ARTICLE

A clinical consensus guideline for nutrition in infants with congenital diaphragmatic hernia from birth through discharge

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OBJECTIVE: To develop a consensus guideline to meet nutritional challenges faced by infants with congenital diaphragmatic hernia (CDH).

STUDY DESIGN: The CDH Focus Group utilized a modified Delphi method to develop these clinical consensus guidelines (CCG). Topic leaders drafted recommendations after literature review and group discussion. Each recommendation was sent to focus group members via a REDCap survey tool, and members scored on a Likert scale of 0–100. A score of > 85 with no more than 25% outliers was designated a priori as demonstrating consensus among the group.

RESULTS: In the first survey 24/25 recommendations received a median score > 90 and after discussion and second round of surveys all 25 recommendations received a median score of 100.

CONCLUSIONS: We present a consensus evidence-based framework for managing parenteral and enteral nutrition, somatic growth, gastroesophageal reflux disease, chylothorax, and long-term follow-up of infants with CDH.

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INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a congenital anomaly with high morbidity that occurs in 1 in 2500–3500 births [1] with survival of 71% reported by the Children's Hospitals Neonatal Consortium (CHNC) [2], and individual centers reporting survival up to 79% [3]. Survivors may have impaired neurodevelopment, malnutrition and growth failure, gastroesophageal reflux disease (GERD), and chronic respiratory disease. Delayed enteral feeds, difficulty supplying optimal parenteral nutrition, limitations on direct breastfeeding, intolerance of enteral feeds, and higher calorie needs due to increased metabolic demand all contribute to poor somatic growth in these patients. Malnutrition is common amongst CDH survivors with incidences reported from 16 to 45% [4–8] at hospital discharge, and is associated with worse neurodevelopmental outcomes [9, 10]. GERD is diagnosed frequently in 20–84% [11, 12] of infants with CDH and can persist through early childhood and into adulthood. The CHNC CDH Focus Group developed a nutritional consensus guideline to address the unique nutritional challenges and long-term morbidities that infants with CDH face in the intensive care unit and after discharge to home.

METHODS

The CHNC consists of 46 Level IV regional referral neonatal intensive care units (NICUs) across the US and Canada (www.thechnc.org). The 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 is comprised of 56 individuals from 27 of the 46 centers

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currently participating in the CHNC. Focus group members include neonatologists, pediatric surgeons, advanced practice providers, registered dietitians, and registered nurses with a clinical and/or research interest in CDH.

The CDH Focus Group utilized a modified Delphi method to develop clinical consensus guidelines (CCG) for management of nutritional support for infants with CDH. The focus group met bimonthly from March 2022 to May 2023, and received education related to the Delphi method process at the onset of the project [13–15]. The *target audience* for the CCG is practicing clinicians caring for infants diagnosed with CDH, including physicians, pediatric surgeons, dietitians, speech and occupational therapists, feeding specialists, and nurses. The *target population* was defined as neonates with a diagnosis of CDH during their initial hospitalization. Two physicians were designated as the co-chairs for the project.

Existing published guidelines for CDH clinical management were reviewed and the group determined the focused topics to be addressed. A comprehensive literature review was conducted over a nine-month period, limited to English publications since January 2010, accessed through PubMed (https://pubmed.ncbi.nlm.nih.gov) using individualized search strategies without the assistance of a research librarian. Each publication was classified by the category of evidence (Metanalyses of randomized clinical trials: A- expert opinion: D) [14, 16] (Table 1). Two to three topic leaders were assigned to review and present a summary of the literature related to each of the ten topics (Table 2) to the focus group and to propose recommendations. An open discussion occurred during the literature review with the focus group members.

Following the completion of the literature review, 25 recommendations were drafted. Two rounds of asynchronous and anonymous surveys were sent to focus group members via a REDCap survey tool [17, 18]. Each recommendation was scored on a Likert scale of 0–100 (0- strongly disagree with recommendation; 25- disagree with recommendation; 50- neutral; 75- support with reservations; 100- fully support recommendation as written). A score of >85 with no more than 25% outliers was designated a priori as demonstrating consensus among the group.

