



Congenital diaphragmatic hernia: a narrative review of controversies in neonatal management

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Abstract: The consequences of most hernias can be immediately corrected by surgical repair. However, this isn't always the case for children born with a congenital diaphragmatic hernia. The derangements in physiology encountered immediately after birth result from pulmonary hypoplasia and hypertension caused by herniation of abdominal contents into the chest early in lung development. This degree of physiologic compromise can vary from mild to severe. Postnatal management of these children remains controversial. Although heavily studied, multi-institutional randomized controlled trials are lacking to help determine what constitutes best practice. Additionally, the results of the many studies currently within the literature that have investigated differing aspect of care (i.e., inhaled nitric oxide, ventilator type, timing of repair, role of extracorporeal membrane oxygenation, etc.) are difficult to interpret due to the small numbers investigated, the varying degree of physiologic compromise, and the contrasting care that exists between institutions. The aim of this paper is to review areas of controversy in the care of these complex kids, mainly: the use of fraction of inspired oxygen, surfactant therapy, gentle ventilation, mode of ventilation, medical management of pulmonary hypertension (inhaled nitric oxide, sildenafil, milrinone, bosentan, prostaglandins), the utilization of extracorporeal membrane oxygenation, and the timing of surgical repair.

Keywords: Hernias; diaphragmatic; congenital; treatment; medicine; surgery

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A congenital diaphragmatic hernia (CDH) results from the inadequate formation of the diaphragm during embryogenesis and causes a cascade of events which can present in a newborn child varying clinically from mild to very severe to fatal. The incidence of CDH is 1 in 2,500 to 1 in 3,500 live births and occurs 90% of the time in the posterolateral aspect of the diaphragm known as a Bochdalek hernia with over 85% occurring on the left side (1). The diaphragmatic defect in the embryo allows for abdominal viscera to enter the thoracic cavity causing a

mass effect on the developing lungs resulting in pulmonary hypoplasia and pulmonary hypertension. The degree of clinical severity is often proportional to the size of the defect (*Figure 1*) (2,3). Although the consequences of other hernias can be avoided when repaired surgically, often there is no quick fix to this underlying dysgenesis of the lungs. In fact, past review of immediate repair demonstrated a worsening in the physiology of CDH neonates, which helped shift repair to a more delayed approach (4). These issues are most often addressed through medical management

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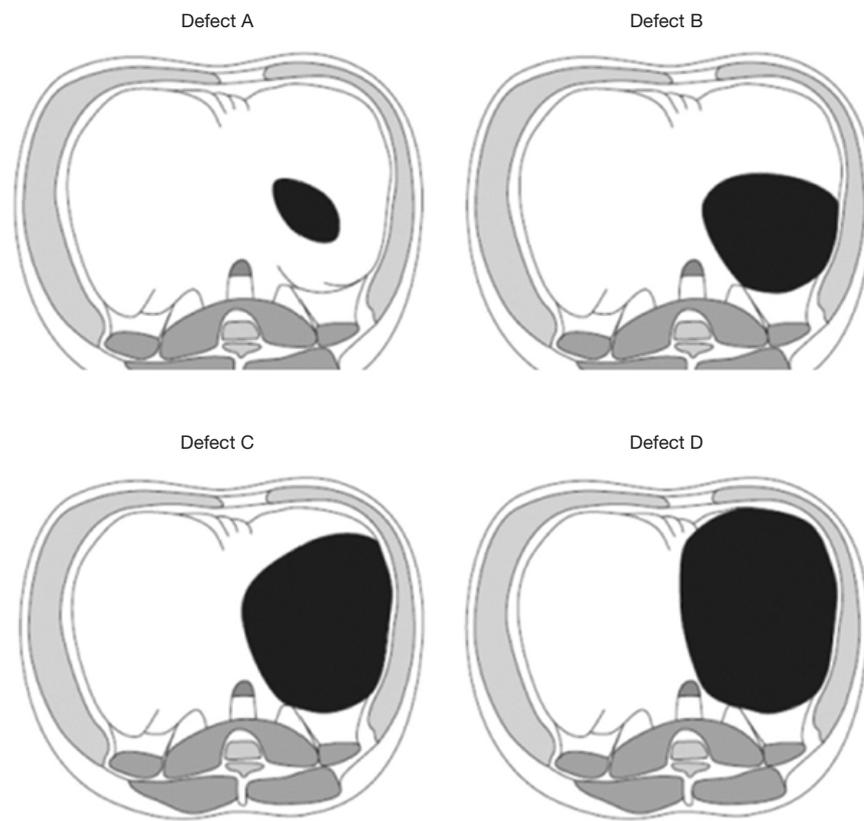


Figure 1 CDHSG staging system. This figure was published in *Journal of Pediatric Surgery*, Vol 48, Lally KP, Lasky RE, Lally PA *et al.*, Standardized reporting for congenital diaphragmatic hernia--an international consensus, pages 2408-2415, Copyright Elsevier (2013) (2). Right to reproduce obtained by Elsevier.

in a neonatal intensive care unit (NICU) or pediatric intensive care unit (PICU). Given the complex medical and surgical nature of these infants, many collaboratives have sought to standardize management guidelines to decrease variation in care and improve overall outcomes (5-7). With few exceptions, such guidelines are almost entirely based on expert consensus driven recommendations. Few multicenter, randomized control trials exist to help guide the treatment of children with CDH and severe pulmonary hypertension. This review aims to discuss important and somewhat controversial aspects of neonatal management in these challenging children, mainly: the use of fraction of inspired oxygen, surfactant therapy, gentle ventilation, mode of ventilation, medical management of pulmonary hypertension (inhaled nitric oxide, sildenafil, milrinone, bosentan, prostaglandins), the utilization of extracorporeal membrane oxygenation, and the timing of surgical repair. We present the following article in accordance with the Narrative Review reporting checklist (available at [http://](http://dx.doi.org/10.21037/tp-20-142)

dx.doi.org/10.21037/tp-20-142).

