal evaluation

Ultrasound screening examination in the prenatal period will generally diagnose a congenital diaphragmatic hernia. Prenatal evaluation of CDH is important for parental counseling, prognostication, and postnatal management. The prenatal evaluation of the postnatal prognosis of CDH is improving, but better standardization of evaluation methods is needed to compare results.

The prenatal ultrasound diagnosis is based on the following factors:

1. The presence of *abdominal organs visualized within the thoracic cavity*. Ultrasound may reveal a left-sided CDH if the stomach or loops of bowel are partially or totally within the thorax.
2. The heart position may shift, or cardiac compression may be observed, from the organs in the thoracic cavity.
3. *Polyhydramnios* is common, either due to esophageal compression or reduced absorption of fluid by the hypoplastic lungs, but it is rarely observed before 24-week gestation.

Any *mediastinal shift* or hydrothorax, abnormal position of the gallbladder, hepatic veins, or even umbilical veins should arouse suspicion of a right-sided hernia. It may be a challenging diagnosis because the lungs and liver have similar echogenicity.

At antenatal diagnosis, the following studies and consultations are recommended:

1. chromosomal analysis
2. serial prenatal ultrasound examinations
3. a fetal echocardiograph
4. pediatric surgery consultation

These investigations are relevant, even in the third trimester of pregnancy, because knowledge that the fetus is chromosomally and otherwise structurally normal allows the parents, obstetrician, pediatrician, and surgeon to discuss the mode, place, and timing of delivery.

Prognosis: The primary determinants of survival for infants with CDH are the presence of associated anomalies, pulmonary hypoplasia, and pulmonary hypertension. Prenatally discovered cases and cases diagnosed before 24-week gestation have a worse prognosis because of the early stage of the lung development when the anomaly has occurred. Mortality in this group is reported as high as 60–80% [10].

4.2. Pulmonary hypoplasia

Pulmonary hypoplasia occurs in CDH and is the main cause of mortality. Pulmonary hypoplasia is defined as incomplete development of the lungs with decreased bronchopulmonary segments and diminished alveolar septation [11]. Incomplete development results in a decreased total lung volume.

Much prenatal investigation is directed toward the accurate evaluation of pulmonary hypoplasia. Its antenatal prediction remains one of the challenges of prenatal diagnosticians. Accurate case selection identifies those cases that may benefit from prenatal surgery.

Fetuses with CDH and a "poor prognosis" with postnatal treatment have

- a low lung-to-head ratio (LHR) on ultrasound
- a diagnosis before 25-week gestation
- liver herniation on prenatal ultrasound
- a fetal magnetic resonance imaging (MRI) consistent with a low lung volume.

4.3. Lung to head ratio

The lung-head ratio (LHR) is calculated by 2D ultrasound. For accurate prognostication, the measure must be performed between 22 and 28-week gestation. The length and width of the right lung is measured and multiplied to calculate the right lung area. The right lung area is then divided by the head perimeter measure **Figure 1**.

For example:

- Right lung area: 21 mm × 10 mm = 210 mm^2
- Head perimeter: 200 mm

Lung-to-head ratio (LHR): 210/200 = 1.05

A lung-to-head ratio of 1.0 or less has a poor prognosis, despite ECMO. If the ratio is greater than 1.4, the prognosis is much better. Lung-to-head ratios between 1.0 and 1.4 have about a 38% survival rate. Most cases with an LHR in this range require ECMO. Overall, survivors have a mean lung-to-head ratio in the range of 1.4 ± 0.33 and nonsurvivors, 1.05 ± 0.3 [12].

The presence of liver in the chest on prenatal ultrasound is a poor prognosticator for survival [13, 14].

A recent meta-analysis analyzed the ability of lung-to-head ratio (LHR), observed-to-expected LHR (o/e LHR), total fetal lung volume (TFLV), o/e TFLV, percentage predicted lung volume (PPLV), and degree of liver herniation to predict neonatal morbidity and mortality in fetuses with CDH.

The primary outcome was perinatal survival and the secondary outcome was the use of extracorporeal membrane oxygenation (ECMO).

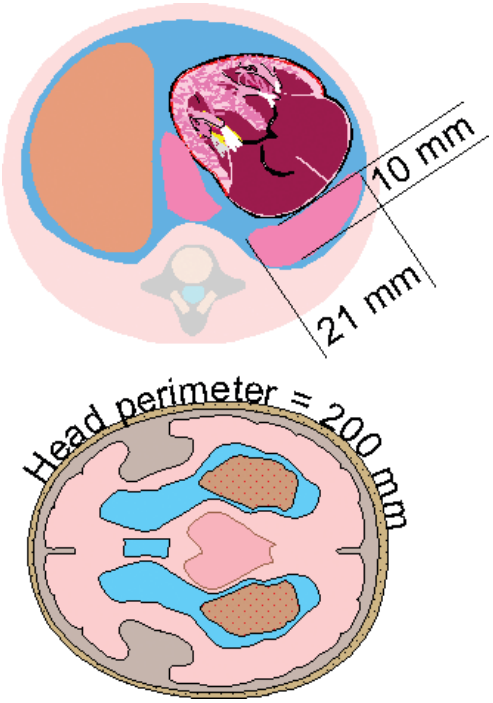

Figure 1. Calculation of lung: head ratio from 2D ultrasound. (From: 2000-05-29-17 Diaphragmatic hernia © Novakov www.thefetus.net).

Twenty-two articles published before April 2016 met the inclusion criteria.

The odds of survival with LHR <1.0 was 0.14 (CI: 0.10–0.27) and with liver herniation on ultrasound it was 0.21 (CI: 0.13–0.35).

The O/E LHR and O/E TFLV performed best in this prediction model. The most discriminatory threshold for lung volume and mortality was O/E LHR <1 and for O/E TFLV, it was 25%. LHR <1 was predictive of extracorporeal life support (ECLS) use. Overall, the O/E LHR <1, O/E TFLV (thresholds of 25%), and liver herniation are good predictors of mortality in CDH [13].

Similarly, Partridge reports that serial lung to head growth measures are a better prognosticator for lung growth and survival. Of 226 CDH infants identified over 10 years, 72 died (32%). Liver in the chest or use of patch for closure of the defect were associated with mortality. The rate of lung to head ratio increase, as measured by linear regression and slope analysis, was significantly better in survivors [15].

