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A Clinical Consensus Guideline for Hemodynamic Management of Infants with Congenital Diaphragmatic Hernia: A Delphi Study

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A Clinical Consensus Guideline for Hemodynamic Management of Infants with Congenital Diaphragmatic Hernia: A Delphi Study

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ABSTRACT:

Objective:

To develop consensus guidelines for the hemodynamic management of infants with congenital diaphragmatic hernia (CDH).

Methods:

A systematic review of the literature on hemodynamic management for infants with CDH was conducted using major databases from January 2000 to November 2023. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method. Where evidence was insufficient, expert statements were developed based on the results of a national survey on hemodynamic management practices for infants with CDH. Statements were distributed to members of the Children's Hospitals Neonatal Consortium (CHNC) CDH Focus Group using three-rounds of modified Delphi methodology.

Results:

Consensus was reached on 20 statements addressing baseline physiological assessment, echocardiographic parameters, hemodynamic monitoring, physiology-based phenotyping, and phenotype-based vasoactive management of infants with CDH.

Conclusion:

These guidelines provide a consensus-driven and evidence-based framework for the hemodynamic management of infants with CDH. Future studies should assess the impact of guideline implementation and adherence on clinical outcomes.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a congenital anomaly of the diaphragm that results in herniation of abdominal contents into the thoracic cavity, hindering pulmonary vascular, parenchymal, and cardiovascular development.[1] CDH occurs in 1 in 2500-3500 births and is associated with significant adverse clinical outcomes, with an estimated mortality of approximately 26-31%.[2–4] While lung hypoplasia and abnormal pulmonary vasculature are well-established in the pathophysiology of CDH, in-utero herniation may also impair cardiac chamber and outflow tract including left ventricle (LV) and aorta growth and development, which is increasingly recognized as the third important component of the pathophysiology of CDH.[5] Collectively, these pathologic mechanisms may lead affected infants to present along a spectrum of three hemodynamic phenotypes in CDH, each requiring a tailored respiratory and cardiovascular management strategy, incorporating approaches that range from cautious, gentle ventilatory support to targeted use of pulmonary vasodilators, inotropic support, or therapies aimed at improving biventricular performance.[5,6] The phenotypes have been described as follows[5]:

- Mild pulmonary hypertension (PH): Mild PH with mild or no right ventricular (RV) dysfunction and no LV dysfunction.
- Pre-capillary phenotype: Resistance-mediated PH with primary RV dysfunction; pulmonary to systemic (right to left) shunting across a patent ductus arteriosus (PDA), and bi-directional or right to left shunting across a patent foramen ovale (PFO)/atrial septal defect (ASD).

- Post-capillary phenotype: Flow-mediated PH with primary LV dysfunction, right to left shunting across the PDA, and systemic to pulmonary (left to right) shunting across the PFO/ASD.

Abnormal LV function, severe PH from all causes, and the need for vasoactive agents have been recognized as predictors of mortality and morbidity in multiple single-center retrospective studies.[7–14] Current literature emphasizes the need for early recognition of hemodynamic instability, hemodynamic phenotyping, physiology-based management, and understanding of evolving physiology in infants with CDH.[5,15–17] However, recognizing these phenotypes and understanding the physiology based on bedside assessments of vital signs and laboratory markers can be difficult, especially as infants transition and potentially shift primary underlying disease phenotype. Neonatologists can readily recognize the challenges of caring for infants with CDH, given their propensity for rapid and significant hemodynamic instability. However, much of what has been published to date in literature attempts to silo these infants and their care plans into well-defined buckets rather than along the complex spectrum in which they often present.

We utilized a modified Delphi methodology to develop evidence-based expert consensus guidelines for the hemodynamic management of infants with CDH through the Children's Hospitals Neonatal Consortium (CHNC) CDH Focus Group. Evidence-informing hemodynamic management in CDH remains limited because available studies are small and focused, disease severity is heterogeneous, treatment approaches continue to evolve, and large randomized trials are lacking. In addition, key aspects of cardiovascular management, including echocardiographic assessment, selection of vasoactive agents, timing of interventions, monitoring strategies, and definitions of hemodynamic instability, remain institution-specific and, in most centers, heavily reliant on cardiology or PH consulting teams with differing experiences. In the absence of

nationally standardized consensus-based guidance, we used a modified 3-step Delphi process to incorporate consensus from CHNC centers and develop expert consensus in areas where high-quality evidence is limited or incomplete. These guidelines focus on hemodynamic management during the acute, pre-repair phase of care, defined as ≤ 28 days of life or the duration of the first extracorporeal life support (ECLS) run, whichever is longer.

METHODS:

Description of focus group:

The CHNC consists of 52 Level IV regional referral neonatal intensive care units (NICUs) across the United States and Canada (www.thechnc.org). CHNC hosts a large data registry (Children's Hospitals Neonatal Database; CHND), research and focus groups, and quality improvement initiatives. The CHNC CDH Focus Group consists of participants from multiple specialties, including neonatology, neonatal hemodynamics, pediatric surgery, advanced practice providers, registered dietitians, and registered nurses with clinical and/or research interests in CDH.

Delphi methodology:

A modified Delphi methodology was utilized to develop clinical consensus guidelines for hemodynamic management of infants with CDH (**Figure 1**). The Credes checklist can be found in **Supplementary 1**.[18] A CDH hemodynamic subgroup was created in October 2023 to review the process and delineate steps for the Delphi process.[19,20] The target audience is interprofessional multidisciplinary clinicians caring for infants with CDH, including physicians, pediatric surgeons, and non-physician practitioners.

