Local Guideline and Procedure

John Hunter Children's Hospital
CHILDREN, YOUNG PEOPLE AND FAMILIES

NSW GOVERNMENT Health
Hunter New England Local Health District

Congenital Diaphragmatic Hernia Management in the Neonatal Unit

Sites where Local Guideline and Procedure applies	Neonatal Intensive Care Unit, JHCH
This Local Guideline and Procedure applies to:	
1. Neonates – less than 29 days	Yes
Target audience	Clinicians caring for infants diagnosed with Congenital Diaphragmatic Hernia (CDH)
Description	Provides information to clinicians about diagnosis, management and treatment options for CDH

Hyperlink to Procedure

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Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- NSW Health Policy Directive 2014_036 Clinical Procedure Safety http://www0.health.nsw.gov.au/policies/pd/2014/pdf/PD2014_036.pdf

Prerequisites (if required)	N/A
Local Guideline and Procedure note	This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure/s **require mandatory compliance**. If staff believe that the procedure/s should not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patients health record.
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RISK STATEMENT

This local guideline has been developed to provide guidance to clinical staff in NICU to assist in assessment and management of Congenital Diaphragmatic Hernia (CDH) in the neonate. It ensures that the risks of harm to the infant whilst being assessed and managed for CDH are identified and managed.

Any unplanned event resulting in, or with the potential for injury, damage or other loss to infants/staff/family as a result of this management must be reported through the Incident Information management System and managed in accordance with the Ministry of Health Policy Directive: Incident management PD2007_061. This would include unintended injury that results in disability, death or prolonged hospital stay.

Risk Category: *Clinical Care & Patient Safety*

GLOSSARY

Acronym or Term	Definition
ABG	Arterial blood gas
CDH	Congenital Diaphragmatic Hernia
cGMP	Cyclic guanosine monophosphate- relaxes smooth muscle tissues. In blood vessels, relaxation of vascular smooth muscles lead to vasodilation and increased blood flow
CHARGE	Genetic disorder which stands for coloboma, heart defect, atresia choanae (also known as choanal atresia), retarded growth and development, genital abnormality, and ear abnormality
CVAD	Central Venous Access Device
CNS	Central Nervous System
CXR/AXR	Chest XRay & Abdominal XRay
EBM	Expressed breast milk
ECMO	Extracorporeal membrane oxygenation
FBE	Full blood evaluation
FiO_2	Fraction of inspired oxygen
FISH	Fluorescence in situ hybridization (FISH) provides researchers with a way to visualize and map the genetic material in an individual's cells
HFV/HFOV	High frequency Ventilation/High Frequency Oscillation Ventilation
iNO	Inhaled Nitric Oxide
LHR	Lung to head ratio
LV	Left ventricle
MAP	Mean airway pressure
MRI	Magnetic Resonance Imaging

PaO_2	Partial pressure of oxygen
PGE1	Prostaglandin E1
PAP/SAP	Pulmonary arterial pressure/Systemic Arterial pressure
PIP	Peak Inspiratory Pressure
PH	Pulmonary Hypertension
SaO_2	Oxygen Saturation measurement
SIPPV	Synchronised Intermittent Positive Pressure Ventilation
Tc CO_2	Transcutaneous carbon dioxide monitoring
U&E	Urea and Electrolyte study
VILI	Ventilator induced lung injury