4.4. Fetal MRI consistent with a low lung volume

Fetal magnetic resonance imaging (MRI) has undergone major technical improvement since it was first performed over 30 years ago. It complements US studies by providing better

visualization when ultrasound is limited by oligohydramnios or maternal obesity. Other advantages include a larger field of view and better tissue contrast than US. It is not limited by shadowing from osseous structures. However, the limitations include a decreased resolution compared with US, less availability, and increased cost.

Multiple MRI studies have reported normal fetal lung volumes based on gestational age. In cases of CDH, the risk for pulmonary hypoplasia can be assessed by comparing the lung volume measured by MRI with a normal value for the gestational age; however, the literature results have been inconsistent and have not reliably predicted outcome. There is a lack of standardization of MRI technique in the literature.

A curve of normal fetal lung volume values plotted against gestational age has been established and validated for fetal MRI [16]. The observed/expected total fetal lung volume (O/E-TFLV) ratio is calculated by dividing the measured fetal lung volume by the expected mean fetal lung volume for a given gestational age [16].

The fetal MRI planimetric measurements of ipsilateral, contralateral, and total fetal lung volume (TFLV) are performed with T(2)-haste sequences in transverse, coronal, and sagittal planes. All values are expressed as a ratio of what was observed over what is expected for a gestation age matched normal fetus.

One study reports the measurement of O/E LHR on ultrasound allowing a reasonable estimation and correlation of O/E contralateral FLV as well as TFLV as measured by MRI [17]. Additional parameters such as gestational age, liver position, and side of defect improved the estimation of TFLV.

Others report that lung size and liver herniation predict the need for ECMO but do not predict pulmonary hypertension [18].

A review of articles that provided normal fetal lung volumes for gestational age revealed much variability in absolute lung volume within each individual study. Each study had a solitary reporter. The best-fit curves ranged from 20 to 35 ml at 25 weeks' gestation and 58 to 95 ml at 35 weeks' gestation [19]. The study by Rypens et al. included the largest number of fetuses and, in contrast, included measurements by several observers at different institutions [16]. The ability of MRI to predict prognosis and survival for CDH is inconsistent, although multiple studies have shown a correlation between fetal lung volume in CDH and postnatal outcomes of neonatal survival and ECMO.

Infants with CDH generally have O/E-TFLV measurements ranging from 25 to 45% or lower. They require more pulmonary support than omphalocele and congenital lung malformation infants. Clinical-radiologic correlation studies support the use of prenatal MRI to predict perinatal and postnatal outcomes. The measurements may guide fetal therapy with improved postnatal results. An O/E TFLV below 35% is associated with increased ECMO use and a higher mortality [20].

One review of articles encompassing 269 fetuses with congenital diaphragmatic hernia reported areas under the receiver operating characteristic (ROC) curves ranging from 0.786 to 0.900 in the prediction of survival. Two others involving MRI-measured fetal lung volume reported

the area under the ROC curves to range from 0.653 to 0.770 in the prediction of extracorporeal membrane oxygenation requirement. All of the above studies utilized MR measurements of fetal lung volume compared with normal lung volume data from either the Rypens et al. study or formulas based on gestational age or biometric parameters [19].

Further studies are needed to assess and develop the full potential of MRI measurement of fetal lung volume in predicting neonatal prognosis.

4.5. Prenatal surgery

If LHR is <1, LHR 0/E is less than 25%, or liver is in the thorax, survival for CDH infants is less than 25%. In these fetuses, in utero treatments are sometimes offered such as fetal endotracheal occlusion (FETO) [10, 21].

Many experimental models of in utero surgery for CDH exist. Prenatal treatment of the fetus has been proposed to avoid pulmonary hypoplasia. However, a hysterotomy is required. The subsequent caesarian section on an otherwise healthy mother has significant morbidity and risk of premature labor.

Open fetal surgery, while feasible, does not improve survival over standard postnatal treatment in the subgroup of congenital diaphragmatic hernia fetuses without liver herniation. The data from this randomized trial suggest that fetuses with a prenatally diagnosed CDH without evidence of liver herniation should be treated postnatally [10].

Fetal endotracheal occlusion (FETO) is thought to prevent outward movement of pulmonary fluid. The retention of lung fluid may improve lung expansion and even possibly promote reduction of the viscera into the peritoneal cavity [21]. The placement of a "tracheal clip" may accelerate lung growth and avoid the development of fatal pulmonary hypoplasia [22]. Endoscopic techniques decrease the risk of preterm labor and other complications of open fetal surgery.

The best candidates for this procedure are fetuses with a left CDH, liver herniation, and a low lung-to-head ratio that are at high risk of neonatal demise [23]. A minimally invasive intraluminal tracheal occlusion technique, which avoids laparotomy, hysterotomy, and fetal neck dissection, has been recently accomplished. This technique may change the surgical approach to the fetus with severe CDH [24].

In 2017, 20 fetuses with CDH, an LHR<1 and liver herniation were reviewed [24]. Nine were managed without tracheal balloon occlusion; tracheal occlusion was offered in 11 and in 10, it was successful. The mean gestational age at FETO was 27.9 (1.1) weeks. The occlusion was reversed at 34 weeks and the infants were delivered at 35 weeks. One required an EXIT procedure to remove the balloon. All underwent postnatal repair of CDH with patch. The 6-month, 1-year, and 2-year survival were significantly higher in the treated than nontreated cohort. They concluded that FETO is feasible and associated with improved postnatal outcomes in severe Left CDH infants. A large multicenter randomized trial is still needed to demonstrate the real benefits of FETO [25].

5. Pulmonary hypertension

The developing lung is subject to genetic, pathological, and environmental influences that affect lung adaptation, development, and growth.

Neonates with CDH are primarily classified as having vascular hypoplasia, yet lung histology of fatal cases typically shows marked muscularization of pulmonary arteries, and clinically, these patients frequently respond to vasodilator therapy.

An early developmental arrest in the normal pattern of airway branching in both lungs, resulting in reduced lung volume and impaired alveolarization, will present as a severely symptomatic CDH after birth [26].