The following steps were conducted to reach group consensus.

1. *Systematic review of existing evidence*: We conducted a systematic review of literature using predetermined inclusion and exclusion criteria with assistance from a research librarian. The search strategy is provided in **Supplementary 2**. MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were searched in November 2023, with the search restricted to studies published between January 2000 and November 2023. Based on the search strategy and MeSH terms, 315 articles were identified and screened by members of the CDH hemodynamic subgroup for eligibility and subsequent assessment of the evidence. A detailed PRISMA diagram is shown in **Figure 2.** A total of 36 studies were included in the subgroup review. The studies were reviewed by members of the subgroup and subsequently presented to the CHNC CDH Focus Group for discussion and input. The review process included critical appraisal of each study, assessment of eligibility, consensus regarding study inclusion, assignment of GRADE levels of evidence, and formulation of recommendation statements based on the available evidence.[21] Following CDH Focus Group discussion and feedback, 15 studies were ultimately retained for inclusion in the final review, and recommendation statements were generated from these studies.
2. *Recommendations from a national survey*: Members of the subgroup had previously conducted a national survey of hemodynamic management practices for infants with CDH across centers in the United States, the results of which were presented at the CHNC Symposium in 2023(**Supplementary 3**).[22] Given the limited evidence in the literature regarding hemodynamic practices in CDH, findings from this survey were reviewed and used to inform additional recommendation statements reflecting contemporary real-world practices across United States (US) centers. These survey-based

recommendation statements were incorporated alongside those derived from the systematic review of the literature.

3. *Delphi rounds*: Following the development of recommendation statements from the systematic literature review and the national survey, 26 statements were included for the Delphi process. Three rounds of anonymous surveys were sent to CDH Focus Group members using a REDCap survey tool.[23] Participants rated each recommendation on a 0-100 Likert scale, where 0 indicated strong disagreement and 100 indicated strong agreement. Consensus was defined a priori as a median Likert score >85 with no more than 25% outliers.
    a. Delphi Round 1: Recommendation statements derived from the systematic literature review and the national survey were evaluated in separate sections. A total of 29 responses were received. Consensus was achieved for 11 of 14 statements derived from the literature review and for 11 of 12 statements derived from the national survey. Statements that did not meet predefined criteria for consensus were reviewed, discussed, and revised for inclusion in the subsequent Delphi round.
    b. Delphi Round 2: Recommendation statements from the systematic literature review and the national survey were no longer distinguished into separate sections, but were combined and organized into five domains of hemodynamic management:
        i. Establishing baseline physiology
        ii. Echocardiographic markers
        iii. Hemodynamic monitoring

iv. Physiology-based phenotyping

v. Physiology-based management

This second-round survey containing 24 revised statements was distributed to CDH Focus Group members, and 34 responses were received. Following the second Delphi round, three statements did not achieve consensus and were removed. One statement was revised, and two statements were subdivided for clarity, resulting in five statements that were carried forward to a third and final Delphi round.

c. Delphi Round 3: A total of 29 responses were received. Of the five statements evaluated, three did not achieve consensus and were subsequently excluded from the final guidelines. The final consensus guidelines consist of 20 recommendation statements across five domains of hemodynamic management, as summarized in **Figure 3**. GRADE levels of evidence were provided for recommendation statements derived from the systematic literature review.

CLINICAL GUIDELINES FOR HEMODYNAMIC MANAGEMENT

Section 1: Establishing baseline physiology

The dynamic and acute clinical presentation of infants with CDH is primarily driven by three interrelated pathophysiologic processes: pulmonary hypoplasia, pulmonary hypertension, and ventricular dysfunction. Over the past decade, both clinical experience and emerging research have increasingly highlighted the important role of cardiac dysfunction in this population.[16,24–35] Pulmonary hypertension resulting from pulmonary hypoplasia and abnormal pulmonary vascular development frequently contributes to RV dysfunction. Through ventriculo-ventricular interactions, interventricular septal bowing into the LV, and reduced LV preload

secondary to diminished pulmonary blood flow, RV dysfunction may subsequently lead to impaired LV function. In addition to this secondary LV dysfunction, there is growing recognition that primary LV hypoplasia and intrinsic LV dysfunction may also contribute significantly to adverse outcomes in infants with CDH.[15,16,27,29,31,34] While cardiac catheterization remains the gold standard for estimating pulmonary artery pressures (PAP), it is neither practical nor feasible in all infants with CDH, particularly during the acute and labile phase of critical illness pre-repair. Echocardiography has become the primary modality of early prognostication, assessment of pulmonary hypertension and cardiac dysfunction, guidance of targeted therapies, and longitudinal hemodynamic surveillance in this population.[17] The primary objectives of the initial postnatal echocardiogram are to assess indirect markers of elevated PAP and quantify the severity of pulmonary hypertension, evaluate left and right ventricular function, and identify critical congenital heart defects (e.g., coarctation of aorta, hypoplastic left heart syndrome). Fetal echocardiography also plays an important role in identifying coexisting congenital heart defects, which have been reported in 10-35% of patients with CDH and may significantly influence clinical management and outcomes.[17,36] Previous studies have demonstrated that fetal echocardiography is generally sufficient for detecting major congenital cardiac anomalies in CDH with regards to ECLS candidacy.[37] This may allow the initial postnatal echocardiographic assessment to be more focused and efficient, thereby minimizing stimulation and physiologic stress in critically ill infants. There is substantial variability in both the timing of initial postnatal echocardiogram and the recommendations provided by national and international CDH guidelines, including those from Canada, Europe, and Japan.[38–40] Proponents of early postnatal echocardiograms (within the first 24 hours after birth) cite evidence demonstrating that early hemodynamic phenotyping and physiology-based management may improve clinically important