This narrative review was compiled through study, analysis, and discussion of previously published journal articles specific to the treatment of congenital diaphragmatic hernia. An emphasis was placed on recent literature over the past 10 years, 2010–2020, however, older studies were included when necessary. Published material was identified utilizing the PubMed® (National Center for Biotechnology Information, United States National Library of Medicine, National Institutes of Health) database using multiple combinations of the keywords: congenital diaphragmatic hernia, CDH, ECMO, management, pulmonary hypertension, repair, surgery, and ventilation. The articles were then read for relevancy and the bibliographies reviewed for additional citations. Importance of the publications were based on previously described levels of evidence (8). Article inclusion within this review was determined by the authors after their evaluation, analysis and interpretation.

Fraction of inspired oxygen (FiO₂)

Historically, resuscitation of CDH neonates has been to start with an FiO₂ of 1.0 (9-11). However, there is concern that oxygen itself increases the risk of oxidative stress and decreases the effectiveness of nitric oxide induced vasorelaxation (12-15). A review of 68 CDH care guidelines from North American institutions noted that more than half of them (58%) did not provide initial FiO₂ recommendations (16). Currently, the revised 2016 EURO CDH Consortium recommends initiating resuscitation at an FiO₂ of less than 1.0 (7). Recent literature is emerging that resuscitation with an FiO₂ of less than 1.0 may be safe without worsening outcomes of survival, extracorporeal membrane oxygenation (ECMO) use or duration of mechanical ventilation (17,18). Riley *et al.* compared a historical control group starting resuscitation at FiO₂ of 1.0 to their study cohort that initiated resuscitation with FiO₂ of 0.5 (17). They noted that FiO₂ of 1.0 was associated with lower survival (69% *vs.* 95%, P=0.005), increased incidence of ECMO (38% *vs.* 15%, P=0.034), longer time to repair (24.5 *vs.* 14.2 days, P=0.023) as well as higher incidence of periventricular leukomalacia (18% *vs.* 0%, P=0.01) and lower motor scores at 12 months (mean 75.8±18.1 *vs.* 91.7±12, P=0.0037). Another study demonstrated similar outcomes, including increased survival to discharge and overall decreased use in ECMO when initiating resuscitation using an FiO₂ of 0.4 compared to 1.0 (18). Interestingly, only 18% of those children that started at an FiO₂ of 0.4 required an increase to 1.0. These studies suggest that it may be beneficial to initiate resuscitation with an overall lower FiO₂ and raise as needed, versus starting at 1.0 and weaning as able. However, the data supporting this are lacking, therefore, it is more appropriate to target a pre-ductal O₂ saturation level of 80–85% using the FiO₂ as necessary to do so. If an FiO₂ level of 1.0 is initiated, it should be weaned as able to maintain the appropriate level of oxygen support.

Surfactant

Animal studies suggested that surfactant deficiency may contribute to CDH pathophysiology with a decrease in lung compliance, decreased concentration of alveolar phospholipids (especially phosphatidylcholine), and higher lung concentrations of total DNA and glycogen (19,20). Although a limited number of case reports observed possible benefit with surfactant therapy in CDH infants (21,22),

this was not supported in studies reviewing its use in CDH neonates using the CDH study group (CDHSG) registry (23,24). Currently, routine surfactant administration is not recommended in children born with CDH (7).

Gentle ventilation

In the past, CDH was considered a surgical emergency (25). Early mortality rates were high, and often attributed to pulmonary hypertension (4). Historically, management strategies targeted hyperventilation (i.e., hypocarbia) with high respiratory rates and variable peak inspiratory pressures in an effort to promote pulmonary vascular relaxation (25). However, this method often resulted in iatrogenic barotrauma of the hypoplastic lungs leading to chronic lung disease (26). Upon review of 68 CDH autopsy specimens, Sakurai and colleagues noted 91% of the cases had evidence of ventilator induced injury with diffuse alveolar injury in the setting of hyaline membrane deposition (27). They speculated that mechanical ventilation played a significant role in the mortality for the CDH cohort when using hyperventilation with higher inspiratory pressures, leading to overdistention of alveoli. In 1985, Wung *et al.* first described success using a less aggressive approach to mechanical ventilation in neonates with severe respiratory failure complicated by persistent fetal circulation (28). They focused on minimizing pressure/volume delivery and lung over-distention with tolerance for higher PaCO₂ into the 50–60 torr range. This same group subsequently reported the use of this approach in a CDH cohort accompanied by decreased barotrauma, lower ECMO use and improved survival (29). Subsequently, this approach, commonly referred to as “gentle ventilation”, was adopted and reported by other institutions associated with improved survival rates and decreased use of ECMO (9,22,30-33). Wilson and colleagues reviewed their experience, comparing their eras of hyperventilation to that of gentle ventilation, reporting improved survival from 44% to 69% (P<0.007) (33). Kays *et al.* showed an improvement in survival from 15% in an era of hyperventilation, to 44% with the use of ECMO and hyperventilation, and even greater to 78% with the use of gentle ventilation and ECMO (P<0.001) (32). More recently, in a study that compared lower versus higher end-expiratory pressures in post-repair CDH neonates on conventional mechanical ventilation (CMV), Guevorkian and colleagues reported improved lung mechanics and perfusion with lower distending pressures, further supporting the benefits of minimizing pulmonary