This arrest may occur in pulmonary arterial branching and result in a reduced cross-sectional area of the vascular bed, thickened media, and adventitia of small arterioles, and abnormal medial muscular hypertrophy that extends distally to the acinar arterioles. Although in utero lung compression by herniated viscera may be the primary mechanism of the lung abnormalities of CDH, decreased pulmonary blood flow alone may cause lung hypoplasia [27].

After birth, pulmonary vascular resistance (PVR) often remains at suprasystemic levels. This increased pulmonary right-to-left shunting across the foramen ovale and ductus arteriosus manifests in the infant as profound hypoxemia. High PVR is related to multiple factors, including the small cross-sectional area of pulmonary arteries, structural vascular remodeling, vasoconstriction with altered reactivity, and left ventricular dysfunction. The mediators of altered pulmonary vascular reactivity in CDH are not well understood, although much evidence points to disruptions in nitric oxide (NO), cyclic guanosine monophosphate (GMP) and endothelin signaling [28].

The pathophysiology of hypoxemia in CDH is also related to abnormalities of cardiac development and function. The left ventricle, left atrium, and intraventricular septum are hypoplastic in infants that die of CDH relative to age-matched controls, perhaps from low fetal and postnatal pulmonary blood flow and/or compression by the dilated right ventricle [28].

CDH is also associated with increased resistance of the pulmonary vasculature. Pulmonary hypertension (PHN) is characterized by elevated pulmonary vascular resistance, resulting in right to left shunting and hypoxemia. Differential hypoxemia is observed between the preductal- and postductal saturation monitors. Pulmonary hypertension is confirmed and monitored by serial echocardiography. Studies that aim to diagnose impaired vascular development are needed.

Yamoto et al. investigated the prenatal echocardiography factors that relate to outcomes in left-sided CDH [29]. Data were collected between 2006 and 2010. Severe cardiac anomalies and chromosomal anomalies were excluded. Of 84 patients, 8 died before 90 days (9.5%). Initial analysis revealed that the postnatal echo predictors of poor outcome were continuous right to left shunting, left pulmonary artery diameter of <2.7 mm, a right pulmonary artery diameter of <3.3 mm, and a left ventricular diameter of <10.8 mm. Logistic regression analysis found a small right pulmonary diameter and a smaller left ventricular diastolic diameter that were independently associated with poor outcomes. However, the postnatal echo was sometimes performed within 24 hours after birth, during the time of transitional circulation, and is a limitation of this study.

The optimal management of the structural and functional changes in the heart, pulmonary vasculature, airways, and lung parenchyma is challenging. The treatment of PHN in infants with CDH evolves and changes as the underlying pathophysiology evolve in the days and weeks after birth. Unlike other diseases resulting in persistent pulmonary hypertension of the newborn, infants with CDH are often refractory to inhaled nitric oxide (iNO). Nitric oxide mediates pulmonary vasodilatation at birth in part via cyclic GMP production. Evidence suggests several disorders exist in CDH infants (e.g., surfactant deficiency, decreased antioxidant activity, increased vascular reactivity with decreased nitric oxide and increased endothelin 1 activity, and left heart hypoplasia) which may be associated with impaired lung development. It is unclear at present how nitric oxide, sildenafil, and bosentan will modulate pulmonary hypertension in CDH infants. Chronic pulmonary hypertension can persist into childhood and may contribute to late mortality [26].

6. Postnatal management

It is recommended that CDH infants are delivered as close to 39 weeks as possible. Neuromuscular blockade is avoided in the delivery room. The preductal saturation is kept between 80 and 95%, and the postductal at greater than 70%. The target pCO_2 is 50–70 mmHg on conventional ventilation. Intravenous sildenafil should be administered in the presence of severe pulmonary hypertension.

6.1. Immediate postnatal resuscitation and medical management

In fetuses known antenatal to have CDH, the aim of resuscitation at birth is to obtain cardiopulmonary stability, and interrupt the progression to hypercapnia, hypoxemia, acidosis, and worsening PHN. Infants are intubated, and mechanically ventilated. The initial ventilation mode is conventional mandatory ventilation (CMV). High frequency oscillatory ventilation (HFOV) is initiated when criteria for transition from conventional to HFOV are met. HFOV offers more invasive ventilation support, while minimizing barotrauma to the lungs. Cardiovascular support to avert PHN is needed. ECMO is reserved for patients with severe pulmonary or cardiac compromise refractory to medical management.

Carbon dioxide level and subsequent management can provide predictive information regarding the outcome of CDH. The initial CO_2 is significantly higher and PaO_2 is lower in 30-day mortalities than in survivors. Infants who remain hypercarbic after resuscitation also have a worse prognosis. $PaCO_2$ levels are a biomarker of successful management. The best oxygen index on the first day of life has been shown to predict outcome. Park et al. reported the PaO_2 and $PaCO_2$ from the first blood gas after birth predicted the need for ECMO and mortality [30].

Initial management includes nasogastric decompression, central venous access, total parenteral nutrition, and careful fluid management to optimize cardiopulmonary stability. Frequent echocardiography is required to identify structural cardiac anomalies and assess function and response to therapy [31].

6.2. Score for neonatal acute physiology (SNAP score)

Predictive outcome models are essential for outcome analysis of CDH. The ideal equation should generalize across CDH datasets. Existing mortality-predictive models include those of the CDH study group (CDHSG) based on birth weight and 5-minute Apgar score, the score for Neonatal Acute Physiology version II, and the Wilford Hall/Santa Rosa clinical prediction formula (WHSR(PF)) derived from blood gas measurements. The score for neonatal acute physiology (SNAP 2) score is one of the most applicable scoring systems for CDH infants.

The CDH EURO consortium expanded the implications of the SNAP score first published by Skarsgard et al. [32]. A prospective randomized study of 11 centers that participate in the CDH EURO consortium was undertaken [33]. Data were collected between 2008 and 2013 (SNAP 2). High volume centers were included and were defined as centers that treat at least 10 CDH infants per year. Infants with prematurity below 34 weeks were excluded, so those with premature lung physiology would not influence results.