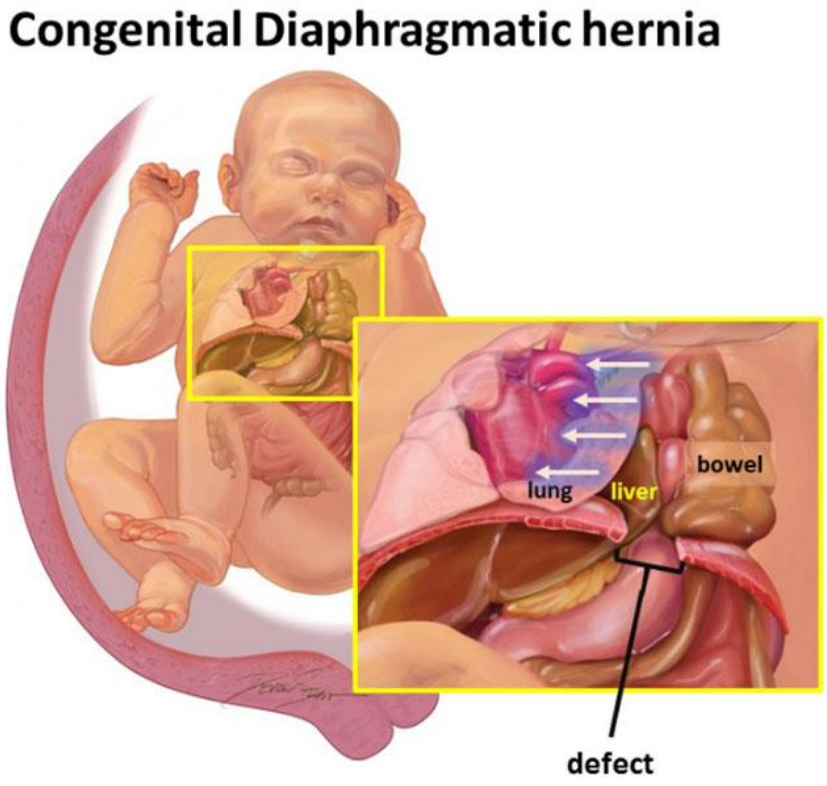
GUIDELINE

This Guideline does not replace the need for the application of clinical judgment in respect to each individual patient.

Congenital Diaphragmatic Hernia Management in the Neonatal Unit

Congenital Diaphragmatic Hernia (CDH) is a complex congenital malformation consisting of

- A defect in the diaphragm muscle (left sided in 80%).
- Herniation of the abdominal contents into the thorax through the defect.
- Pulmonary hypoplasia with structural and functional immaturity of the lung.
- Pulmonary hypertension.



Pathophysiology

There are two kinds of CDH. The usual defect is in the posterolateral (Bochdaleck) segment of the diaphragm and is due to either failure of closure of the pleuro-peritoneal canals or failure of the migration of the post-hepatic mesenchymal plate. The other is a Morgagni hernia which involves a defect in the front of the diaphragm.

Congenital diaphragmatic hernia is characterized by a variable degree of pulmonary hypoplasia associated with a decrease in cross-sectional area of the pulmonary vasculature and alterations of the surfactant system. The lungs have a small alveolar capillary membrane for gas exchange, which may be further decreased by surfactant dysfunction.

The physiological basis of pulmonary hypertension in neonates with CDH is a decreased number of pulmonary arterial structures associated with significant adventitial and medial wall thickening due to an increased amount of smooth muscle cells in pulmonary arteries. As a result, elevated pulmonary vascular resistance may lead to right to left shunting after birth. This may result in hypoxaemia and a difference in pre-and post-ductal oxygen saturation. However, absence of a pre-/ and post ductal gradient in oxygenation does not exclude the diagnosis of pulmonary hypertension since the right to left shunting may occur through the foramen ovale. [1]

Prognosis

Factors that can guide the prognosis include:

- The type of defect.
- The severity of the defect (see below).
- Degree of left ventricular hypoplasia: development of which is multifactorial but is in part due to mechanical compression by abdominal organs, changing of LV filling heamodynamics during foetal development.
- The presence of associated anomalies: CDH is frequently associated with other anomalies. The most common additional abnormalities include chromosomal anomalies, defects of the heart, central nervous system (CNS), kidneys and the gastrointestinal tract. [2] In cases of intrauterine foetal deaths, the CNS defects predominate. In live-born babies with CDH, the cardiovascular defects are most commonly found and constitute 50% of all morphological defects. Although the precise cause of the majority of CDH cases is unknown, the genetic factors are considered to always be involved. CDH has demonstrated to be associated with more than 50 genetic syndromes.[2]

Survival depends primarily on the degree of pulmonary hypoplasia and the amount of fixed pulmonary hypertension and secondly on the severity of associated anomalies.

Major Factors in Determining Severity of the defect

Only considering CDH, the severity and, thus, the outcome can be guided by two factors:

1) Liver position, and

2) Foetal lung volume.