Results of the Delphi Survey #1 were presented and discussed with the focus group; recommendations with a median score of ≥ 90 were accepted as written (24/25) while those scoring <90 (1/25) were discussed and revised through an iterative process. A second Delphi Survey was sent to the focus group with the revised recommendations and all 25 recommendations received a median score of 100, demonstrating consensus among the group. Two of the 25 recommendations were subdivided into separate recommendations for clarity, thus a total of 27 recommendations are presented. A preliminary CCG document was generated, and all members of the CDH focus group were given an opportunity to review and edit the document (Fig. 1).

CLINICAL GUIDELINES

Parenteral nutrition

Enteral feeding is delayed in infants with CDH prior to operative repair and in the immediate post-operative period due to physiologic instability, concern about mesenteric perfusion, and post-operative ileus. Parenteral nutrition is key to ensuring adequate nutritional intake prior to enteral feeding and during the transition to enteral feeds. Earlier initiation of parenteral nutrition has demonstrated improved weight gain in infants with CDH from birth to 3 weeks of life [19]. Initiation in the first 24 h follows the National Institute for Health and Care Excellence (NICE) parenteral nutrition guideline to start parenteral nutrition as soon as possible [20, 21].

Increased metabolic demands in infants with CDH make it critical to ensure sufficient caloric and protein intake [6, 22]. Parenteral nutrition caloric goals should target 100–110 kcal/kg/day for adequate somatic growth. Constraints such as iatrogenic fluid restriction, hyperglycemia, or clinical instability may delay time to achieve this goal. The American Society for Parenteral and Enteral Nutrition (ASPEN) guideline for parenteral nutrition sets target goals of 2.5–3 gm/kg/day of lipids and protein for term infants [23]. The NICE parenteral nutrition guideline sets target goals for protein at 2.5–3 gm/kg/day and 3–4 gm/kg/day for lipids. A retrospective review found that a minimum protein threshold for improved growth for infants with CDH was ≥ 2.3 gm/kg/day [5]. Based on the published guidelines and available CDH data, we advise a minimum protein requirement of 3 gm/kg/day in parenteral nutrition. This target is in line with Extracorporeal Life Support Organization (ELSO) recommendations for protein requirements to prevent catabolism in neonatal extracorporeal membrane oxygenation (ECMO) patients [24]. For lipid requirements, we propose 3 gm/kg/day as a target based on center consensus and the ASPEN and NICE guidelines.

Recommendations:

1. Parenteral nutrition should be initiated within 24 h of admission. (grade of recommendation = C)
2. Parenteral nutrition caloric goal should be 100–110 kcal/kg/day. (grade of recommendation = C)
3. Parenteral nutrition should meet a minimum protein goal of 3 gm/kg/day. (grade of recommendation = C)
4. Parenteral nutrition should meet a lipid goal of 3 gm/kg/day. (grade of recommendation = C)

Cholestasis

Parenteral nutrition associated liver disease (PNALD) is a potential complication with significant morbidity [25]. A conjugated bilirubin level between 1.5 and 2.0 mg/dl can be utilized as the definition for PNALD according to the ASPEN guidelines [26]. Initial cholestasis may progress with time to cirrhosis and liver failure in the most affected patients. Infants with CDH receive an average of 22 days of parenteral nutrition [27], with high-risk patients needing substantially longer, and are at risk for PNALD. Regular monitoring for cholestasis as well as markers of liver biochemistry such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (GGT) should be followed in patients on long-term parenteral nutrition [25]. Doses of IV lipids > than 1 gm/kg/day have been associated with an increased risk for PNALD [25, 28] and strategies to reduce PNALD are to restrict lipid administration or to utilize a mixed-lipid source such as SMOFLipid (Fresenius Kabi, Germany) or Omegaven (Fresenius Kabi, Germany) if serum conjugated bilirubin is above 1.5–2.0 mg/dl. There is a lack of clear data as to what is the best approach to prevent or treat PNALD [29].

Recommendation:

5. Clinicians should restrict intralipids or switch to mixed-lipid emulsions in infants with cholestasis or at high risk of developing cholestasis. (grade of recommendation = C)

Parenteral nutrition on ECMO

Patients who require ECMO therapy may have persistently high energy needs, and high protein intake is critical to prevent a

Table 1. Grades of Recommendation based on AAP guidelines.