Table 1 Ventilatory recommendations per current available guidelines

	CDH EURO Consortium (7)	APSA (6)	Canadian CDH Collaborative (5)
Initial mode	CMV	CMV or HFOV	CMV
Rescue mode	HFOV	HFOV	HFOV or HFJV
Ventilator settings	PIP <25 cmH ₂ O PEEP 3–5 cmH ₂ O Rate 40–60/min	PIP <25 cmH ₂ O PEEP 3–5 cmH ₂ O	NA
HFOV settings	NA	P _{aw} 13–15 cmH ₂ O Δ pressure 30–40 cmH ₂ O	NA
Goal SpO ₂	Pre-ductal 80–95% Post-ductal >70%	Pre-ductal >85%	Pre-ductal 85–95%
Goal ABG values	PaCO ₂ 50–70 mmHg	PaCO ₂ <60 mmHg	pH 7.25–7.40 PaCO ₂ 45–60 mmHg
Weaning	FiO ₂ if pre ductal >95% PIP/PEEP if PaCO ₂ <50 mmHg	NA	FiO ₂ if pre ductal >95%

ABG, arterial blood gas; APSA, American Pediatric Surgical Association; CMV, conventional mechanical ventilation; FiO₂, Fractional inspired oxygen; HFJV, high frequency jet ventilation; HFOV, high frequency oscillatory ventilation; P_{aw}, mean airway pressure; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure.

overdistention in infants with relative lung hypoplasia (34). Currently, all published guidelines recommend preferential lower airway pressures while allowing for permissive hypercapnia (5–7,35). *Table 1* summarizes the findings above. These systematic reviews support the use of gentle ventilation strategies to achieve improvements in survival while minimizing iatrogenic lung injury.

Mode of ventilation

Though it is now “standard of care” to use a gentle ventilation approach, optimal initial mode of ventilation for the CDH cohort has yet to be determined. Theoretically, the use of high frequency ventilation may allow for optimal gas exchange and minimization of ventilator induced lung injury via application of adequate distending pressure to optimize lung inflation and prevent atelectasis while using very low tidal volumes to minimize stretch-related “volutrauma” to the hypoplastic lungs (36). In Sakurai’s review of CDH autopsy cases, in contrast to babies managed via CMV, they noted very low rates of hyaline membrane formation in cases with early high frequency oscillatory ventilation (HFOV) use, supporting the possibility of lower ventilator induced lung injury with high frequency ventilation. There are several retrospective single-center

reports describing success with HFOV as the initial ventilatory support mode in neonates with CDH (9,37–40). Reported starting frequencies ranged from 10–15 Hz with mean airway pressures (Paw) typically initiated at 13–15 cmH₂O range. The exception is the report by Reyes *et al.* who described an initial Paw range from 5–20 cmH₂O, with more than 50% starting at less than 12 cmH₂O (41). The importance of not over-distending the hypoplastic lungs of the CDH infant was emphasized by the authors and discussants in all of the above cited studies.

One of the few randomized control trials performed in neonates with CDH is the multi-center VICI-trial, where investigators randomized CDH neonates to either CMV or HFOV (42). The trial was stopped after enrollment of 171 of a planned 200 participants in an inclusion period of 5 years because of lower than anticipated recruitment rates and limited financial resources. They observed no significant difference in the primary outcome of death or bronchopulmonary dysplasia between the two arms (CMV 45% *vs.* HFOV 54%, OR 0.62, 95% CI: 0.25–1.55, P=0.31). However, neonates randomized to HFOV were more frequently treated with iNO, vasoactive infusions, and ECMO. It is important to note that calculation of the initial Paw used in the CMV group was approximately 7–10 cmH₂O, while the initial Paw in the HFOV group was

Table 2 Comparison of HFOV settings and outcomes between Snoek *et al.* and Yang *et al.* related to starting mean airway pressure (P_{aw})

	Snoek <i>et al.</i> (42) Study Group		Yang <i>et al.</i> (18) P_{aw} Era	
	CMV	HFOV	“High”	“Low”
P_{aw} on HFOV (cmH ₂ O)	7–10	13–17	13–15	10–12
iNO	43%	56%	81%	44%
Vasoactive medication use	80%	91%	83%	65%
ECMO	26%	51%	37%	13%
Survival	69%	77%	74%	89%

CMV, conventional mechanical ventilation; ECMO, extracorporeal membrane oxygenation; HFOV, high frequency oscillatory ventilation; iNO, inhaled nitric oxide; P_{aw} , mean airway pressure.

