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Evidence-based management of chylothorax in infants

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ABSTRACT

Purpose: Management guidelines for infants with chylothorax lack substantial evidence. We sought to identify variables that impact outcomes in these patients in order to develop an evidence-based management algorithm.
Methods: We retrospectively reviewed the medical records of all infants diagnosed with chylothorax from June 2005 to December 2014 at our institution. Data collected included demographics, chest tube output (CTO), medical and dietary interventions, surgical procedures, and absolute lymphocyte count (ALC). Outcomes analyzed included death, sepsis, necrotizing enterocolitis (NEC), requiring surgery, and success of therapy, defined as CTO decrease by >50% within 7 days.
Results: Of 178 neonates with chylothorax, initial therapy was high medium chain triglyceride (MCT) feedings in 106 patients, nothing by mouth (NPO), total parenteral nutrition (TPN) in 21, and NPO/TPN plus octreotide in 45. Octreotide use in addition to NPO/TPN revealed no significant differences in any outcome including success (47% vs. 43%, $p = 0.77$). Initial CTO and ALC correlated with needing surgery ($p = 0.002$ and $p = 0.006$, respectively), and with death ($p = 0.028$ and $p = 0.043$, respectively). ALC also correlated with sepsis ($p < 0.001$).
Conclusions: Octreotide has no advantage over NPO/TPN alone in infants with chylothorax. CTO and ALC predict requiring surgery. We propose a management guideline based on CTO and ALC without a role for octreotide.
Type of study: Retrospective case–control study.
Level of evidence: 3

Chylothorax in infants is associated with significant morbidity, including respiratory compromise, malnutrition, immunodeficiency, and infection [1,2]. Causes include congenital anatomic malformations, syndromes, and thoracic trauma, in particular from surgical intervention [1]. Nonsurgical management often consists of high medium chain triglyceride (MCT) enteral nutrition, or by withholding enteral nutrition (NPO) and giving total parenteral nutrition (TPN), with or without intravenous lipid administration. When chylothorax is very high volume, has clear anatomic etiology, or is not improved with conservative management, surgical intervention may be required, such as thoracic duct ligation/embolization, pleurectomy, or pleurodesis.

Despite the numerous strategies for managing chylothorax in infants, there is no substantial evidence for particular medical treatments or surgical interventions. Octreotide, a synthetic somatostatic analog, has been used in multiple small series and case studies of congenital chylothorax with unclear benefit [3,4], and a Cochrane review was unable to draw any meaningful conclusions regarding its use [5]. Outcomes of octreotide use for postoperative chylothorax related to congenital heart disease and congenital diaphragmatic hernia (CDH) are similarly mixed [6–10]. Furthermore, there is no consensus regarding the timing of surgical intervention, with strategies ranging from nonoperative management for 2–4 weeks to early surgical intervention in children with large-volume chylothorax [11,12].

The benefit of establishing a management algorithm for chylothorax has been established in the congenital cardiac literature [13], but the current guideline also lacks substantial evidence. We sought to create an evidence-based management guideline for infants with chylothorax. We reviewed the records of infants with chylothorax at our institution to elucidate the benefits and risks of octreotide, and to identify variables that predict the need for surgical intervention, as well as the outcomes of death, NEC, and sepsis.

1. Methods

After institutional review board approval (HUM #00093133), we conducted a retrospective review of all infants in the neonatal and cardiac ICUs at our institution diagnosed with chylothorax from June, 2005 to December, 2014. Data were collected from the medical record as well as the Vermont Oxford Network (VON) database. In addition to

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demographics, we collected data on chest tube output (CTO), medical and dietary interventions, surgical procedures, and laboratory values. We recorded 24-h CTO on the day therapy for chylothorax was initiated, as well as CTO 7 days later, or when treatment modality was changed if this occurred before 7 days. If therapy was initiated concurrently with chest tube insertion, we measured CTO for 24 h starting 2–8 h following insertion to avoid the initial "dump" of fluid from tube insertion. Because chylothorax has been shown to cause lymphopenia [2,14], we recorded the minimum absolute lymphocyte count (ALC) for each patient, if obtained, over the course of his/her hospitalization.