Liver position refers to whether or not any portion of the liver has herniated, or gone up into the chest of the foetus. The liver has always herniated in right sided defects.

Foetal lung volume can be estimated from ultrasound with by the lung-to-head ratio, or LHR. It is a numeric estimate of the size of the foetal lungs, based on measurement of the amount of visible lung. The LHR ratio is used to assess the extent of pulmonary hypoplasia. High LHR values greater than 1.0 are associated with better outcomes. LHR value should not be performed < 24 weeks gestation. [3]

Summary: _

Foetuses with the liver up in the chest have a more severe form of CDH and a lower survival rate.

A lung-head ratio less than 1.0 have a more severe form of CDH.

Foetal lung volumes can also be estimated with foetal MRI. An estimated foetal lung volume <25% is associated with high (>80%) mortality.

Other severity tools include the assessment of the size of a diaphragmatic defect, the lung-to-thorax transverse area ratio (L/T ratio- assesses pulmonary hypoplasia), lung volume calculations, determination of the heart axis, position of the stomach, and presence of pleural or pericardial effusions. [4]

Timing and Mode of Delivery

There is still some doubt about the preferred mode of delivery and the timing of delivery in case of a CDH pregnancy. Studies from the CDH study group reported no significant differences in overall survival between patients with CDH born by spontaneous vaginal delivery, induced vaginal delivery and elective caesarean section. [5, 6]

So recommendations are:

- Planned vaginal delivery or caesarean section after a gestational age of 37 weeks in a designated tertiary centre.[7]
- In case of preterm labour prior to <38 weeks of gestation, antenatal steroids should be given (strong evidence). [7]
- The use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 37 weeks' and 6 days gestation if there is known foetal lung immaturity (as would be the case in CDH) is considered an acceptable practice point.[23]
- Discussion between neonatal and obstetric team in all cases to facilitate optimal care.

Management

Management strategies aim to:

- Optimise ventilation strategies to limit ventilator induced lung injury.
- Management of pulmonary hypertension.
- Optimise haemodynamic and respiratory status before surgery.

Labour Ward Management

- The immediate management is to intubate and ventilate to minimise gas distention of the intra thoracic bowel.
- Place saturation probe on right hand.

- If the heart rate is >100 and saturations are improving, aim to keep inspiratory pressures low (<26 cm H2O) and watch chest wall movement.
- At 10 minutes, aim for saturation between 80% - 95%.
- Insert large bore orogastric tube and keep on open drainage.

Stabilisation and Admission to Neonatal Intensive Care Monitoring and Vascular Access (Quick Guide)

- Minimal handling.
- Normothermia.
- Blood sampling. The frequency of sampling for ABGs and other parameters (FBE, U&E, Cr, Ca, Mg, coagulation profile, glucose, and lactate) will largely be determined by the cardiorespiratory status of the neonate as well as previous results. A plan for frequency of blood sampling should be clarified at each ward round.
- Monitor urine output (keep > 1 mL/kg/hr). Insert a urinary catheter if the neonate is heavily sedated or muscle relaxed.
- Pre and post ductal SaO2.
- Continuous invasive arterial monitoring (right radial preferable).
- Central venous access: if the umbilical vein is used, a double or triple lumen UVC should be inserted. After 5 - 7 days of umbilical vein use or pre-operatively (whichever is sooner), a peripherally inserted CVAD should be considered.
- TcCO2 monitoring.
- CXR and AXR.

Other investigations

- Chromosome, FISH (e.g. 8p23.1, one of the recurrent chromosomal causes of CDH) and micro array studies. There are a number of non-chromosomal causes to consider e.g. CHARGE, overgrowth conditions (e.g. Beckwith or Simpson-Golabi- Behmel), Cornelia de Lange syndrome, Donnai-Barrow).
- Every infant with a CDH should have a head, heart and renal ultrasound performed.
- A genetics referral will depend on the presence or absence of associate anomalies.