Level A	Well designed or conducted trials, meta analyses on applicable populations
Level B	Trials or diagnostic studies with minor limitations, consistent findings from multiple observational studies
Level C	Single or few observational studies or multiple studies with inconsistent findings or major limitations
Level D	Expert opinion or case reports

Table 2. Topic categories utilized by the individual groups to identify clinical consensus guidelines.

Clinical Guideline Topic Categories
1. Parenteral Nutrition
2. Cholestasis
3. Parenteral Nutrition on ECMO
4. Enteral Nutrition
5. Mode of Feeding
6. Calorie Goals
7. Oral Feeding
8. Gastroesophageal Reflux Disease
9. Chylothorax
10. Long Term Monitoring and Follow-up

catabolic state [24]. Neonates can lose up to 15% of their lean body mass during a 7-day course of ECMO [30, 31]. Iatrogenic fluid restriction and multiple drips for patients receiving ECMO therapy present a challenge to meeting protein and caloric intake goals. It is critical to meet nutrition goals for these patients and our consensus is to consider augmenting fluid removal with interventions such as diuretics, slow continuous ultrafiltration (SCUF) or continuous renal replacement therapy (CRRT) to maintain caloric goals while on ECMO. Early initiation of CRRT in neonatal ECMO has demonstrated improved parenteral nutrition volumes and protein delivery [32].

Recommendation:

6. Augment fluid removal on ECMO with diuretic therapy or CRRT to maintain nutrition goals. (grade of recommendation = C)

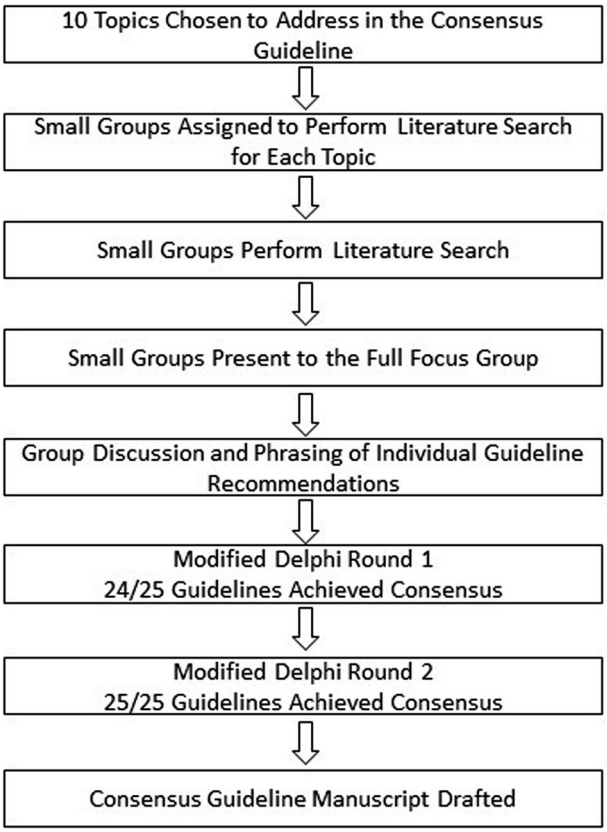

Fig. 1 Evidence appraisal and modified Delphi approach for the guidelines.

Enteral nutrition

Early initiation of parenteral nutrition is important for infants with CDH, but transition to enteral feeding is the goal. Enteral feeding should start after surgical repair of the diaphragmatic defect when there is evidence of return of bowel function (passing stool and decreasing non-bilious gastric output) and discontinuation of vasoactive agents. In addition, the patient should have evidence of adequate oxygen delivery and systemic perfusion as assessed by a normal lactate and consistent urine output. This approach of enteral feeding should also apply to patients who remain on ECMO after surgical repair. Trophic or small volume enteral feedings should be considered in infants with CDH on ECMO after repair if evidence of adequate oxygen delivery and systemic perfusion is present. A recent review of enteral nutrition on ECMO in neonatal and pediatric patients demonstrated limited complications, reduced mortality rates, and underutilization of enteral feeding [33]. Recent ELSO guidelines for nutritional support in neonatal and pediatric patient populations published by Lee et al. recommend initiation of enteral nutrition in neonatal patients on ECMO [24]. Contraindications to enteral feeding on ECMO are an unrepaired CDH, hemodynamic instability with vasoactive requirement, significant ileus, and/or intra- abdominal pathology [24, 33, 34].