higher at 13–17 cmH₂O. Though most experts recommend setting the P_{aw} 2–3 cmH₂O higher when transitioning from CMV to HFOV, CDH infants in the VICI-trial averaged about 6–7 cmH₂O higher in the HFOV group. Although the authors concluded that there was no difference between CMV or HFOV as the primary mode of ventilation, based on their primary outcome, many institutions and guidelines recommend initiating respiratory support with CMV because of the increased rates for iNO, inotrope infusions, and ECMO in the HFOV study group (42). However, the large difference in airway pressures make it challenging to draw comparative conclusions between the two groups, as the much higher P_{aw} in the HFOV group could contribute to relative lung over-inflation in the hypoplastic lungs of these CDH neonates. In that context, we recently reported the effect associated with a change in our approach to CDH management, including a lower initial P_{aw} during HFOV support, our primary ventilatory mode for CDH (18). We found a significant decrease in the use of iNO, inotropes and ECMO in the cohort of CDH neonates primarily managed with HFOV initiated at a significantly lower P_{aw} {median 11 [10–12] vs. 13 [12–15] cmH₂O} (18). This comparison is summarized in *Table 2*.

In the context of fragile, hypoplastic lungs, high frequency jet ventilation (HFJV) may have theoretical and clinical advantages over HFOV. Both *in vitro* and *in vivo* studies suggest that HFJV can be used to support gas exchange at P_{aw} comparable to or lower than CMV, and with less adverse effect on cardiopulmonary hemodynamics than either CMV or HFOV (43–47). One of the earliest reports to describe HFJV in neonates with CDH was by Boros *et al.* who reported improvement in arterial blood gas measures with HFJV as a “rescue” mode (43). Subsequently, Kuluz *et al.* reported using HFJV to rescue 16 CDH

neonates with respiratory failure on CMV, though they did not find significant survival benefit in their small cohort (48). More recently, Attar *et al.* reviewed their experience using high frequency ventilation as a rescue modality with 22 CDH neonates managed on HFJV and 17 on HFOV (n=44). They observed an improvement in ventilation with high frequency rescue in general (P=0.001) and a significant decrease in PaCO₂ for the HFJV cohort (P<0.001). In this small series they found no improvement in oxygenation, but P_{aw} was significantly increased in the HFOV managed infants compared to those on HFJV support. They suggest that HFJV may be a superior ventilatory modality for optimizing ventilation with lower P_{aw} compared to HFOV for rescue of CDH neonates but note that prospective studies are needed to better define the optimal mode and approach (49). Current published guidelines recommend the use of high frequency ventilation (HFOV or HFJV) as a possible rescue mode at this time although several studies mentioned above demonstrate the value of this modality as the initial ventilatory management.

Management of pulmonary hypertension

Pulmonary hypertension is a significant cause of morbidity in children with CDH. It arises from abnormal pulmonary vasculature development due to increased arterial remodeling, decreased vascular bed density and altered vascular responsiveness (50,51). Autopsy specimens of CDH neonates show more abundant, mature contractile smooth muscle cells in the adventitial and medial layers of the pulmonary vasculature (52). In a rabbit CDH model, Schmidt *et al.* noted increased phenylephrine induced contractions of the left pulmonary artery with decreased relaxation compared to the aorta (53). Many

different pathways have been implied in the underlying pathophysiology, with treatments specifically targeting these pathways, such as inhaled nitric oxide (iNO), sildenafil, milrinone, bosentan, and prostaglandins. Each will be discussed below.

iNO

The nitric oxide pathway is an important contributor to postnatal pulmonary vascular relaxation. Nitric oxide synthase (NOS) present in the endothelium catalyzes the production of nitric oxide (NO), allowing for NO diffusion to vascular smooth muscle cells where it promotes vasodilation via a guanylyl cyclase induced cyclic GMP (cGMP) mediated pathway. In both animal models and human postmortem lungs, varying reports of either under-expression (54-56) or over-expression of endothelial nitric oxide synthase (eNOS) has been reported (57,58). Solari and colleagues observed a significant decrease in eNOS expression from pulmonary hypertension complicated deceased CDH neonates (56). Mous *et al.* showed an increase in eNOS expression and theorized that this may be secondary to decreased NO availability or by increased eNOS uncoupling which leads to increased oxidative stress (57). Recently, Nakamura and colleagues provided data suggesting decreased production of nitric oxide synthase interactive protein (NOSIP) in pulmonary vascular smooth muscle cells, which normally reduces endogenous NO production by interactions with eNOS (59). They suggest that NOSIP may contribute to increased eNOS and NO production, which in turn would lead to desensitization of downstream guanylyl cyclase and ultimately vasoconstriction.

Given this disturbed physiology, iNO was thought to be a promising therapy for CDH related pulmonary hypertension. Early case reports described temporary benefits in oxygenation for some CDH patients (60,61). However, a large multi-center, randomized control trial (NINOS-trial) conducted in 1997 concluded no difference in the combined outcome of survival or need for ECMO with the use of iNO in CDH infants, though the trial was stopped early given lack of efficacy (62). Limitations of the NINOS-trial included enrollment during a different respiratory management era which was prior to the standard of the gentle ventilation method. Also, iNO was administered as a late rescue modality rather than as early treatment of pulmonary hypertension. Review of the prospective CDHSG database noted variable practice in the use of iNO amongst enrolling institutions (63). These