outcomes, including reduced ECLS utilization, decreased inhaled nitric oxide (iNO) use, and improved survival.[41–45] Conversely, proponents of delaying or limiting postnatal echocardiographic assessments emphasize the principles of minimal stimulation, gentle handling, and the "less is more" approach advocated in the management of infants with CDH. Yang et al. reported that implementation of standardized management guidelines incorporating delayed echocardiographic assessment was associated with lower ECLS utilization, improved survival, and reduced iNO use.[46] Concerns regarding clinical instability during echocardiogram also contribute to variability in practice. However, Wren et al. reported that an early, focused targeted neonatal echocardiography (TnECHO) was well-tolerated and could provide actionable information with a mean study duration of only seven minutes.[47] Similarly, studies in extremely preterm infants have demonstrated the relative safety and feasibility of performing focused, targeted echocardiograms in hemodynamically unstable infants.[48] Taking into consideration the comprehensive evidence for the "why", balanced with the paucity of evidence for the "when", the CDH Focus Group developed the following consensus recommendations for establishing baseline physiology in infants with CDH:

1. *Comprehensive echocardiography within the first 24 hours after delivery is recommended to assess cardiac anatomy, determine RV/LV systolic and diastolic dysfunction, LV size, and characterize PH phenotype. This first echocardiogram should be reviewed by a pediatric cardiologist to assess congenital heart disease in addition to function.*

   [1B (Strong recommendation, moderate-quality evidence)]

2. *Frequent echocardiographic reassessments at feasible intervals should be considered with the understanding that the phenotype of infants with CDH is dynamic.*

[2C (Weak recommendation, low-quality evidence)]

3. *Consider serial targeted echocardiograms to assess biventricular function, direction of shunting across a PDA and PFO, ductal restriction, and PH status for infants with significant hemodynamic lability to assess response to pulmonary vasodilators and vasoactive medications.*

   [2C (Weak recommendation, low-quality evidence)]

Section 2: Echocardiographic markers

Echocardiographic assessments during the acute neonatal period provides a minimally invasive means of characterizing PH, defining the underlying hemodynamic phenotype, and identifying both subclinical and overt cardiac dysfunction. Common echocardiographic markers of elevated PAP include the direction of shunting across the PDA, ASD or PFO, and ventricular septal defect (VSD), as well as interventricular septal position, tricuspid regurgitation velocity, and RV geometry and configuration.[49] Evidence supporting specific echocardiographic markers of elevated PAP and cardiac dysfunction in infants with CDH remains limited. Assessment in this population can be particularly challenging given herniated abdominal content frequently results in cardiac dextroposition, making standard echocardiographic views more difficult to obtain and interpret. Consequently, comprehensive evaluation of PH and cardiac function in infants with CDH often requires a multimodal echocardiographic approach that integrates subjective and objective measures, supplemented by advanced techniques such as speckle-tracking echocardiography for myocardial strain analysis.[17] Existing studies in CDH have used a wide range of echocardiographic, clinical, and biomarker-based criteria to define PH and cardiac dysfunction, resulting in considerable heterogeneity across the literature. Despite this variability,

studies evaluating ductal shunting patterns suggest that the direction of ductal flow during the early neonatal period may have important prognostic implications and may be associated with adverse clinical outcomes in infants with CDH.[50,51]

Several echocardiographic parameters have been investigated for objective assessment of RV function in this population. These include RV myocardial performance index, tissue Doppler imaging (TDI)-derived myocardial velocities (RV s'), speckle-tracking echocardiography (STE)-derived RV free-wall strain, RV fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE). Studies have demonstrated associations between abnormalities in these measures and adverse outcomes, including the need for ECLS and mortality.[16,30,33,35] LV function in infants with CDH has been assessed using a variety of echocardiographic parameters, including STE-derived global longitudinal strain (GLS), LV ejection fraction (EF), fractional shortening (FS), myocardial performance index, and cardiac index.[16,29,31,34,52]

TnECHO facilitates a focused and objective assessment of both PH and cardiac dysfunction.[53] However, substantial variability exists in the echocardiographic measures used to assess cardiac function across studies and clinical centers. This heterogeneity, combined with limited feasibility of consistently obtaining specific quantitative parameters in all patients, precluded consensus on the use of individual quantitative markers for routine assessment of RV function. Although several studies have demonstrated associations between LV and RV diastolic dysfunction and disease severity in infants with CDH,[54–56] diastolic function parameters are not widely reported by outside centers without TnECHO expertise or dedicated research programs. While assessment of diastolic function may provide valuable physiologic information, the current evidence and variability in clinical practice limited the ability to make specific consensus recommendations regarding individual diastolic markers.