Human milk administration is the standard for infant nutrition [35]. Guidance from the American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for 6 months after birth [35]. Many of the practices that improve breastfeeding success are not possible for infants with CDH due to respiratory failure and hemodynamic instability following delivery. These include breastfeeding in the first hour of life, rooming-in, breastfeeding on demand, and skin-to-skin [36]. Despite this challenge, lactating parents of infants with CDH can establish their milk supply and provide human milk for the entire hospital stay [37]. However, they face environmental stressors, challenges with milk supply maintenance, and inadequate education on maintaining milk supply through pumping [38, 39]. Therefore, it is critical that all parents of infants with CDH receive lactation consultation and encouragement with initiating pumping on the first day of life.

Recommendations:

7. All parents of infants with CDH should receive lactation support in the first day of life. (grade of recommendation = D)
8. The clinician should initiate enteral feeds after surgical repair when bowel function has returned. (grade of recommendation = D)
9. Trophic enteral feeding should be administered for post-surgical repair patients who are receiving ECMO therapy if the patient has evidence of adequate oxygen delivery. (grade of recommendation = C)

Mode of feeding

There is little evidence to provide guidance on the mode or volume of enteral feeding to initiate in infants with CDH. However, standardized feeding protocols have demonstrated benefit in other at-risk populations such as neonates with congenital heart disease and premature babies. With the use of standardized feeding protocols, extremely low birth weight (ELBW) infants have reduced parenteral nutrition days, improved growth, and decreased complications such as necrotizing enterocolitis [40] and increased weight gain and decreased malnutrition have been seen in neonates with congenital heart disease [41]. For infants with CDH, there is no clear evidence to support initiation with bolus versus continuous enteral feedings. Low-risk patients are

more likely to tolerate bolus feeds, which can simplify the transition to oral feeding. A subgroup of infants with CDH are at higher risk for malnutrition and delayed time to reach full enteral feedings. This includes those with intrathoracic liver position, receipt of ECMO, patch repair, severe pulmonary hypertension, or GERD [8, 42]. These high-risk infants may benefit from the initiation of transpyloric continuous feedings if bolus feeds are unsuccessful on initial attempts. Infants with persistent evidence of gastroparesis or severely delayed gastric emptying with high-volume gastric output may also benefit from transpyloric enteral feeding with an indwelling orogastric (OG)/sump tube until gastric output improves. Although there is not clear evidence, in patients with symptomatic GERD, continuous enteral feedings may be considered to reduce the risk of aspiration.

Recommendations:

10. High-risk infants who do not tolerate gastric feeding may benefit from transpyloric feeding. (grade of recommendation = D)
11. Infants with persistent gastroparesis may receive a trial of transpyloric feeding with an indwelling OG/sump until gastric output improves. (grade of recommendation = D)
12. In high-risk infants, continuous feeds may be trialed to reduce the risk of aspiration. (grade of recommendation = D)

Calorie goals

Malnutrition is common amongst CDH survivors with 16-45% demonstrating failure to thrive at hospital discharge [4–8]. Haliburton et al. demonstrated that the resting energy expenditure (REE) is higher than predicted [6] and several studies demonstrate that infants with growth failure can take 1-2 years to achieve catch-up growth [4, 7]. Multiple studies have demonstrated that higher than normative calories are required for infants with CDH to demonstrate appropriate weight gain [6, 7, 22], with ranges from 122 to 140 kcal/kg/day. To minimize malnutrition and to promote growth, enteral nutrition caloric intake should target > 120 kcal/kg/day to start; calories and volume should be adjusted to promote appropriate growth. The optimal rate of enteral nutrition advancement is not yet delineated, and earlier transition from parenteral to enteral nutrition has not been associated with improved weight gain. Our group previously reported that the group with the best survival and highest median weight at discharge remained on parenteral nutrition 12 days longer on average [27], suggesting a more gradual transition from parenteral to enteral nutrition may lead to better weight gain. Target daily weight gain for infants with CDH should be comparable to other infants (approximately 25–35 gm/day). Standard NICU practices, including weekly head circumference and length via length board should be used for CDH patients.