investigators reported an association between the trend of iNO use and mortality, with a 15% higher absolute mortality rate (95% CI: 0.1–0.2). Despite this, recent reports suggest that there may be subgroups of CDH neonates who respond to iNO therapy (64,65). For example, older CDH neonates with late pulmonary hypertension on minimal respiratory support benefited from iNO when administered through non-invasive measures such as nasal cannula (65). Herich *et al.* noted that of 265 CDH neonates, approximately 31% responded within 1 hour of iNO administration with an increase in PaO₂ of 10–20% and a decrease in oxygenation index by greater than 5 points (P<0.0001) (64). Additionally, ECMO utilization (67% *vs.* 48%, P=0.0024), and mortality (17% *vs.* 29%, P=0.04) were both decreased compared to non-iNO responders. Finally, a retrospective study of a single institution with 73% of CDH neonates treated with iNO for severe pulmonary hypertension reported a 40% response rate in those with preserved left ventricular systolic function (66). Response was defined by improvements in PaO₂ levels of greater than 20mmHg and subsequent improvements in alveolar-arterial gradients and PaO₂/FiO₂ ratios (both P<0.01). In contrast to non-responders, they reported a decreased need for ECMO (24% *vs.* 50%, P=0.02). These investigators concluded that iNO treatment may be beneficial in a subset of CDH neonates with normal left ventricular systolic function and pulmonary hypertension (66). As iNO use can lead to increased pulmonary venous return, this might precipitate cardiopulmonary failure in a left ventricle that is compromised in size and/or function. Given the transient nature of response to iNO, its utility may actually be significantly limited in even these infants. In summary, a trial of iNO for severe pulmonary hypertension may be reasonable, however, cessation should occur if a response is not observed within 24 hours, as is currently the recommendation of various practice guidelines (5-7).

Sildenafil

Along the NO pathway, cGMP is hydrolyzed and inactivated by the enzyme phosphodiesterase-5 (PDE-5). One method to enhance the effect of endogenous or supplemented NO would be to target cGMP catabolism. There is concern that PDE-5 is abnormally upregulated in the CDH cohort (67). Vukcevic *et al.* hypothesized that the decreased postnatal response to nitric oxide for CDH is due to altered postnatal PDE-5 activity. They tested this theory by inhibiting PDE-5 activity in postnatal nitrofen-induced

CDH rat pulmonary arterioles. Following sildenafil citrate exposure, they observed an increased vasodilatory response to cGMP, similar to that seen with the control arterioles (67). Thus, the use of PDE-5 inhibitors such as sildenafil citrate, may be beneficial for CDH related pulmonary hypertension.

Case reports exist detailing the use of sildenafil for CDH related pulmonary hypertension with improvement in oxygenation (68,69). Noori *et al.* reviewed 7 CDH patients with pulmonary hypertension noting improvement in cardiac output due to acute decrease in pulmonary arterial pressures within 1–4 hours after administration of sildenafil, with improvement in oxygenation (69). Similar improvement in oxygenation with improvement in echocardiographic markers of pulmonary hypertension was noted with IV sildenafil administration in 9 CDH cases (68). None of the reports to date include untreated/control patients and there is concern for increased vasopressor support with the use of IV sildenafil secondary to systemic hypotension, especially during the first hours of therapy (70), thus, some caution is warranted. Currently, a multi-center, randomized control trial is ongoing in Europe comparing iNO to IV sildenafil therapy (NTR6982) (71). In theory, combined use of these agents may be most effective at lowering pulmonary vascular resistance (72). These studies suggest that earlier administration of sildenafil may be most effective, however, the benefit of this effect remains unclear due to limited data and lack of randomized trials.

Milrinone

Milrinone is a selective phosphodiesterase-3 (PDE-3) inhibitor that prevents the breakdown of cAMP, resulting in increased cardiac contractility, relaxation and vasodilation. Given these properties, it is commonly used in the pediatric population for low cardiac output syndrome (73). It has also been used for persistent pulmonary hypertension of the newborn (74,75) with a pilot, randomized control trial studying the use of milrinone with iNO currently in the process of enrolling participants (ISRCTN 12949496;EudraCT 2014-002988-16) (76). In the CDH cohort, the first study reported on milrinone used as adjunct therapy to other vasodilators in six patients with pulmonary hypertension and right heart dysfunction (77). They reported a decrease in oxygenation index and improvement in diastolic function, as well as a trend towards improving right ventricular systolic function. The author saw no changes to pulmonary nor systemic pressures (77). Kumar

et al. reviewed 12 CDH neonates managed with milrinone and iNO and also reported improvements in oxygenation index and left ventricular ejection fraction compared to pre-milrinone measures (78). Unfortunately, neither of these reports included a control study group. Subsequently, Mears and colleagues reported a retrospective study analyzing 48 CDH neonates matched by oxygenation index, 24 of whom were treated with milrinone (79). Both groups showed similar rates of improvement in oxygenation index, ductal shunt and left ventricular size over time, with no measurable changes in calculated pulmonary artery pressure. There was no difference in oxygenation index, pulmonary arterial pressure nor echocardiographic measures of left ventricular size over time between the milrinone treated versus untreated groups. Currently, a multi-center, placebo controlled, randomized control trial is ongoing to evaluate the use of milrinone in CDH (NCT02951130) (80). Thus, despite wide-spread use, data are limited into the usefulness of milrinone in CDH. Hopefully, ongoing randomized trials will help clarify the role of milrinone in treatment of CDH associated pulmonary hypertension.