4. *Assessment of PH on echocardiography should include, at a minimum:*
    a. *Presence and directionality of intra- and extracardiac shunts such as the ASD, VSD and PDA.*
    b. *Interventricular septal configuration (to delineate the relationship of pulmonary-to-systemic pressures).*
    c. *Tricuspid regurgitation jet velocity (which requires a complete Doppler envelope).*
    d. *RV configuration (including chamber dilation and hypertrophy).*

    [Based on expert consensus and national survey results]
5. *Assessment of LV systolic function should include objective markers such as ejection fraction and fractional shortening. LV diastolic function assessment should be included when available.*

    [1B (Strong recommendation, moderate-quality evidence)]

Section 3: Hemodynamic monitoring

Growing evidence suggests that standardized management guidelines for infants with CDH are associated with improved clinical outcomes, including reduced use of vasopressors, ECLS, iNO, and pulmonary hypertension medications at discharge.[38,40,42–44] Kuan et al. reported that implementation of a care bundle emphasizing structured hemodynamic assessments was associated with reduced mortality.[44] In addition to echocardiographic evaluation, comprehensive hemodynamic monitoring should incorporate standardized physiologic and clinical parameters, including target blood pressure ranges, blood gas analysis, urine output, capillary refill time, and serum lactate levels. Prognostic and severity assessment tools, such as the vasoactive-inotropic score (VIS) and respiratory severity score, may further support clinical decision-making and longitudinal assessment of disease trajectory. Collectively, these parameters provide a more

comprehensive assessment of cardiopulmonary status and may assist in determining surgical readiness, with the goal of optimizing hemodynamic stability before operative repair.[57,58]

6. *The clinical bundle for patients with CDH should include guidelines regarding hemodynamic assessment and support.*

   [Based on expert consensus and national survey results]

7. *Incorporating a multiparametric approach for hemodynamic status including echocardiographic parameters, targeted blood pressure values, and signs of adequate tissue perfusion (i.e., acid-base status, urine output, and serum lactate) may provide a comprehensive clinical and physiological basis for interventions.*

[2C (Weak recommendation, low-quality evidence)]

Section 4: Physiology-based phenotyping

There is increasing recognition that PH in infants with CDH encompasses distinct physiology-based phenotypes, including pre-capillary (resistance-mediated) PH and post-capillary (flow- or LV-mediated) PH. These phenotypes are characterized by differences in RV and LV function, as well as atrial and ductal shunting patterns.[5,6,41,59]

Pre-capillary PH is primarily attributed to pulmonary parenchymal hypoplasia and abnormal pulmonary vascular development, resulting in elevated pulmonary vascular resistance.[1,60] Infants with a predominant pre-capillary PH phenotype may demonstrate RV dysfunction accompanied by right-to-left shunting at both the atrial and ductal levels. Management strategies for pre-capillary PH are generally directed toward reducing pulmonary vascular resistance through therapies targeting the cyclic guanosine monophosphate (cGMP) pathway (e.g., iNO, sildenafil), cyclic adenosine monophosphate (cAMP) pathway (e.g.,

milrinone), prostacyclin pathway (e.g., epoprostenol, Treprostinil, iloprost), or endothelin pathway.[61,62]

In contrast, post-capillary PH occurs in the setting of impaired LV function and elevated left atrial pressure, resulting in increased pulmonary venous pressure. Echocardiographic features of this phenotype are characterized by left-to-right shunting at the atrial level and bidirectional or right-to-left shunting across the ductal level.[5] Distinguishing between pre-capillary and post-capillary PH is important, as management strategies differ substantially between these phenotypes. Pulmonary vasodilatory therapy may be ineffective or potentially detrimental in infants with a predominantly post-capillary PH phenotype.[62]

Our guidelines focused on reaching consensus for how these two phenotypes can be described, rather than clinical management once pre- or post-capillary PH is identified. Although described as distinct entities, these phenotypes should be viewed as dynamic rather than static states. Hemodynamic physiology may evolve during postnatal transition or in response to clinical factors such as metabolic acidosis, myocardial dysfunction, or changes in pulmonary vascular resistance. Furthermore, features of both pre-capillary and post-capillary PH may coexist in the same patient, particularly in those with more severe disease and complex cardiopulmonary physiology.

8. *Pre-capillary PH is characterized by PH/suprasystemic right ventricular pressure (RVP) with intact LV function such that there is right-to-left shunting at the atrial and ductal levels.*

[2C (Weak recommendation, low-quality evidence)]

9. *Post-capillary PH is characterized by PH and primary LV dysfunction such that there is left-to-right shunting at the atrial level and right-to-left or bidirectional shunting at the ductal level.*

[2C (Weak recommendation, low-quality evidence)]

Section 5: Phenotype-based management

The hemodynamic effects of commonly used vasoactive and inotropic medications on systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and stroke volume are summarized in **Table 1.**[63] Before initiating vasoactive or inotropic therapy, potentially reversible contributors to hemodynamic instability, including metabolic acidosis, electrolyte abnormalities, and other factors that may impair myocardial function, should be identified and addressed.[62] Given the dynamic nature of cardiopulmonary physiology in neonates with CDH, frequent reassessment of the underlying hemodynamic phenotype is also important to guide ongoing management and therapeutic adjustments.