Recommendations:

13. The initial enteral caloric goals should target 120–140 kcal/kg/day. (grade of recommendation = C)
14. Target daily weight gain should be comparable to other term infants (25–35 gm/day). (grade of recommendation = C)
15. Weight, length, and head circumference should be measured at least weekly and a length board should be used to measure length. (grade of recommendation = D)

Oral feeding

Delayed oral feeding is a common co-morbidity for infants with CDH [4, 8]. Consensus regarding the timing of initiation of oral feeding was that oral feeding at breast or bottle should begin at ≤ 2 LPM of respiratory support and in the absence of any contraindication to oral feeding. While some centers allow oral feeding on higher respiratory support levels, a review by Canning et al. did not find evidence for improved feeding outcomes in neonates allowed oral feeding while on nasal continuous positive airway pressure (CPAP) or higher rates of high flow nasal cannula [43].

Recommendation:

16. Oral feeding should be offered when the patient is on ≤ 2 LPM of respiratory support. (grade of recommendation = D)

Gastroesophageal reflux disease

GERD is the most common gastrointestinal co-morbidity associated with infants with CDH [11]. GERD occurs in 20–84% of infants with CDH [11, 12] via the following proposed mechanisms: esophageal dysmotility, higher intra-abdominal pressure after surgical repair, shortening of the esophagus, or weakness of the crura [11, 44, 45]. It is more prevalent in patients with larger defects (type C or D), those who underwent patch repair, required ECMO therapy, intrathoracic stomach position, and longer duration of mechanical ventilation [45, 46]. GERD persists through early childhood with incidences reported of 46% at 1 year [12, 45] and 24% at 2 years [46]. Barrett's esophagus and esophagitis have been reported in adult survivors with CDH [12, 47–50]. In many cases of esophagitis, the child remains asymptomatic [50] and therefore infants with CDH should be followed longitudinally to ensure they receive appropriate medical surveillance for GERD and the subsequent complications that can occur.

While the literature is clear that there is a high incidence of GERD in infants with CDH, there is little guidance on pharmacologic therapy. Although the reflux contents are typically non-acidic [51], the most commonly used pharmacologic options target acid blockade. Guidance from the AAP is that nutritional management should be the initial approach to gastroesophageal reflux in infants less than 1 year [51] and that acid blockade medication should only be used in the first year of life in the presence of esophagitis. Non-pharmacologic options supported by the AAP include restricting cow's milk intake in breastfeeding mothers and a trial of hydrolyzed formula or amino-acid based formula [51]. Empiric medical prophylaxis with an acid-blocking medication in all infants with CDH is not indicated. Medical treatment for GERD with acid-blockade medications must weigh the benefit of decreased acidic reflux with the risk associated with acid suppression, which include increased risk of upper respiratory and *Clostridium difficile* infections [51] and an increased risk of fractures in preterm infants.

Preventive anti-reflux surgery has been performed on infants with CDH are at high risk for developing GERD. However, multiple studies have shown no long term benefit to anti-reflux surgery at the time of CDH repair [52–54], and no decrease in the need for a second anti-reflux surgery [54]. Anti-reflux surgery may be considered for the management of patients with severe symptomatic GERD who have failed medical therapies and lifestyle changes but should not be performed as a "preventive" measure.

Recommendations:

17. Patients with CDH have a long-term risk of GERD and should be followed longitudinally to ensure they receive appropriate medical surveillance. (grade of recommendation = C)
18. In infants with symptoms of GERD including poor weight gain, AAP guidance should be followed which includes restricting cow's milk intake in breastfeeding mothers and using hydrolyzed or amino-acid based formulas. (grade of recommendation = C)
19. Empiric medical prophylaxis with an acid-blockade medication in all infants with CDH should not be started. (grade of