The exclusion criteria were gestation below 34 weeks, severe chromosomal anomalies, severe cardiac anomalies with need for operation within 60 days, renal anomalies associated with oligohydramnios, and severe orthopedic, skeletal, and central nervous system (CNS) anomalies. All infants were inborn. The out-born infants were excluded because out-born survivors tend to have less severe disease and therefore contribute bias to the results.

The aims of the SNAP 2 study were to prospectively evaluate whether SNAP 2 predicted mortality, the need for ECMO or bronchopulmonary dysplasia (BPD) development.

All infants were randomized to a standard protocol of CMV or HFOV.

The SNAP 2 was collected in the first 12 hours of life and included the worst score of each of the following data points: mean blood pressure, temperature, PaO_2, inspired oxygen concentration (fi02), serum pH, the presence of multiple seizures, and the lowest urine output.

Infants met the criteria for ECMO if they met the following failure criteria for 3 hours: inability to maintain a preductal saturation above 85%, or a postductal saturation above 70%, an increase in CO_2 of greater than 65 mmHg, a peak inspiratory pressure of greater than 28 cm of H_2O, inadequate O_2 delivery with metabolic acidosis defined as pH < 7.2 or an oxygen index consistently greater than 40.

Of 171 infants, 46 died (27.0%). Of 108 treated at ECMO centers, 40 received ECMO (37.0%) and 27 died (25%). Of those treated in 63 centers without ECMO, 19 died (30.0%). The difference in mortality rate between ECMO and nonECMO centers was not significant ($p = 0.46$). Of 125 survivors, 39 developed BDP (31.2%).

In nonsurvivors, the median SNAP 2 was 42.5, and in survivors it was 16.5, a significant difference ($p < 0.001$). Of 108 born in ECMO centers, the median SNAP 2 was 35 in those treated with ECMO and 16 in those that did not undergo ECMO, also a significant difference ($p < 0.001$). The median SNAP 2 was also significantly different for ECMO survivors and nonsurvivors: 32 vs. 40, $p = 0.04$. Logistic regression and ROC analysis showed the SNAP 2 was significantly associated with mortality, need for ECMO and BPD.

This large study of prenatally detected CDH infants concluded that the SNAP 2 calculated in the first 12 hours of life reliably predicts survival outcomes and the need for ECMO in inborn infants with CDH with gestational age > 34 weeks. The SNAP takes only 2–4 minutes to calculate. The SNAP 2 score is considered independent of initial ventilation strategy [34].

Some now report the use of the SNAP 2 score with perinatal extension—the SNAPPE. This score includes APGARS, birth weight and gestational age, but it is time consuming to calculate. The report also includes out-born infants which is a confounder [35].

Implementation of the SNAP 2 score will provide insight into prognosis and can be used to compare severity of illness and evaluate differences in outcomes between centers.

6.3. Permissive hypercapnia and avoidance of lung injury

In the 1990s, the realization that aggressive overventilation causes barotrauma and a worse outcome leads to the introduction of minimal ventilation and permissive hypercapnia. This approach involves decreased airway pressures to reduce barotrauma, spontaneous respiration where possible, and acceptance of higher $PaCO_2$ and lower pH than previously accepted. The introduction of this strategy had the most significant influence on mortality reduction for CDH infants over the past three decades [36].

Barotrauma is commonly attributed as the principal cause of death in autopsy studies of CDH infants [37].

Complications such as pneumothorax have a detrimental effect on CDH infants. In more than one study, all infants with pneumothorax died [38].

The usual limit of permissive hypercapnia in many studies are a $PaCO_2$ within the 40s and pH of 7.2. The oxygen saturation is kept at 90–95%. Postductal oxygen saturation is correlated to other measures of adequate perfusion including lactate, blood pressure, and urine output, while maintaining acceptable ventilator parameters.

The next step in management is the introduction of HFOV. Pressure limits range from 12 to 15 cm H_2O. The benefit of HFOV has not been completely established. It is often used with other management strategies. A trial comparing CMV and HFOV is presently underway [39].

7. Management of PHN

Ensuring good oxygenation is the first step in preventing or treating PHN. The institution of effective ventilation is critical. Fluids and inotropes maintain perfusion and should be guided by serial echocardiography. When PHN worsens, a cycle of worsening hypoxia and hypercapnia from right to left shunting at both the preductal and postductal levels occurs and sets off a vicious cycle of deterioration.

Inhaled nitric oxide (iNO) is a direct pulmonary vasodilator. The inhalation dose ranges between 5 and 20 ppm. Although it may reduce the need for ECMO in other newborns without

CDH, it has not been shown to reduce the need for ECMO in CDH. Response to NO should be confirmed by echocardiography [40].

Sildenafil is a selective cGMP phosphodiesterase inhibitor that can be administered intravenously or as an oral medication. It may enhance inhaled NO-mediated vasodilation. Sildenafil Infusion has been shown to be associated with improved oxygenation in CDH. Overall, its use is increasing. Presently, conflicting reports exist as to whether it improves outcome or not [41].

Milrinone is a phosphodiesterase 3-inhibitor and acts to decrease pulmonary vascular resistance and improve cardiac function. There are few case reports of its efficacy in neonates. Although it is widely used, there is no literature that documents an advantageous effect in CDH [42, 43].

7.1. ECMO

The most severe CDH cohort fails conventional management and utilizes ECMO for support. Infants that undergo ECMO are typically profoundly hypoxemic and acidotic prior to and during ECMO cannulation. ECMO benefits infants with reversible lung disease, however infants with reversible versus irreversible lung disease can be challenging to identify. Infants with reversible lung disease, without CDH, have better documented outcomes. The advantage of ECMO in CDH infants requires continuous evaluation to resolve the issue of whether ECMO actually provides benefit.

A Cochrane review into the randomized controlled trials that investigated the benefits of ECMO in neonates concluded the benefit in CDH infants is unclear. The morbidity in those that do survive is high and can be costly from complications such as intracranial hemorrhage (ICH), bleeding, seizures, or infection. One fifth of infants with CDH that undergo ECMO have severe neurodevelopmental problems [42, 43]

The introduction of gentle ventilation strategies, permissive hypercapnia and spontaneous respiration had a more significant effect on survival than HFOV or ECMO as rescue therapy [35, 39]. These strategies increased survival from 50 to nearly 75% for CDH. Standardized postnatal treatment protocols at ECMO centers is associated with significantly improved survival [44].