Despite predominant use of dopamine use as a first-line agent for hypotension in neonatology, there is ongoing consensus regarding precision medicine understanding the ongoing physiology to provide tailored hemodynamic care.[64] In the setting of PH, dopamine may be suboptimal as it has a dose-dependent increase in PVR via α-1 adrenergic receptors.[64]A single-center series reported longer duration of hospitalization in newborns with CDH treated with higher doses of dopamine for left ventricular dysfunction.[65] Adrenal insufficiency has also been described in neonates with CDH, and the use of corticosteroid therapy as an adjunct for vasoactive support has been reported in retrospective studies and incorporated into clinical consensus guidelines.[40,66,67]

10. *Physiological stability relies upon a multitude of factors, including maintenance of normal blood pH and electrolytes (particularly potassium and calcium), optimal lung recruitment and gastric decompression, normothermia, and minimization of activity/agitation. These factors should be optimized when escalating therapies, including vasoactive medications.*

[Based on expert consensus and national survey results]

11. *Caution is recommended with the use of dopamine as it may increase pulmonary vascular resistance, especially at higher doses.*

[Based on expert consensus and national survey results]

12. *Hydrocortisone may be considered in vasoactive-refractory hypotension.*

[Based on expert consensus and national survey results]

Section 5A: RV dysfunction with intact LV function

In infants with RV dysfunction and intact LV function, the ductus arteriosus may play a critical role in maintaining cardiopulmonary stability. In the absence of other intracardiac shunts such as ASD/VSD/PFO, the only conduit for continued blood flow to the lungs is the ductus arteriosus, resulting in ductal-dependent physiology.[61,68–71] Physiologic benefits of keeping the ductus arteriosus open in this scenario are-

a) Offloading the failing RV to allow the ductus arteriosus to act as a pop-off valve
b) Direct pulmonary vasodilatory effects by prostaglandin E1 (PGE1)
c) In the event of subsequent LV failure, the ductus arteriosus can augment systemic blood flow by facilitating right to left shunting.[61,62]

The use of PGE1 has been recommended in clinical consensus guidelines and national guidelines for CDH management[40,42] and its use has been reported in 11% of infants with CDH.[29] While the specific criteria for consideration of PGE1 varies, in general, PGE1 is considered in the setting of clinical or echocardiographic evidence of a closing or restrictive ductus arteriosus in the setting of RV or LV failure.[62]

Retrospective studies have reported that vasopressin may improve oxygenation and hemodynamic status in patients with CDH.[72,73] Vasopressin is a neuropeptide that acts by binding to V1 (impacting vascular tone, cortisol and platelet function) and V2 receptors (impacting fluid balance and vascular tone).[63,74] Infants with RV failure may demonstrate impaired diastolic filling, which may be exacerbated in the setting of tachycardia. In PH, the coronary perfusion gradient is reduced due to increase in RV and aortic pressures, which predisposes to RV wall ischemia, RV dysfunction and subsequently, RV failure.[75,76] Vasopressin has been shown to have pulmonary vasodilatory and coronary vasodilatory properties, which are beneficial for management of CDH pathophysiology. Additionally, unlike catecholamines, vasopressin has minimal direct chronotropic effects. In a patient with ventricular failure or severe resistance-mediated pulmonary hypertension, tachycardia can hinder pulmonary capillary transit time, further impair cardiac performance with shorter diastolic filling time, and decrease coronary artery perfusion time. Additionally, tachycardia increases myocardial oxygen consumption and in a dysfunctional LV/RV, may lead to an imbalance between oxygen supply and demand, resulting in worsening ischemia, decreased contractility, and delayed cardiac recovery.[62] Potential adverse effects with vasopressin include fluid retention and hyponatremia, which may increase chest wall edema and indirectly impair pulmonary compliance; however, these may not occur if increased renal perfusion with vasopressin instead leads to improved diuresis. Cautious use of vasopressin

in the setting of LV failure is warranted due to its effect on increasing SVR,[63] and may necessitate additional use of inotropes (epinephrine, dobutamine, milrinone) to support cardiac function. In this case, careful titration of multiple vasoactive may be a beneficial way to maintain hemodynamic homeostasis rather than seen as a failure of a single agent, as has been the traditional mindset.

Norepinephrine acts via α-1 adrenergic receptors and can cause an increase in SVR and diastolic blood pressure, similar to vasopressin. Experimental animal studies have shown that norepinephrine has pulmonary vasodilatory effects,[77,78] however data in the CDH population is limited, with additional concern for increase in PVR via α-1 receptors.[40] Reports of improvement in coronary perfusion pressure and improvement in lung function in non-CDH infants with persistent pulmonary hypertension of the newborn have been reported,[79,80] but further research is warranted to describe specific hemodynamic scenarios where norepinephrine may be considered. As it increases SVR, norepinephrine should be used cautiously in infants with LV dysfunction for the same reasons as vasopressin, and the concomitant use of positive inotropes can be useful to maintain contractility with increasing SVR. Given the limited and inconsistent evidence in neonates with CDH, the Focus Group was unable to reach consensus regarding the role of norepinephrine for the management of RV dysfunction with intact LV function.

Milrinone is a phosphodiesterase-3 inhibitor that causes pulmonary vasodilation via the cAMP pathway. It is an inotropic and lusitropic agent, used in practice to support both the right and left ventricle by decreasing LV and RV afterload. Milrinone utilization in infants with CDH has been explored in retrospective studies with improvements in cardiac function and oxygenation, prompting an ongoing multicenter randomized controlled trial on the use of milrinone for infants with CDH.[81–83] While optimal to support biventricular function, milrinone

has an increased risk of systemic hypotension, which may necessitate the addition of vasopressin or norepinephrine to support SVR. One primary concern with milrinone is that it has a relatively long half-life compared to other vasoactive medications, which may be further prolonged in the setting of impaired renal function leading to delayed drug clearance.[62] For these reasons, milrinone should be used cautiously in the setting of renal dysfunction to avoid worsening or prolongation of associated systemic hypotension.