Ventilation

- In preparation for the arrival of a neonate with CDH –the ventilator should be set up and inhaled nitric oxide available for immediate use. *Please refer to 'Nitric Oxide (iNO) Therapy in NICU' guideline for details.*
- Monitor **pre-ductal SaO2** which reflects cerebral oxygenation and **post ductal SaO2** as a guide to the degree of ductal right to left shunting.
- **TcCO2** monitoring should be obtained.
- **Lung Protective Strategy:** accept pre ductal SaO2 > 85%, post ductal SaO2 >70%, PaCO2 < 65, and pH > 7.25. In individual cases, however, levels down to 80% may be accepted, providing organs are well perfused as indicated by a pH above 7.2, lactate levels < 5 mmol/l and urinary output above 1 ml/kg/h. [7] Over 90% of centres participating in the International CDH Registry programme report that the peak airway pressure should be limited and find permissive hypercapnia advisable; low values of PaCO2 as management reducing the pulmonary vascular resistance, are not considered necessary. [8, 9]
- **Ventilation Mode:** Most commonly used in our unit are **SIPPV with volume Target or HFV +/- volume target.** The optimal initial ventilation mode for newborns with CDH is not clear but there is accumulating evidence that ventilator-induced lung injury may have a significant negative impact on outcome in newborns with CDH. [10] Permissive hypercapniaand 'gentle ventilation' in neonates with CDH has been reported to increase

survival. The indications for HFOV are not clearly defined and in some centres it is the standard initial ventilation mode. [11]

- Initial strategy may involve SIPPV with volume targeting and if PIP < 26, continuing with this mode is acceptable. Target volumes of 4 ml/kg and no more than 5 ml/kg.
- If unable to meet required parameters, HFV should be initiated, **aiming to keep MAP < 16** to achieve adequate expansion of the lungs. The optimal starting MAP on HFOV will vary between infants: start at, or 1-2 cm H2O above CV MAP and then slowly increase the MAP until an acceptable SaO2 is achieved. **Further increases in MAP, as per Lung Recruitment Strategies, should be used very carefully in babies with CDH.** Remember you are ventilating the infant on 'one lung'. The physiological rationale for use of high-frequency oscillatory ventilation (HFOV) derives from its ability to preserve end-expiratory lung volume while avoiding over distension, and therefore lung injury, at end-inspiration. Retrospective studies have demonstrated effective CO 2 reduction and increased survival in neonates with CDH. [12, 13] However, a prospective randomized controlled trial on the use of HFOV as an initial ventilation mode in infants with CDH is still lacking. [12]
- In all patients, a chest and abdominal X-ray should be made as soon as possible to assess the initial condition. **Chest radiographs should be repeated guided by the patient's clinical condition and mode of ventilation-bolded.**

Circulation

- Haemodynamic management is aimed at achieving appropriate end organ perfusion determined by heart rate, blood pressure, capillary refill, urine output and lactate level.
- Invasive blood pressure monitoring should be obtained as soon as possible; pre ductal (right radial) arterial access is preferred.
- A central or peripheral venous line should be inserted to allow the administration of fluids and, if necessary, inotropic vasopressor drugs.
- An echocardiogram is required to evaluate cardiac structure, degree of pulmonary hypertension, ductal status and ventricular function. As pulmonary hypertension is a dynamic process, repeat echocardiograms are often needed to monitor progress.
- The ***general aim*** is to maintain a normal systemic mean arterial blood pressure in the term neonate, and in the preterm neonate equivalent to their gestational age (the 10th percentile for each gestation) but it is a balanced approach of targeting lower PAP and not solely increasing SAP by using high doses of inotropes as it may have deleterious effect on the PAP: SAP ratio.
- The initial management of hypotension is a normal saline bolus (up to 20mL/kg). Further fluid boluses should not be given unless discussed with the neonatologist or neonatal fellow.

Fluids

- Commence TPN at 60mls/kg/day.
- Thereafter, fluid and caloric intake should be increased based on clinical condition.
- Early administration of parenteral nutrition is recommended.
- Diuretics should be considered where fluid balance is overtly positive.
- Enteral feeding should be started postoperatively combined with anti-reflux medication.
- EBM/colostrum can be commenced from birth at trophic levels (no more than 1mL 4th hourly) via gastric tube. Patency and continuous free drainage of the gastric tube must be maintained to allow adequate venting of the stomach.