7.2. Selection criteria

ECMO is useful if lung disease is reversible. Careful infant selection is critical. Due to the fact that the identification of specific CDH infants that will benefit from ECMO is not clear, some advocate that all infants with respiratory failure should get ECMO as many with poor prognosticators have been shown to survive. It is difficult to identify the influence of inadequate lung volume (pulmonary hypoplasia) versus reversible pulmonary hypertension in CDH infants and the overlap of the two entities. Many infants with CDH will have a honeymoon phase where they demonstrate sufficient lung parenchyma for gas exchange prior to clinical deterioration secondary to pulmonary hypertension. Some authors advocate utilizing clinical parameters and offering ECMO to any patient who can sustain a preductal oxygen saturation ≥90% for

at least 1 hour, a PaO_2 of 100 on FiO_2 1.0 and at least one recorded $PaCO_2 < 50$ mmHg [45]. CDH infants with progressive hypoxemia who meet these initial criteria supported with ECMO have 85% survival to discharge [46].

7.3. Factors associated with survival

A retrospective review of the CDH Study Group database found that the overall survival for CDH infants was 67% and for those requiring ECMO, it was 61%. Of the infants that required ECMO and underwent surgical repair, survivors had greater gestational age (>38 weeks), greater birth weight (>3 kg), were less likely to be prenatally diagnosed, less likely to have Apgar <7 at 5 minutes, less likely to have a patch repair and had shorter ECMO runs of median 9 +/- 5 days [47].

7.4. Oxygen index and alveolar-arterial oxygen gradient ($AaDO_2$)

Objective criteria for ECMO patient selection have been suggested in the literature. The two most commonly utilized measures are oxygenation index (OI) and alveolar-arterial oxygen gradient ($AaDO_2$).

The mortality risk in neonatal respiratory failure can be measured by an OI which is based on Pao_2, and mean airway pressure (MAP).

It is computed by:

$$OI = MAP \times FiO_2 \times 100/PaO_2. \quad (1)$$

In early ECLS studies, OI >40 in three of five postductal arterial blood gas measures 30–60 minutes apart, a mortality rate > 80% (8, 9) was predicated. Some advance initiation of ECLS based on an OI of 25 or greater which has a mortality of 50%. ECMO is considered when respiratory failure exists and the OI is calculated at between 25 and 40 [39].

Alternatively, $AaDO_2$ has also been shown to be sensitive for predicting mortality [48].

$$AaDO_2 = (P_{ATM} - 47)\left(FiO_2\right) - \left[\left(PaCO_2\right)/0.8\right] - PaO_2 \quad (2)$$

When the OI ≥ 40 or $AaDO_2 > 625$ mmHg for 4 hours (or >600 mmHg for 12 hours), ECMO is considered mandatory.

7.4.1. Contraindications to ECMO

In addition to unique clinical parameters to assess pulmonary hypoplasia in CDH, there are generalized contraindications to neonatal ECMO that correspond to high mortality:

- Prematurity: gestational age <34 weeks (high risk of intracranial hemorrhage) [49]
- A known pre-ECMO IVH greater than grade 2 [50]
- Weight <2 kg (technical limitation due to cannula size)
- Mechanical ventilation >7–14 days due to risk of fibroproliferative pulmonary disease [51]

- Hypoxic ischemic encephalopathy [52]
- Chromosomal abnormalities (other than trisomy 21) [53].

7.4.2. Relative contraindications

- Multisystem organ failure or irreversible critical illness [54]
- Evidence of bleeding diathesis/disseminated intravascular coagulation (DIC) (correct prior to ECMO) [55]
- Immune compromise [56]
- Seizures prior to ECMO [57]
- Cardiac arrest was previously considered a contraindication but now survival of up to 40% after cardiac arrest is reported. The causes of the arrest are variable and the identification and treatment of the underlying cause will influence outcome [58]. Of those who survive, at least 60% have a reasonable neurologic outcome.

7.4.3. ECMO complications

Complications during ECMO support are associated with worse outcomes. Complications increase with prolonged ECMO support.

7.4.3.1. Bleeding:

Bleeding is associated with heparinization. It is the most common complication, occurs in 10–30% of ECMO runs, and can be devastating [59].

- Intracranial hemorrhage (ICH): ICH is the most common cause of death in newborns on ECMO. The etiology is multifactorial. After heparinization, platelet function remains disrupted for 48 hours after ECMO is discontinued [60]. This effect is increased in infants below 37 weeks' gestational age.
- Bleeding at extracranial sites, e.g., gastrointestinal (GI) hemorrhage
- The incidence of bleeding attributed to technical failure is between 2 and 5%. Cannula site bleeding may be as high as 6%. Cardiac patients requiring ECMO have a higher incidence of bleeding.

In order to decrease the risk of bleeding, the platelet count is kept above 100,000 mm^{-3}. The ACT is maintained between 180 and 240 seconds [61]. The occasional discontinuation of heparin may be needed.

7.4.3.2. Neurologic

The most serious post-ECMO morbidities are neurologic. Morbidity and mortality increase with greater prematurity. This implies that factors present prior to ECMO are related to neurologic outcomes. By 2.5–3 years, infants with CDH requiring ECMO had worse neurologic outcomes than nonCDH ECMO survivors [62, 63].

Neonatal seizures are associated with long-term morbidity and poor outcome including cerebral palsy and epilepsy [42, 43]. Clinical seizures occur in 5–10% of ECMO neonates [64, 65]. Abnormal electroencephalogram (EEGs) are predictive of developmental delay. Only 18% of ECMO infants with normal EEGs have developmental delays; 35% with one abnormal EEG, and 58% with two or more abnormal EEGs [66].

Sensorineural hearing loss occurs in 5% of ECMO survivors, though this rate is comparable to nonECMO PPHN infants [67].