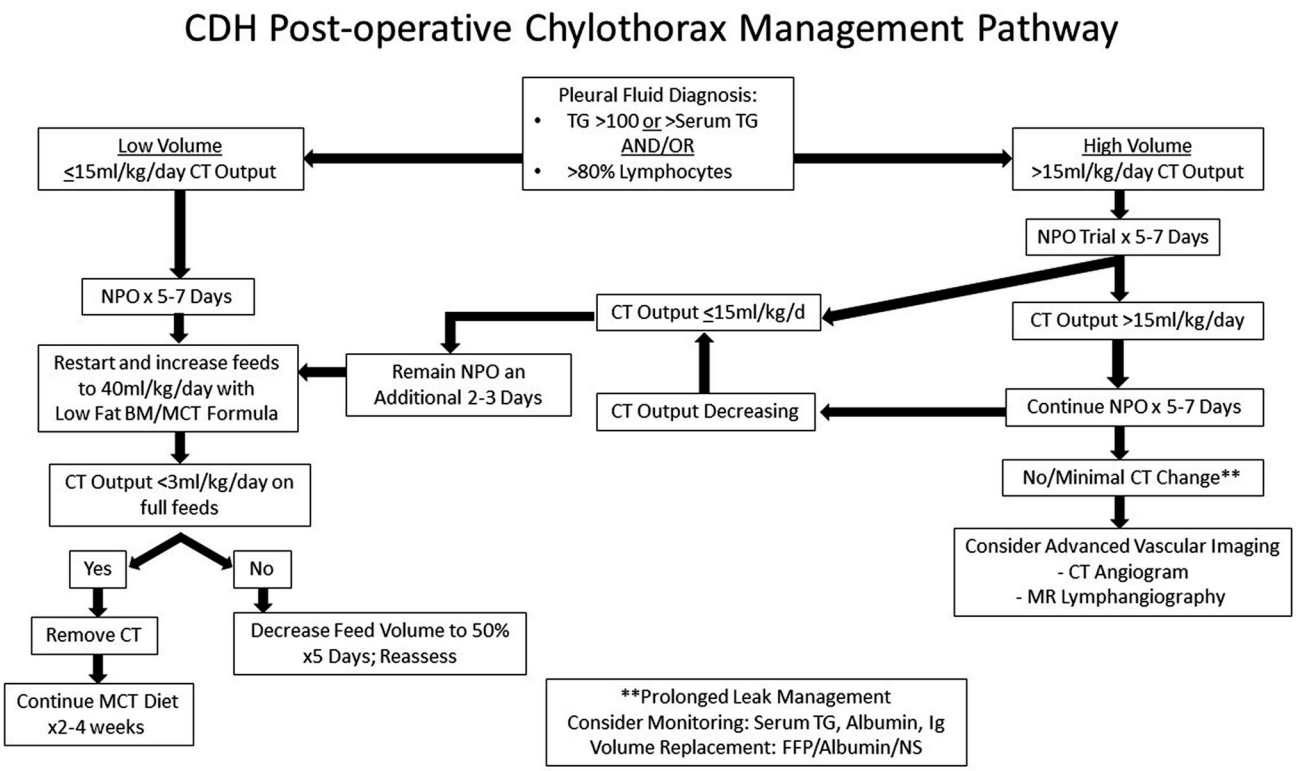

Fig. 2 CDH Post-operative Chylothrorax Management Pathway, utilizes chest tube output to guide therapy. TG triglycerides, CT Chest tube, ml/kg/d milliliters/kilogram/day, BM Breastmilk, MCT Medium change triglyceride, FF Full feeds, Ig Immunoglobulins, FFP Fresh frozen plasma, NS Normal saline, CT angiogram, computed tomography angiogram, MR Magnetic resonance.

recommendation = C)

20. Medical treatment for reflux with acid suppression medications should weigh the benefits of prevention of reflux of acidic material with the risk associated with acid suppression. (grade of recommendation = C)
21. Preventive anti-reflux surgery at the time of CDH repair should not be performed. (grade of recommendation = C)
22. Anti-reflux surgery should only be performed for patients with severe GERD who have failed lifestyle changes and medical therapy. (grade of recommendation = C)