Finally, in the setting of decreased RV preload and/or poor perfusion, judicious use of fluid bolus may be considered, and has been supported by national consensus guidelines, with the understanding that in the presence of right or left ventricular dysfunction, excessive fluid resuscitation may worsen ongoing hemodynamics.[39,40]

13. *In the presence of a restrictive ductus arteriosus and suprasystemic PH, consider starting PGE1 to maintain ductal patency and offload the RV.*

    [2C (Weak recommendation, low-quality evidence)]
14. *Vasopressin may be considered in the context of RV dysfunction and intact LV function.*

    [2C (Weak recommendation, low-quality evidence)]
15. *Consider milrinone if not hypotensive or after initial hypotension is resolved.*

    [2C (Weak recommendation, low-quality evidence)]
16. *If there are concerns about decreased RV preload clinically or on echocardiography, consider cautious volume repletion for hemodynamic compromise and maintenance of adequate left ventricular preload. Caution should be used with volume expansion in the setting of diminished systolic and/or diastolic left ventricular, right ventricular, or biventricular dysfunction.*

    [2C (Weak recommendation, low-quality evidence)]

Section 5B: Biventricular dysfunction

Epinephrine acts via α- and β-adrenergic receptors, with β-1 effects resulting in inotropy, β-2 effects resulting in vasodilation, and α effects resulting in SVR augmentation. The inotropic effect of low-dose epinephrine supports both right and left ventricular function.[6,84] However, caution must be exercised due to common side effects seen with higher doses of epinephrine, including hyperglycemia, lactic acidosis, and peripheral vasoconstriction.[6,62,63] Other inotropic agents such as dobutamine may be considered in biventricular dysfunction. Dobutamine acts via β-1 receptors that improve inotropy, but has the potential to worsen hypotension due to β-2 receptor vasodilatory effects, and causes tachycardia that may impair diastolic filling and coronary perfusion.[6,62] Due to the lack of data on dobutamine use in infants with CDH and potential adverse effects, we did not reach consensus on its use. The use of hydrocortisone in refractory hypotension and milrinone to support biventricular function were discussed but did not reach consensus due to nuanced patient- and physiology-specific approaches.

17. *Consider low-dose epinephrine for inotropic support.*

    [2C (Weak Recommendation, Low-Quality Evidence)]

Section 5C: Primary LV dysfunction

In infants with primary LV dysfunction, an inotropic agent such as epinephrine can be considered given its β-1 receptor effect.[6,62,84] Potential adverse effects of epinephrine such as tachycardia, pulmonary vasoconstriction, and lactic acidosis need to be considered and monitored. Due to limited data of specific inotropes such as dobutamine and milrinone in the management of CDH, the group could not reach consensus on an agent beyond epinephrine for

primary LV dysfunction. In addition to consideration of inotropes, it is important to replete and normalize calcium levels (>1.2 mmol/L) to support myocardial function.

18. Replete calcium as needed.

[Based on expert consensus and national survey results]

19. 1st line vasoactive medication: Epinephrine titration to effect.

[Based on expert consensus and national survey results]

20. When titrating epinephrine, consider the following: The use of higher doses of epinephrine has an α-adrenergic activity predominance, so patients should be monitored for potential adverse effects of peripheral vasoconstriction.

[Based on expert consensus and national survey results]

STRENGTHS AND LIMITATIONS:

Despite the sparse evidence and wide variability in practice, this study has several strengths. First, we utilized a rigorous and structured Delphi methodology based on established guidelines, incorporated evidence from a systematic review of the literature, and supplemented with results of a national survey to consider real-word practices prevalent in NICUs across the US. This allowed us to incorporate available evidence with contemporary management for a patient population where large prospective trials are challenging and limited due to rarity of the disorder. The CHNC includes high-volume level IV NICUs, multiple subspecialists, and international CDH experts, which allowed for diversity of multidisciplinary perspectives.

Limitations of this study include that many recommendations are based on expert consensus and retrospective observational studies due to the lack of high-quality randomized

controlled trials evaluating hemodynamic management for infants with CDH. Some recommendations reflect expert opinion rather than evidence-based practice and hence could not be designated a GRADE level. These guidelines are intended to complement, rather than replace, institution-specific protocols and clinical judgment. Many of the included papers were performed in centers with TnECHO, which limited generalizability to centers without TnECHO expertise. There were challenges with reaching consensus on several clinically relevant topics, particularly regarding specific echocardiographic markers and vasoactive strategies, highlighting ongoing uncertainty, paucity of evidence, and variability in practice.

CONCLUSION:

Despite growing recognition that hemodynamic status in infants with CDH evolves rapidly in the acute neonatal period, high-quality evidence to guide cardiovascular management remains limited. Performing large clinical trials in this population is inherently challenging, given the rarity of CDH, the heterogeneity of its pathophysiology, and the frequent co-occurrence of congenital heart disease and other congenital anomalies. These challenges underscore the need for expert consensus to bridge the gap between advancing pathophysiologic understanding and clinical practice.

The proposed consensus guidelines represent a collaborative effort by the CHNC CDH Focus Group, developed through a structured Delphi process that integrates the best available evidence, current institutional practices, and multidisciplinary expert opinion. By providing a framework for early detection and physiology-based hemodynamic management, these guidelines aim to standardize care while preserving the flexibility needed for individualized decision-making. Future investigations should focus on validating and refining phenotypical

characterization of hemodynamic profiles in CDH, with the goal of advancing individualized management strategies that improve outcomes for these critically ill infants.