7.4.3.3. Pneumothorax

Boloker et al. reported 120 consecutive inborn infants managed with a care strategy based on permissive hypercapnia, spontaneous respiration, and elective repair [39]. The overall survival rate was 75.8%, but, excluding 18 of 120 not treated for lethal anomalies, overwhelming pulmonary hypoplasia, or prerepair ECMO-related neurocomplications, 84.4% survived to discharge. In this series with excellent outcomes, the need for tube thoracostomy was rare, however, every inborn patient (n = 11) requiring a chest tube for pneumothorax died. Generally, the incidence of pneumothorax is reported between 4 and 14% and carries a grave prognosis.

7.4.3.4. Mechanical failure

Mechanical failure of the ECMO circuit can occur [65]. Examples included: thrombus in the circuit (65%), cannula problems (12%), failure of the oxygenator (6%), pump malfunction (2%), and air in circuit (5%). The effect of technical complications on survival is not as great as other physiologic complications.

7.4.3.5. Timing of operation

Although surgical management was historically an emergency for infants with CDH, this is no longer the approach. Previously, CDH was associated with a poor prognosis and a survival rate of approximately 50% with significant morbidity. The aim of medical management in infants with CDH is to stabilize for operation. The results of several studies suggest that delayed repair of CDH after prolonged stabilization has a beneficial effect on the survival rate. Other authors report conflicting results. The optimal time for surgical repair remains controversial and is not completely established.

The primary goal of preoperative stabilization is resolution of pulmonary hypertension. However, complete resolution of PHN can be challenging. Preliminary experience with the use of nitric oxide in infants with CDH has suggested that most infants with hypoxic respiratory failure did not show a sustained response.

Almost 500 infants undergoing early (<48 hours) versus delayed (>48 hours) were recently compared. The primary outcome was 90-day survival, and treatment duration (ventilation, oxygen, and hospitalization) was the secondary outcome. To adjust for disease severity, infants were stratified into three severity groups by Apgar score at 1 minutes (“mild” had an Apgar of 8–10, “moderate” 4–7, and :severe” 0–3). Outcomes were compared between early repair and delayed repair within each severity group [68].

Although 90-day survival was significantly different among the three severities ("mild" 97%, "moderate" 89%, and "severe" 76%, $p = 0.002$), there were no differences in 90-day survival between delayed repair and early repair in each group. In "mild," there were no differences in treatment duration between early and delayed repair. In "moderate," treatment duration was shorter in the early repair group (ventilation 11 vs. 16 days, oxygen 15 vs. 20 days, and hospitalization 34 vs. 48 days). In the "severe" group, treatment duration was shorter in the early repair group.

The timing of CDH repair appeared to have no influence on 90-day survival regardless of disease severity. Infants in the moderately severe category may benefit from the early repair by reducing treatment duration.

Some reports suggest that early repair on ECMO was associated with a decreased time on ECMO, decreased complications, and increased survival [69]. Others refute this and report increased survival if repair can be delayed until the infant is discontinued from ECMO [70].

Over about one decade (1992–2000), a single institution challenged conventional CDH management in the context of a clinical care strategy based on permissive hypercapnia and gentle ventilation. All infants underwent a respiratory care strategy based on permissive hypercapnia and spontaneous respiration, combined with elective repair. Arterial blood gas values and concomitant ventilator support were recorded.

All CDH infants and the following criteria were retrospectively reviewed: (1) respiratory distress requiring mechanical ventilation, (2) in-born infants, or (3) infants transferred preoperatively within hours of birth. Outcome markers such as the need for ECMO, time to discharge to home, need for supplemental oxygen at discharge, and the influence of nonECMO ancillary therapies (surfactant, nitric oxide, and high-frequency oscillatory ventilation) were examined.

For 120 consecutive infants with CDH, the overall survival rate was 75.8%. When 18 of 120 that were not treated were excluded (6 lethal anomalies, 10 overwhelming pulmonary hypoplasia, 3 prerepair ECMO-related neurocomplications), 84.4% survived to discharge. A total of 67/120 were inborn (55.8%). NonECMO ancillary treatments, such as iNO, HFOV, or surfactant, had no impact on the survival rate. ECMO was used in 13.3%. Surgery was transabdominal in all and 7% required a patch. Tube thoracostomy was rarely required, but every inborn patient ($n = 11$) who required a chest tube for pneumothorax died. The overall mean settings for respiratory support before surgery in survivors were: PIP: 22, FiO_2: 43%, PaO_2: 66 Torr, $PaCO_2$: 41 Torr and Ph: 7.32. Two infants that were successfully discharged on oxygen died at 4 and 7 months, respectively and the cause of death was not recorded.

The majority of infants with life-threatening CDH treated with a care strategy of permissive hypercapnia, spontaneous respiration, and elective surgery survive to discharge with minimal pulmonary morbidity [42, 43].

Overall, the approach of delayed surgery after stabilization is based on clinical evaluation, best practices, and retrospective evidence. Delay of operation while waiting for physiologic stabilization may shift mortality from post-op to pre-op in infants that do not survive. The delayed operation approach favors better resource utilization and physiologic stress reduction during

hemodynamic instability and pulmonary hypertension. The delayed approach also favors infant self-selection as they demonstrate that they can stabilize during the waiting period.

8. Low risk CDH infants

There are few data in lower risk infants to support specific timing of repair of elective CDH after hemodynamic stability is achieved. The CDH study group data for low risk CDH infants were analyzed. The aim of the analysis was to understand the effect of timing of repair on survival in patients who did not require ECMO. Delayed repair did not appear to improve survival and if surgery is significantly delayed, there is an incidence of bowel obstruction and even volvulus in CDH infants [70].

8.1. Right-sided CDH

Previously, right-sided CDH was considered a subgroup of CDH infants with a poor prognosis. Twenty-seven cases of right CDH that presented for prenatal evaluation (MR or fetal echo) or postnatal treatment between 1995 and 2002 were retrospectively reviewed. In all cases, the fetal liver was herniated into the right chest [71].

The mean gestational age at evaluation was 26.1 weeks. The lung area to head circumference ratio (LHR) ranged from 0.32 to 2.5. Associated anomalies were common. There were four terminations. Fifty percent of continuing pregnancies had polyhydramnios, premature rupture of membranes, or preterm labor. The mean gestational age at birth was 36.8 weeks. One patient underwent tracheal occlusion at 27 weeks and two died before postnatal repair. The overall survival rate was 70% and the postnatal survival rate was 83%. A patch was utilized in 67% of neonates undergoing surgery. Fifty percent required ECMO with a 75% survival rate. Significant morbidity occurred in 53% of survivors and included neurologic sequelae in 32%.