Bosentan

Another known regulator of pulmonary vascular tone is the endothelin system, including endothelin-1 (ET-1). ET-1 acts through two different receptors subtypes: vasoconstricting ET-A and the vasodilatory receptor subunit, ET-B (81). de Laguasie *et al.* provided one of the earliest reports studying CDH autopsy specimens using immunohistochemistry and real-time PCR with laser microdissection (81). They observed significant over-expression of ET-A and ET-B in CDH pulmonary arteries compared to controls. Mous *et al.* also found an increased expression of ET-A and B receptors in both the rat model and human CDH patients (57). Keller and colleagues noted significantly higher plasma ET-1 levels in their combined outcome of death or supplemental oxygen at time of discharge, compared to those who survived to hospital discharge on room air (82). Bosentan is a competitive inhibitor of ET-A and ET-B, with a higher affinity for ET-A. Theoretically, this could induce pulmonary vasodilation and work as a therapeutic modality for CDH related pulmonary hypertension. A randomized trial comparing the use of bosentan with placebo as treatment for neonates with persistent pulmonary hypertension (not from CDH) noted a favorable response as defined by an oxygenation index less than 15, normal pulmonary

arterial pressures and no premature discontinuation of the medication secondary to lack of efficacy or toxicity (83). Bosentan therapy was superior when compared to placebo (88% *vs.* 20%, $P < 0.0001$). To our knowledge, there are no studies on bosentan in the CDH cohort.

Prostacyclin

Prostacyclin (PGI₂) is an endogenous eicosanoid that has vasodilatory effects on the pulmonary vasculature via cyclic AMP mediated decreases in endothelial intracellular calcium (84). IV prostacyclin has a short half-life, requiring continuous infusion (85). Treprostinil is a prostacyclin analog which can be administered subcutaneously (86). There are only limited studies on the use of prostacyclin analogues in the CDH pulmonary hypertension population (84–87). A retrospective study with 52 CDH neonates had a 46% incidence of pulmonary hypertension where either tolazoline or prostacyclin was administered (85). The group noted a significant decrease in both alveolar-arterial oxygen difference and oxygenation index without complications of systemic hypotension ($P < 0.05$) (85). A case series reviewed 14 CDH patients treated with subcutaneous treprostinil for late-onset, confirmed pulmonary hypertension by echocardiography who were unresponsive to iNO and sildenafil therapy (86). Improvement in oxygenation and increased pulmonary blood flow was noted with initiation of therapy, and patients tolerated the treatment well. Another small retrospective study reviewed 17 CDH neonates who were treated with treprostinil for extreme pulmonary hypertension (88). A significant decrease in b-type natriuretic peptide (BNP) levels at 1 week and 1 month of treatment was observed and corresponded to echocardiographic improvement of severe pulmonary hypertension. Moreover, treprostinil was well tolerated without need for therapy discontinuation or dose reduction secondary to adverse events. Although promising, larger, multi-center, randomized controlled trials are needed to evaluate the safety and efficacy of prostacyclin use in neonates with CDH associated pulmonary hypertension.

Prostaglandin

With severe, uncontrolled pulmonary hypertension, mortality may be related to right ventricular failure. In the CDH cohort, the left ventricle is often underdeveloped due to decreased pulmonary blood flow, leading to decreased fetal preload (89). With severe CDH cases, systemic

output could be more dependent on right ventricular function. Given this, the use of prostaglandin E1 (PGE1) to provide ductus arteriosus patency may allow for right ventricular pressure relief, leading to improved right ventricular function and allowing time for pulmonary vascular relaxation. Shiyanagi and colleagues reviewed 49 cases with CDH related pulmonary hypertension where 19 were managed with iNO and PGE1 and 30 neonates with iNO alone (90). They noted no difference in survival to discharge, however, a shorter duration of hospitalization and earlier dates of repair was observed for those on iNO alone. Lawrence *et al.* reviewed their experience using PGE1 for severe pulmonary hypertension with CDH ($n=57$) (66). Although most of these patients were initiated on iNO (88%), the addition of PGE1 had an improvement in pulmonary hypertension evidenced by a significant reduction in BNP biomarker levels and echocardiographic evidence of decreased supra-systemic right ventricular pressures. Unfortunately, no prospective studies have been conducted to date comparing the use of PGE1 alone or in combination with other therapies targeting pulmonary hypertension in neonates with CDH. All studied therapies for pulmonary hypertension reviewed above are summarized in *Table 3*.

Extracorporeal membrane oxygenation (ECMO)

When a newborn with CDH remains critically ill from pulmonary hypoplasia, the use of extracorporeal membrane oxygenation should be considered before severe lung injury has occurred. It is important that the utilization of ECMO be anticipated in these infants with early cannulation prior to levels of ventilator support that can permanently damage the fragile lung tissue. Approximately a third of babies with CDH are managed with ECMO therapy (91), however, its utilization across differing centers within North America is highly variable (16). Despite advancement in ECMO therapy, the survival rate of CDH infants rescued with ECMO has remained approximately 50% for the last 30 years (92). Although, it is likely that over this period of time, due to improvements in ventilation strategies, only the most severe cases now require ECMO therapy (91). We recently reported a decrease in overall ECMO utilization from 37% to 13% after a change in our CDH clinical practice guideline (18). However, this begs the question of whether the proper selection criteria are known to initiate ECMO rescue in infants with severe CDH associated pulmonary hypoplasia. More importantly, are there variables