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51. Wilmington, Nemours/Alfred I. duPont Hospital for Children (Kevin Sullivan)
52. Winston-Salem, Brenner Children's Hospital (Cherrie Welch)

Figure legends:

Figure 1: Delphi process flow diagram showing the goals, steps and consensus threshold for the modified Delphi methodology.

Figure 2: PRISMA flow diagram showing included and excluded studies in the systematic review.

Figure 3: Summary of consensus statements on hemodynamic management of infants with CDH.

Drug	Stroke Volume	SVR	PVR
Dopamine			
Low dose (0.5-3mcg/kg/min)	**↑/=**	=	=
Medium dose (3-10 mcg/kg/min)	**↑↑↑**	**↑**	**↑**
High dose (> 10 mcg/kg/min)	**↓/=**	**↑↑↑**	**↑↑↑**
Dobutamine	**↑↑↑**	**↓/=**	**↓/=**
Epinephrine			
Low dose (0.01-0.1 mcg/kg/min)	**↑↑↑**	=	=
High dose (>0.1 mcg/kg/min)	**↑/↓**	**↑↑↑**	**↑↑**
Norepinephrine	**↑/=**	**↑↑↑**	=
Vasopressin	**↓** /=	**↑↑↑**	=
Milrinone	**↑↑**	**↓↓**	**↓↓**

↑↑↑ - strong increased effect, ↑↑- moderate increased effect, ↑- mild increased effect,