MRI was considered helpful in the determination of liver position and confirmation of the diagnosis. This subgroup has a high incidence of preterm complications, comorbidities, and a frequent need for ECMO. Close prenatal surveillance and delivery at a tertiary care center with ECMO capability is recommended.

In contrast, a more recent series found right CDH was not associated with increased mortality, but it was associated with increased requirement for pulmonary vasodilatory therapy and requirement for tracheostomy [72]. However, the conclusion was similar in that the high incidence of pulmonary complications indicates an increased severity of pulmonary hypoplasia in right CDH and supports a role for delivery in tertiary centers with expertise in CDH management.

9. Repair on ECMO

In contrast to some that recommend delayed operation, others report that, if data are unadjusted for severity of disease, delaying CDH repair is associated with increased mortality [70].

One multivariate analysis of early versus late repair reports that timing of repair confers no difference in outcomes [73]. Most recommend CDH repair should be based on the optimization of clinical parameters as opposed to a specific time period to improve outcome.

Others report that surgical repair on ECMO may confer a slight survival advantage and the complications from bleeding may be lessened by the use of tranexamic acid [74]. Others contradict this recommendation [75]. Similarly, there are significant differences between repaired and nonrepaired CDH infants and significant center variation in the rate of nonrepair exists. Aggressive surgical management, leading to a low rate of nonrepair, is associated with improved risk-adjusted mortality [76].

An increase in survival to surgery does not always equate to increased survival overall. Some authors suggest that if the liver is down, the PHN is less severe, the defect tends to be smaller, and the recommended approach is stabilization and delayed repair [76]. For those with the liver up, the PHN tends to have increased severity with a larger defect and those may benefit from repair on ECMO, but more investigation is needed [77].

9.1. Care strategy for repair of CDH

It is recommended that the operation is delayed until $FIO_2 < 50\%$, PIP < 25 cm H_2O, MAP < 12, with resolution of pulmonary hypertension by clinical criteria and echo. The infant should have a normal acid base balance, stable blood pressure, resolution of anasarca, and almost meet parameters for ECMO discontinuation or have undergone decannulation.

If the infant is on ECMO, consider the use of an AMICAR infusion @20 mg/kg/hour, following a loading dose of 100 mg/kg. One must prepare for the large transfusion protocol, and blood products should be prepared to allow rapid infusion if needed during operation. The infant must have access from anesthesia and surgery and adequate venous and arterial access for administration of blood products, medications, and monitoring. Both preductal and postductal saturation monitors must be in full view. Blood gases will be monitored at baseline and then approximately every 30 minutes during the operation. Extensive team communication between anesthesia, surgery, and neonatology is imperative during the CDH repair operation.

9.2. Outcomes and long-term follow-up

The improvement in ventilation and resuscitation modalities in recent years has improved survival in CDH infants. The increased survival led to an increase in the long-term morbidity burden. As more survivors are advancing in years, our understanding of the complexity of the CDH pathology has improved [78, 79].

The CDH patient is a complicated patient with an intricate disease course. Follow-up should be composed of a multifaceted approach as there are surgical and nonsurgical consequences to the disease process.

9.3. Hernia recurrence

Recurrence of the diaphragmatic hernia has been reported in 8–50% of CDH survivors. The size and the type of repair (patch vs. primary closure and thoracoscopic vs. open repair)

appear to be the most commonly reported factors affecting recurrence [80–84]. Survivors with large defects or who underwent patch or laparoscopic repair tend to be more prone to have a recurrence. Recurrence can occur months to years from the initial repair. Recurrences can present with a spectrum of findings from the asymptomatic patient to a patient with bowel obstruction.

9.4. Thoracoscopic versus open repair

Conflicting studies exist regarding the hernia recurrence rate after thoracoscopic or open repair for infants with CDH. Many studies report an increased incidence of recurrence after thoracoscopic repair. In general, these are poorly controlled, retrospective studies. It has been difficult to determine if the increased recurrence is secondary to patient selection, technical variations in repair, experience of the surgeon, or a combination of all of the above. The International Pediatric Endoscopic Group (IPEG) reported one of the first multiinstitutional studies across seven tertiary care pediatric hospitals and attempted to address these questions. IPEG attempted to specifically evaluate the technical variations of thoracoscopic repair of CDH to identify if certain methods are associated with recurrence [85].

They compared primary versus patch repair, type of patch and suture utilized, technique of patch application, and use of extracorporeal/rib fixation sutures. The study concluded there was no statistically significant technical factor related to recurrence to currently recommend a standardized surgical approach to thoracoscopic repair [85].

9.5. Pulmonary outcomes

CDH survivors are more prone to experience a pulmonary morbidity. Around 25% of CDH survivors develop an obstructive airways disease [86, 87]. An estimated 55% of survivors develop recurrent respiratory infections regardless of their chronic pulmonary or airway morbidity [88]. Pulmonary hypertension can also persist and correlates with early mortality [89].

9.5.1. Neurological and developmental outcome

Longitudinal neurodevelopmental and neuroimaging studies of CDH survivors have demonstrated the survivors' susceptibility to neurodevelopmental delay. Magnetic resonance studies revealed anatomic abnormalities in 17% of CDH patients [90]. Delayed brain maturation appears to be prevalent, especially in infants with severe CDH [91]. Such findings correlate with future cognitive impairment. The findings correlated with ECMO treatment, right-sided CDH, intrathoracic liver, patch repair, and prolonged oxygen use after multivariate analysis [67].

Sensorineural hearing loss, independent of ECMO use, has been described in CDH survivors [92, 93] and is believed to stem in part as a side effect of treatment. Approximately 35% of survivors will require hearing aids [94, 95].

9.5.2. Nutritional, growth, and gastrointestinal outcomes

Failure to thrive has been well documented in CDH survivors, with estimates of between 20 and 50% of survivors experienced growth retardation and remains in the lower percentiles

on the growth chart [96, 97] and it is believe to be a result of complex processes including oral aversion, GERD, increased metabolic stress due to ingoing morbidity. Around 33% of survivors require some form of tube feeding [80, 98].