Table 3 Current available/proposed pulmonary vasodilator therapies and evidence for use in CDH

Therapy	Case series	Controls included	Randomized trials	Results
iNO	Yes (61,62,64,76)	Yes	Yes (62)	No benefit by RCT (+) with targeting by LV function
Sildenafil	Yes (68,69)	No	No, on-going (71)	Suggested benefit
Milrinone	Yes (77,78)	Yes	No, on-going (80)	(+) by case only, (-) with controls
Bosentan	No	No	No	Unknown
PGI	Yes (85,86,88)	No	No	Suggested benefit
PGE	Yes (66,90)	No	No	Suggested benefit

iNO, inhaled nitric oxide; PGI, prostacyclin; PGE, prostaglandin. Referenced articles in parenthesis.

that should be used to help decide which children will actually benefit from ECMO and which children will not? Currently, contraindications for ECMO support are based on weight (<2 kg), gestational age (<32 weeks), presence of cardiac anomalies, lethal chromosomal anomalies, or occurrence of grade III/IV intraventricular hemorrhage (91). These contraindications were further confirmed using the Delphi approach with current and former members of the American Pediatric Surgical Association Critical Care Committee (93). However, this study by Cairo *et al.* also reported a significant variation in responses of whether or not the CDH should be repaired in a child who required ECMO support for 4–5 weeks. The bigger question is whether such children should have been placed on ECMO to begin with? Recently, the Michigan group has presented their yet to be published study of their Severe Pulmonary Hypoplasia and Evaluation for Resuscitation Efforts (SPHERE) protocol to help guide ECMO utilization in the most severe CDH neonates (liver up, LHR <1, MRI O/E TFLV <25%). ECMO was initiated only if the infant could obtain a pH >7.0, pCO₂ ≤100, preductal SpO₂ >80% and PCO₂ ≥40 on gentle ventilation settings for the first 2 hours of life (94). Of the 23 patients with severe CDH included in their initial single institutional retrospective study, 57% fit criteria for ECMO, with the remainder receiving comfort care only. Patient survival was 46% with long-term gastrointestinal, pulmonary, and neurodevelopment sequelae seen in all. When the same criteria were applied to the CDHSG database, no significant difference in survival was seen between patients that would have passed and those that would have failed the SPHERE protocol (53.7% *vs.* 47.4%, P=0.47), however, those that would have failed experienced a significantly longer course on ECMO (11 *vs.* 14 days, P=0.03) and were more likely to still be on ECMO or a ventilator at 30 days (95.8% *vs.* 69.1%, P=0.006) (95).

Amongst the survivors, those that would have failed the SPHERE protocol were more likely to still be on a ventilator or ECMO at 30 days (94.1% *vs.* 59.6%, P=0.006), had a longer overall hospital length of stay (108 *vs.* 81.5 days, P=0.008), and required supplemental feedings (94.4% *vs.* 69.2%, P=0.02). Although when retrospectively reviewed in a larger dataset no difference in survival was identified, criteria like this are worth studying further, especially to look at long-term mortality in those children who would have failed the SPHERE protocol as this was probably not captured once the child was discharged from the hospital.

The mode of ECMO, venoarterial (VA) or venovenous (VV), is a subject of debate and often falls along the line of institutional bias. Several retrospective, single institutional studies have reported that overall survival is equivalent between VV and VA ECMO support (96–99). More recent data using the Extracorporeal Life Support Organization (ELSO) database confirmed no significant difference in the odds of death (OR 1.01, 95% CI: 0.86–1.18, P=0.95) between propensity matched cohorts of CDH infants having undergone VV or VA ECMO (100). In a subgroup analysis of infants with pre-ECMO CDH repair, VV was found to have higher mortality (OR 2.10, 95% CI: 1.19–3.69, P=0.10) with no difference in significant neurologic injury (OR 1.48, 95% CI: 0.59–3.71, P=0.399) when compared to VA. In another subgroup analysis of infants who did not have pre-ECMO CDH repair, VV ECMO was associated with a lower incidence of a significant neurologic injury (OR 0.73, 95% CI: 0.56–0.95, P=0.021). There is an approximate conversion rate from VV to VA ECMO of 15% when support is not adequate with an associated higher mortality rate (63.2%) compared to VA (52.6%) and VV (48.0%) alone (100). It should be noted that no prenatal stratification was provided in any of

these studies, such as liver location or lung measurements, therefore, it is hard to quantify the overall severity of disease in the included patients. Therefore, there may be benefit in using the VV approach in infants who are placed on ECMO prior to CDH repair and the VA approach in only the most severe cases treated with ECMO.

There is no doubt that ECMO serves as an important adjunct in the treatment of the severest of CDH babies, although its rate of use has decreased due to improvement in the overall medical management of these children (18,101). However, the degree to which ECMO improves survival is difficult to determine given the lack of large multi-institutional randomized trials, the wide variation of care between institutions, and overall limitations of the reported literature (92,101). Additionally, not all studies may actually account for late-term mortality, or death that occurs greater than 90 days after ECMO, making the survival benefit seem higher than it really is (102). It is also important to remember that the use of ECMO alone is an independent predictor of long-term neurodevelopmental delay (103) and long-term follow-up and care is required to recognize ECMO-related impairments in order to intervene early (102).