Chylothorax

Chylothorax is a known complication in neonates after a CDH repair with a 4.6% incidence reported from the CDH Study Group (CDHSG) [55] and a 4.5% incidence reported by the Canadian Pediatric Surgery Network (CAPSNet) [56]. Development of chylothorax is associated with more severe defect size and ECMO utilization and adds to morbidity by increasing the duration of mechanical ventilation, length of stay (LOS), and increasing the likelihood of infection or additional surgery [56]. Conservative management with nutritional changes and/or chest drainage is effective in most cases [55, 57]. We propose that therapy should be stratified by volume of output, as outlined in Fig. 2, and initial therapy should include pleural or peritoneal drainage and a period of NPO if the patient is symptomatic. Restart enteral feeds with low-fat/skimmed breast milk or a medium chain triglyceride formula. If there is persistent high-volume output, a longer NPO time may be warranted, and monitoring of serum triglycerides, albumin, coagulation factors, and immunoglobulins should occur. There has not been proven benefit to the use of Octreotide for chylothorax in patients with CDH [57, 58], and there is risk for vascular compromise and necrotizing enterocolitis reported with its use in neonates [59, 60].

Long term monitoring and follow-up

The long-term disease burden associated with CDH includes malnutrition, development and management of GERD, oral aversion, and feeding challenges. A multi-disciplinary follow-up clinic for patients with CDH can help manage these gastrointestinal morbidities. Feeding evaluation and growth monitoring should be a standard part of any CDH follow-up program. Feeding support by pediatric occupational and speech therapists is an important component of outpatient management and should be available for infants with CDH who are not taking full oral feeds at discharge.

There is a high prevalence of discharge home with tube feedings in infants with CDH. Prieto et al. reported from the CDHSG that 13% underwent surgical tube placement [61], and Gien et al. reported from the CHND that 42% are discharged home with tube feedings (including both surgical and nasogastric tubes) [27]. Risk factors associated with increased need for gastrostomy-tube (G-tube) placement include chromosomal abnormalities, GERD, ECMO therapy, liver herniation, and increased defect size [61–63]. The high prevalence of tube feeding at discharge should prompt early discussion with families about the potential need for home tube feeding and the options available. The potential risks and benefits of home nasogastric (NG) or G-tubes must be weighed for individual patient circumstances, and adequate follow-up and home support for the family should be ensured. There is evidence that NG tube feedings are associated with decreased complications, emergency department visits, and hospital readmissions when compared to G-tube feeding in infants discharged from the NICU [64–67]. These studies suggest NG feedings at discharge are a safe alternative to early G-tube placement in some patients, although these studies did not specifically look at the CDH population. The median time for infants with CDH to liberate from tube feedings is 2–3 years of age [68, 69].

Long-term follow-up is necessary to ensure appropriate growth and nutritional support regardless of the mode of feeding, and some patients initially discharged with NG feedings may require a G-tube later. The role of telemedicine is evolving and has been utilized for NICU discharge follow-up by Willard et al. to follow complex surgical NICU patients, including infants with CDH, to identify clinical issues, provide caregiver support, and save travel time for families [70]. Telemedicine was utilized by Vergales et al. to improve nutritional outcomes in infants undergoing single-ventricle palliation [71].

Recommendations:

23. CDH patients should be followed longitudinally in a multidisciplinary clinic with feeding and developmental support. (grade of recommendation = D)
24. Early discussion about the potential need for feeding support and the mode of feeding should occur with families. (grade of recommendation = D)
25. The potential risk and benefit of home NG vs. G-tube should be carefully weighed for each individual patient, with NG tubes being a safe option for home feeding support in the right patient. (grade of recommendation = C)
26. Integrating remote patient monitoring with a home NG program using telemedicine may benefit patients with CDH who are receiving home tube feedings. (grade of recommendation = C)
27. Feeding support by pediatric occupational and speech therapist should be available for infants with CDH discharged with home tube feedings. (grade of recommendation = D)

CONCLUSION

The nutritional challenges and morbidities faced by infants with CDH are common and increase in severity and prevalence with the complexity of the CDH. Our guideline proposes a consensus evidence-based framework for managing parenteral and enteral nutrition to target appropriate linear growth and weight gain, monitor and manage GERD, and ensure long-term follow-up and care of infants with CDH. There remains an opportunity for additional study in each of these domains, but we have worked to compile the most current literature combined with consensus amongst many CDH centers nationally. Future studies should investigate how the impact of this guideline implementation impacts nutritional outcomes to guide further revision and refinement in areas where limited evidence currently exists.

DATA AVAILABILITY

Not applicable.

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COMPETING INTERESTS

The authors declare no competing interests.

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