Gastroesophageal dysmotility and regurgitation has been found to be prevalent in CDH survivors with a prevalence of between 45 and 90% reported [97–101]. The tendency to GERD may contribute to the survivor's failure to thrive. However, at present, there is no evidence that routine fundoplication is needed.

9.5.3. Musculoskeletal outcomes

Chest wall deformities and scoliosis have been reported in CDH survivors. The literature estimates the prevalence of chest wall deformities to be approximately 16–48% [86, 102–105]. While thoracic scoliosis has been reported in 10–27% of survivors [82, 105]. Though prevalent, not all deformities will require intervention. The prevalence of scoliosis has been found to be more prevalent in survivors with big defects who underwent patch repairs [84, 105].

9.5.4. Other outcomes

In addition to the above-mentioned long-term morbidities, associated congenital defects have been reported in around 33–40% of CDH infants [106–112]. Associated congenital anomalies such as cardiac defects, genitourinary abnormalities, and neurological anomalies should be taken into consideration when planning long-term follow-up.

9.5.5. Follow-up

The complexity of the CDH patient mandates a structured multidisciplinary follow-up. In 2008, the American Academy of Pediatrics published an outline for the follow up of the patient with CDH [107]. This was done to identify and treat morbidities to prevent any further disability. The outline is summarized in **Table 1** [107].

	Before discharge	**1–3 months after birth**	**4–6 months after birth**	**9–12 months after birth**	**15–18 months after birth**	**Annual through 16 years**
Weight, length, occipital-frontal circumference	X	X	X	X	X	X
Chest radiograph	X	If patched	If patched	If patched	If patched	If patched
Pulmonary function testing			If indicated		If indicated	If indicated
Childhood immunizations	As indicated throughout childhood	X	X	X	X	X

	Before discharge	1–3 months after birth	4–6 months after birth	9–12 months after birth	15–18 months after birth	Annual through 16 years
RSV prophylaxis	RSV season during first 2 years after birth (if evidence of chronic lung disease)	X	X	X	X	X
Echocardiogram and cardiology follow-up	X	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen	If previously abnormal or if on supplemental oxygen
Head computed tomography or MRI	If (1) abnormal finding on head ultrasound; (2) seizures/ abnormal neurologic findings[a]; or (3) ECMO or patch repair	As indicated	As indicated	As indicated	As indicated	As indicated
Hearing evaluation 44	Auditory brainstem evoked response or otoacoustic emissions screen	X	X	X	X	Every 6 months to age 3 years, then annually to age 5 years
Developmental screening evaluation	X	X	X	X		Annually to age 5 years
Neurodevelopmental evaluation	X			X		Annually to age 5 years
Assessment for oral feeding problems	X	X	If oral feeding problems	If oral feeding problems	If oral feeding problems	If oral feeding problems
Upper gastrointestinal study, pH probe, and/or gastric scintiscan	Consider for all patients	If symptoms	If symptoms	Consider for all patients	If symptoms	If symptoms
Esophagoscopy		If symptoms	If symptoms	If symptoms or if abnormal gastrointestinal evaluations	If symptoms	If symptoms

	Before discharge	1–3 months after birth	4–6 months after birth	9–12 months after birth	15–18 months after birth	Annual through 16 years
Scoliosis and chest wall deformity screening (physical examination, chest radiograph, and/or computed tomography of the chest)				X		X

Notes: The neurosensory tests performed and frequency of surveillance may differ among infants with CDH because of variability in neurologic, developmental, and physiologic impairments. Follow-up should be tailored to each infant. RSV indicates respiratory syncytial virus.

[a] Muscle weakness, hypotonia, hypertonia, or other abnormal neurologic sign or symptom.

Table 1. Recommended schedule of follow-up for infants with CDH [107].

10. Conclusions

The management of congenital diaphragmatic hernia remains a challenge. Mortality is dependent on associated malformations, the severity of pulmonary hypoplasia, pulmonary hypertension, and iatrogenic lung injury associated with aggressive mechanical ventilation. A comparison of the mortality rate of CDH infants in a single center between 1995 and 2005 versus 2006 and 2016 revealed that the mortality rate significantly decreased in the later time period, 17.9 compared to 4.4%. Prenatal diagnosis, intrathoracic liver, low Apgar score, and low birth weight were defined as independent risk factors for mortality. The mortality in ECMO-treated patients was 50% in both time periods [113]. Despite no significant differences in the incidence of independent risk factors and the use of ECMO between the two time periods, mortality decreased over time.

Therefore, there are many important factors involved in a successful outcome after CDH repair. Large multicenter studies are necessary to define those critical factors and to determine optimal treatment strategies.

Infants with CDH should be delivered as close to term as possible. At birth, management includes bowel decompression, avoidance of mask ventilation, and endotracheal tube placement if required. The care strategy includes gentle ventilation, hemodynamic monitoring, and treatment of pulmonary hypertension followed by surgery. Although inhaled nitric oxide is not Food and Drug Administration (FDA) approved for the treatment of pulmonary hypertension in CDH infants, it is commonly used. Extracorporeal membrane oxygenation (ECMO) is considered if conventional medical management fails for infants ≥ 34 weeks' gestation or with weight >2 kg and no associated major lethal anomalies. With advances in CDH management, the overall survival has improved and has been reported between 70 and 90% in non-ECMO infants and up to 50% in infants who undergo ECMO.

There are many important areas of research that may promote better understanding of the development of CDH. Fujinaga et al. reported that cord blood endothelial progenitor cells are

altered in CDH infants, but the mechanism is unknown [114]. Russo et al. reported the use of transplacental sildenafil rescues lung abnormalities in a rabbit model of CDH, improves vascular branching, and reduces pulmonary vascular resistance [115]. This promising research may further alter and improve outcomes for infants with CDH.

Author details

Joanne Baerg*, Arul Thirumoorthi and Rajaie Hazboun

*Address all correspondence to: jbaerg@llu.edu

Loma Linda University Children's Hospital, Loma Linda, CA, USA

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