Timing of surgical repair

With improvement of the overall medical management, the timing of repair remains controversial without any definitive study that demonstrates superiority of early (within 24 hours) or delayed repair (104). In infants with mild pulmonary hypertension, the decision is less challenging, and timing usually varies from institution to institution. In general, a period of neonatal transition is followed by repair as soon as the infant is deemed physiologically stable for surgery by the neonatology and surgical teams. This can be fairly subjective and no objective way of determining proper timing has been published to date, although, it appears that the timing of repair in low-risk children does not have an effect on overall outcomes (105).

For infants with more severe pulmonary hypertension, multiple strategies for repair exist. Sakai *et al.* demonstrated that physiologic deterioration occurs following CDH repair making timing crucial in these children (4). Several studies have demonstrated the benefits of repairing the defect early on ECMO (106-109). In review of the CDHSG database, Glenn *et al.* identified 248 children who were repaired within 72 hours of cannulation and compared them to 922 who remained unrepaired (109). Though the early

repair group had significantly less intraabdominal liver (10.9% *vs.* 11.6%, $P=0.001$) and were less likely to have the presence of a hernia sac (5.2% *vs.* 10.9%, $P=0.009$), they had improved survival to ECMO decannulation (87.1% *vs.* 78.4%, $P=0.002$). The early repair group, however, did have a significantly longer median time on ECMO than the unrepaired group (240.6 *vs.* 196.8 hours, $P=0.001$). In a single retrospective review, Fallon *et al.* demonstrated improved survival in those children repaired early in the course of ECMO versus those late in the course (73% *vs.* 50%, $P=0.27$). This did not reach statistical significance, most likely due to the small numbers of the cohort. Contrary to the study reported by Glenn *et al.*, their study demonstrated a decrease in overall ECMO duration in those children repaired early (12 *vs.* 18 days, $P=0.01$). Another recent study concluded that survival was improved if babies were repaired on ECMO compared to after ECMO and also that early repair on ECMO was superior to late repair (110). Dao *et al.* performed a retrospective study of the CDHSG database using propensity score matching to evaluate 2 individual aims: (I) compare repair on versus after ECMO and (II) compare early versus late repair on ECMO. A total of 1,423 patients were available for analysis spanning a 10-year period. Following propensity score matching, 136 patients were analyzed in each arm of aim 1 ($n=272$). The analysis showed that those repaired on ECMO had an overall lower mortality with a hazard ratio of 0.54 (CI: 0.38, 0.77, $P<0.001$) and odds ratio of 0.52 (CI: 0.32, 0.85, $P=0.01$). Additionally, they were more likely to undergo repair (94.1% *vs.* 66.2%, $P<0.001$). In their analysis of aim 2, a total of 154 patients were available for analysis following propensity score matching, 77 per arm. Those infants repaired early demonstrated an overall lower mortality rate with a hazard ratio of 0.51 (CI: 0.33, 0.77, $P=0.002$) and odds ratio of 0.19 (CI: 0.09, 0.39, $P<0.001$). Again, more were able to be repaired (90.9% *vs.* 55.8%, $P<0.001$) with an overall lower duration of ECMO support (median 13 days *vs.* 15 days, $P=0.02$) and overall hospitalization in survivors (median 54 days *vs.* 95 days, $P=0.004$). They concluded that early repair may be key to higher repair rates and improved mortality at higher volume centers.

Other smaller studies have demonstrated the benefit of repair after decannulation (111,112). Partridge *et al.* compared patients repaired prior to cannulation ($n=3$), during ECMO ($n=41$), and after cannulation ($n=17$) with those repaired after cannulation having a significantly improved survival (67% *vs.* 43.9% *vs.* 100% respectively, $P<0.001$). They also reported that operative bleeding

requiring transfusion occurred significantly more in the group repaired on ECMO compared to those repaired before and after cannulation (29% vs. 0% vs. 0%, $P < 0.01$). More recently, using the ELSO registry, Delapain *et al.* used propensity scores to match infants based on pre-ECMO comorbidity variables then compared those that underwent repair on ECMO ($n=1,112$) to those that underwent repair after completion of ECMO ($n=1,112$) (111). They demonstrated that the mortality of those repaired on ECMO was 3 times higher than those that underwent repair after decannulation (OR 3.41, 95% CI: 2.84–4.09, $P < 0.01$). Additionally, they initially showed an increase in significant neurologic injury in the on ECMO repair group, however, this difference did not maintain significance when an additional sensitivity analysis was performed that included duration of ECMO. Finally, a single-center reviewed 87 children with left-sided CDH, liver up, without associated anomalies, to assess the risk of ECMO as well as to evaluate timing of surgical repair (113). They reported that those children that underwent repair within 60 hours of life and before ECMO cannulation ($n=22$) had a higher survival rate than those that underwent ECMO cannulation first ($n=20$) (95.5% vs. 65.0%, $P=0.018$). However, these outcomes reported are contrary compared to other large registry data previously described. One can see that the literature is not overwhelmingly clear and therefore, ultimately, the decision is typically dependent on both surgeon and institutional discretion.

The care of neonates with CDH remains challenging with a wide variation of care across institutions. This is further highlighted by a recent study demonstrating a lack of CDH clinical practice guidelines at over 1/4 of surveyed centers (16). Although the literature is replete with studies evaluating treatment strategies, no large, multi-institutional studies exist to help determine best practice. Development of multi-institutional treatment guidelines with prospective data collection and review may be the only way to truly answer many of these controversial questions.

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