Inotropic Support

The choice of inotropic support should be considered carefully according to the underlying problem and current cardiovascular status on echocardiography.

- Dobutamine (5 – 20 micrograms/kg/min) raises blood pressure by increasing cardiac output and decreasing peripheral vascular resistance. Compared to dopamine, dobutamine achieves a greater increase in O2 delivery for a given increase in O2 consumption.
- Noradrenaline (0.5-1.5 microg/kg/min) – raises blood pressure mainly by peripheral vasoconstriction or – almost pure αalpha effect and only moderate β1 receptor effects. Indicated where cardiac output is normal but need vasoconstriction. The results of one study demonstrated beneficial noradrenaline-induced effects of increased systemic pressure with simultaneously decreased pulmonary artery/systemic arterial pressure ratio, improved pulmonary flow and increased cardiac output in newborns with persistent pulmonary hypertension of newborn.[14]
- Low dose adrenaline (0.1 -0.5 micrograms/kg/min) – raises the blood pressure by increasing cardiac output and decreasing peripheral vascular resistance. Beware higher doses (>0.5 micrograms/kg/min) will increase systemic vascular tone.
- Milrinone (0.5 -0.75 microg/kg/min) is an ino-dilator which increases cardiac output and lowers peripheral vascular resistance. It is long acting and takes 6-12 hours to reach steady state. This medication has beneficial effects in newborns with right ventricular failure. Right ventricular failure in CDH can occur after several days of PH, and often coincides with closure of the PDA. Be wary as often precipitates systemic hypotension sometime after commencement.
- Hydrocortisone may be used for treatment of hypotension after conventional treatment has failed. Ensure that random cortisol level is sent prior to commencement of this strategy.
- Inotrope infusions must be administered continuously and avoid fluctuations during line changes.
- The excessive use of multiple inotropes can negatively affect cardiac function. Replacing one inotropic agent for another rather than using multiple agents to prevent catecholamine overload is preferable.
- There is evidence that in the presence of PH, dopamine and other adrenergic agents, in high dose raise pulmonary pressures along with systemic pressure and are not recommended in this setting. [15]

Treatment of Pulmonary Hypertension

Echocardiography performed within the first 24 hours after delivery is one of the best methods to assess the diameters of the pulmonary trunk and right ventricular function in real time. [16]

PH is a dynamic process with many changes in pulmonary and systemic pressures, shunt volume and direction, and right and left ventricular functions. Serial ultrasounds are essential for diagnosing such changes.

Adequate intravascular volume should be maintained, transfusion of packed red blood cells may be required to optimize tissue oxygen delivery. No studies have shown the benefit of increasing systemic vascular resistance to treat right to left shunting, but it is accepted practice that inotropes are employed to maintain blood pressure at the normal level for gestational age. [13]

If pulmonary hypertension persists, pulmonary vasodilator therapy should be given, with inhaled Nitric Oxide as the first choice. In newborns with hypoxic respiratory failure, iNO improves oxygenation and decreases the need for ECMO.[17] However, in a subgroup of infants with

CDH with hypoxic respiratory failure; iNO did not improve mortality or ECMO need. When proven to be not effective (non-responder, see iNO guideline), iNO should not be continued.[24]

Medication:

1. **Inhaled Nitric Oxide (iNO)**
   Please refer to 'Nitric Oxide (iNO) Therapy in NICU' guideline for details.

iNO is a selective pulmonary vasodilator and thus improves pulmonary blood flow. It is indicated when there is evidence of severe pulmonary hypertension. This is defined as: In term or near term infants with significant hypoxic respiratory failure defined as PaO2 < 100 mmHg on FiO2 > 8.0 and/or Oxygenation Index (OI) between 15 and 25, start iNO at 20 ppm.

iNO should only be started in infants with CHD after echocardiography documented a reasonable LV size, acceptable LV function and the presence of significant pulmonary hypertension or right ventricular dysfunction.