↓↓ -moderate decreased effect, ↓- mild decreased effect, = - neutral/no effect

DELPHI PROCESS FLOW DIAGRAM FOR CONSENSUS GUIDELINES ON HEMODYNAMIC MANAGEMENT OF CONGENITAL DIAPHRAGMATIC HERNIA

STEP 1
SYSTEMATIC REVIEW OF EXISTING EVIDENCE

STEP 2
DISCUSSION AND GRADE BASED RECOMMENDATIONS FROM FOCUS GROUP DISCUSSIONS

November 2023 December 2024

STEP 3
ADDITION OF NATIONAL SURVEY RESULTS TO LITERATURE REVIEW BASED RECOMMENDATIONS

January- June 2025

29 responses

STEP 4
DELPHI ROUND 1

STEP 5
COLLATING RESULTS OF DELPHI ROUND 1 AND DESIGNING ROUND 2

August-October 2025

34 responses

STEP 6
DELPHI ROUND 2

STEP 7
COLLATING RESULTS OF DELPHI ROUND 2 AND DESIGNING ROUND 3

November- December 2025

29 responses

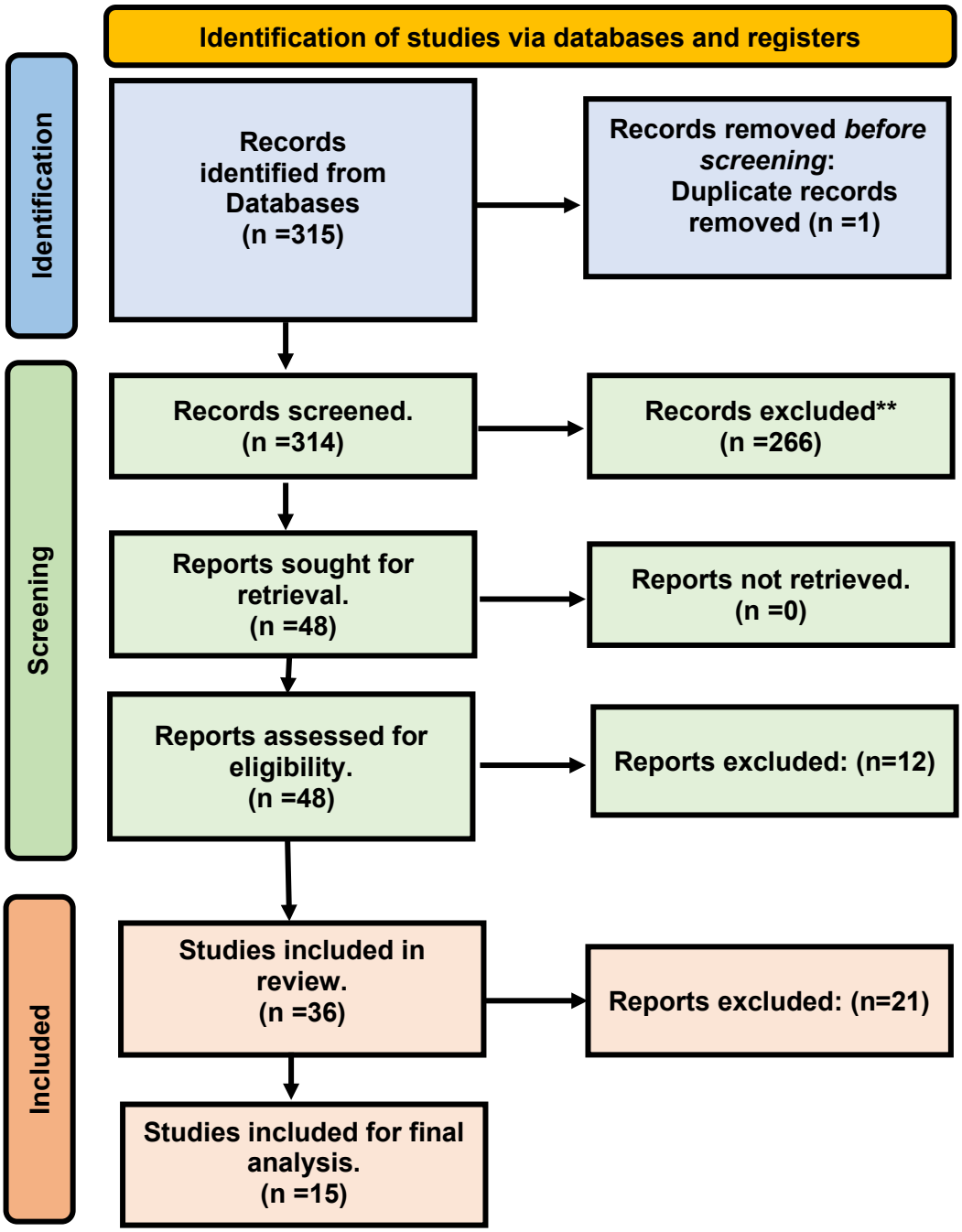
STEP 8
DELPHI ROUND 3

STEP 9
PRESENTATION OF FINAL CONSENSUS STATEMENTS

GOAL
To create consensus guidelines surrounding hemodynamic management for neonates with CDH in the acute phase of care, defined as < 28 days of life or the duration of the first ECLS run, whichever is longer.

CONSENSUS THRESHOLD
Median Likert scale of >85 with no more than 25% outliers

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

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Section 1: Establishing Baseline Physiology
1. Comprehensive echocardiography within the first 24 hours after delivery is recommended in neonates with CDH to assess cardiac anatomy, RV/LV systolic and diastolic dysfunction, LV size, and pulmonary hypertension (PH) phenotype. This first echocardiogram should be reviewed by a pediatric cardiologist to assess congenital heart disease in addition to function. 2. Frequent echo reassessments at feasible intervals should be considered with the understanding that the phenotype of infants with CDH is dynamic. 3. Consider serial targeted echocardiograms to assess for biventricular function, direction of shunting across the PDA and PFO, ductal restriction, and PH status, for neonates with significant hemodynamic lability to assess response to pulmonary vasodilators and vasoactive medications.
Section 2: Echocardiographic Markers
1. Assessment of pulmonary hypertension on echocardiography should include at a minimum: • Presence and directionality of intracardiac shunts such as the PDA, ASD, and VSD • Intraventricular septal configuration • Tricuspid regurgitation jet velocity (with a complete doppler envelope) • RV configuration (chamber dilation and hypertrophy) 2. Assessment of LV systolic function should include objective markers such as ejection fraction and fractional shortening. LV diastolic function assessment should be included when available.
Section 3: Hemodynamic Monitoring
1. The clinical bundle for patients with CDH should include guidelines regarding hemodynamic assessment and support. 2. Incorporating a multiparametric approach for hemodynamic status including echocardiographic parameters, targeted BP values, and signs of adequate tissue perfusion (i.e. acid base status, urine output, and lactate) may provide a comprehensive clinical and physiological basis for interventions.
Section 4: Physiology-Based Phenotyping
1. Precapillary Pulmonary Hypertension (PH) is characterized by PH/suprasystemic right ventricular pressure (RVP) with intact LV function such that there is Right-to-Left shunting at the atrial and ductal levels. 2. Post-capillary PH is characterized by PH + Primary LV dysfunction such that there is a Left-to-Right shunt at the atrial level and Right-to-Left or bidirectional shunt at the ductal level.
Section 5: Phenotype-Based Management
1. Physiological stability relies upon a multitude of factors including maintenance of normal blood pH, electrolytes (particularly K+ and Ca+), optimal lung recruitment and gastric decompression, normothermia, and level of activity/agitation. Ensure these factors are optimized when escalating therapies, including vasoactive medications. 2. Caution is recommended with use of dopamine as it may increase pulmonary vascular resistance, especially at higher doses. 3. Hydrocortisone may be considered in vasoactive-refractory hypotension (i.e. not responsive to dose escalation of epinephrine) in neonates with CDH.
5A: RV Dysfunction + Intact LV Function
1. In the presence of a restrictive ductus arteriosus (DA) and suprasystemic PH, consider starting prostaglandin E1 (PGE1) to offload the RV. 2. Vasopressin may be considered in the context of RV dysfunction and intact LV function. 3. Consider milrinone if not hypotensive or after initial hypotension is resolved. 4. If there are concerns for decreased RV preload clinically or on echocardiography, consider cautious volume repletion for hemodynamic compromise and maintenance of adequate left ventricular preload. Caution should be used with volume expansion in the setting of diminished systolic and/or diastolic left ventricular, right ventricular, or biventricular dysfunction.
5B: Biventricular Dysfunction
1. Consider low-dose epinephrine for inotropic support.
5C: Primary LV Dysfunction
1. Replete calcium as needed. 2. 1st line vasoactive medication: Epinephrine titration to effect. 3. When titrating epinephrine, consider the following: The use of higher doses of epinephrine has an alpha-adrenergic activity predominance, so patients should be monitored for potential adverse effects of peripheral vasoconstriction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S1CREDESChecklist.docx
- S3Surveyresults.docx
- S2SearchStrategy.docx