2. **If iNO fails to control the pulmonary hypertension and hypoxia, several alternatives are described in the literature. Most have not been tested in a randomised trial.**

- **Sildenafil is a phosphodiesterase 5 inhibitor which results in vasodilation by selectively reducing pulmonary vascular resistance.** Consider Sildenafil if proven severe PH is not responding to adequate ventilation and iNO or failed attempt to wean iNO. The data describing newborns with CDH indicate some improvement in oxygenation and cardiac output following the use of sildenafil, both in monotherapy and combined with iNO. [19]
- **Bosentan- is an active dual endothelin receptor antagonist which reduces pulmonary vascular resistance that has been described in small cohorts and case reports in term infants with pulmonary hypertension.**
- **Prostaglandin E1 (PGE1)-**PGE1 can be considered if there is severe PH and RV failure associated with closure of the PDA. It is reported as beneficial in preserving right heart function against strain by reopening the duct. However, the limited available clinical data did not show any benefits from this approach. PGE1 should not be started without echocardiography evidence of RV failure and a closed PDA[25].
- **Prostacyclin - commonly used in adult intensive care setting but there is limited data in newborns.**

Sedation and Analgesia

Neonates with severe pulmonary hypertension will require analgesia and sedation to facilitate optimal ventilation. Pain score assessment needs to be attended and recorded as per protocol "Assessment and Management of Pain in the Neonate" JHCH_NICU_03.04.

- Morphine to be started at 20 micrograms/kg/hr. Clinical evidence of ongoing pain and/or distress (pain scores) should be managed with additional boluses, increased infusion rate and consideration of another drug or additional sedation.
- A midazolam infusion might also be considered in a neonate requiring escalating doses of morphine.
- In addition to optimised analgesia and sedation, muscle relaxation with pancuronium may be considered when sedation is difficult to achieve despite morphine and midazolam. Consider aEEG monitoring in any infant on muscle relaxants.

ECMO

The role of Extracorporeal Membrane Oxygenation in the treatment of neonates with CDH is still unclear[14]. A meta-analysis of retrospective studies suggests that the introduction of ECMO has improved survival in neonates with CDH, [20] however; a meta-analysis of randomized controlled trials with small sample sizes indicated a reduction in early mortality with ECMO, but no long term benefit. [20]

Criteria to consider ECMO

- Clinical instability on maximal medical therapy.
- The impression of a reversible component to an acute cardiopulmonary deterioration.
- Absence of pre-existing major compounding factors, for example, congenital heart disease, sepsis, significant VILI, other congenital or genetic conditions that inform a poor prognosis.

For a neonate born at John Hunter Children's Hospital, the neonate would require transfer to Westmead Children's Hospital for ECMO. This would therefore require detailed discussion between Neonatologists, Paediatric Intensivists, Cardiothoracic Surgeon and neonatal transport service.

Timing of Surgical Repair

Delayed surgical repair is now considered best practice. Surgical repair deteriorates lung compliance; therefore a period of respiratory stabilization is essential. It allows for stabilisation of pulmonary hypertension, the systemic circulation, cardiac function, ventilation and the correction of any haematological or biochemical disturbances. It remains unclear; however, what constitutes an appropriate period of stabilization. Various authors have recommended that patients achieve a minimal level of ventilator support, that pulmonary hypertension be absent, that there be improvement in pulmonary compliance or the lung radiographic appearance be improved prior to repair.

Follow Up

The problems of long-term care include:

- Pulmonary Morbidity- chronic lung disease, bronchospasm, pulmonary hypertension, aspiration, recurrent pneumonia, obstructive airways disease,
- Recurrent hernias reported in 8 to 50 % of patients. The single-most important predictor of hernia recurrence is the presence of a large defect that requires a patch to repair.
- Failure to thrive, poor feeding skills, dependence on total intravenous or gastric tube nutrition, or percutaneous gastrostomy. Early recognition and intervention of growth failure is essential for optimizing both somatic and alveolar growth and long-term outcomes for infants with CDH.
- Gastro-oesophageal reflux and foregut dysmotility (45% to 90%).
- Musculoskeletal deformities- pectus deformities, progressive asymmetry of the chest and scoliosis.
- Developmental delay. Infants treated with ECMO thought to be at highest risk.
- Hearing loss: Sensorineural hearing loss has been described in a number of case series of CDH survivors. Severe hypoxemia, prolonged ventilation, and ECMO are risk factors.

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