The primary outcome evaluated was success of therapy, defined as reduction of CTO by >50% within one week of therapy initiation. Other outcomes evaluated were death, sepsis, necrotizing enterocolitis (NEC), ventilator days, length of stay, and requirement of surgical intervention for chylothorax. Sepsis was defined by the presence of the diagnosis in the patient's discharge summary plus positive cultures. Nonoperative initial therapies compared were high medium chain triglyceride (MCT) enteral feeds, NPO and TPN, and NPO/TPN plus octreotide. After comparing these groups for our entire study population, we then compared groups within those patients with congenital chylothorax, as well as within infants ≤36 weeks GA and >36 weeks GA.

Statistical analysis was performed using SPSS v.22.0 (Armonk, NY: IBM Corp.) and Stata Statistical Software: Release 13 (College Station, TX: Statacorp LP). Comparisons between nonoperative therapies were made using Student's *t*-test, ANOVA, Chi-square analysis and Fisher's exact test, with $p < 0.05$ considered significant. Logistic regression analyses were performed to identify predictors of requiring surgery for chylothorax, death, NEC, and sepsis. All potentially predictive clinical factors were input into the multivariate regression models. The results of these regressions were then used to create a clinical management algorithm.

2. Results

2.1. Study population

178 infants were identified as diagnosed with chylothorax. Baseline characteristics and outcomes for the study population as a whole are seen in Table 1. The majority of patients had chylothorax with a surgical etiology, and of these, most had congenital heart disease. Non-CHD surgical causes of chylothorax were primarily CDH and tracheoesophageal fistula (TEF).

2.2. Nonoperative management

172 patients were initially managed nonoperatively; of the remaining six patients, three received no treatment for chylothorax, and 3 underwent surgical intervention as initial management. 106 patients were managed initially with high MCT enteral feeding, 21 with NPO/TPN, and 45 with NPO/TPN plus octreotide (Table 2). Significant differences were observed in gestational age, initial CTO, success, requiring surgery, ventilator days, and LOS. When initial management with NPO/TPN was compared directly to NPO/TPN + octreotide, the only remaining difference was gestational age (35.4 ± 3.7 vs. 37.8 ± 2.5 weeks; $p = 0.010$). Though not statistically significant, NPO/TPN appeared to correspond to fewer ventilator days, shorter length of stay, and less surgical requirement than NPO/TPN + octreotide, with the rate of surgical intervention in the NPO/TPN group just over half that of that with NPO/TPN + octreotide (38% vs. 62%; $p = 0.067$).

Overall rates of NEC were low (7%). When comparing infants who received octreotide at any point (not just initial therapy) versus those who did not, rates of NEC appeared higher with octreotide than without, though this did not reach statistical significance (11% vs. 5%; $p = 0.15$). The same comparison was then performed with patients divided into two groups based on GA: a premature group (GA ≤ 36 weeks; $n = 40$) and term group (GA > 36 weeks; $n = 138$). Seven patients in the premature group and 6 in the term group developed NEC (18% vs. 4%; $p = 0.011$). Within the premature group, 20 infants received octreotide and 20 did not. Of those who received octreotide, six developed NEC, compared with 1 case of NEC among those who did not receive octreotide (30% vs. 5%; $p = 0.09$). Within the term group, 56 received octreotide and 82 did not. Two infants given octreotide developed NEC, while four without octreotide developed NEC (4% vs. 5%; $p = 1.0$).

Within infants with congenital chylothorax ($n = 16$), five were initially managed with high MCT feeds, seven with NPO/TPN, and three with NPO/TPN + octreotide. One infant did not receive any therapy specific to chylothorax and did well on breast milk alone. One patient managed with NPO/TPN and one managed with NPO/TPN + octreotide developed NEC. Initial therapy was successful in one patient with high MCT feeds (20%), two with NPO/TPN (29%), and one with NPO/TPN + octreotide (33%; $p = 0.91$). Two patients managed initially with high MCT feeds, two managed with NPO/TPN, and one managed with NPO/TPN + octreotide went on to require surgical intervention.

2.3. Predictors of death, NEC, and sepsis

Gestational age, birth weight, etiology of chylothorax (surgical vs. congenital), initial 24-h CTO, and ALC were chosen as possible predictors of death, NEC, and sepsis, and were input into multivariate logistic regression models for these outcomes (Table 3). ALC was recorded during the hospital stays of 161 of 178 patients. Gestational age and birth weight were found to be collinear (condition number = 41.3), so gestational age was removed from the models. Initial CTO and ALC were found to be significant predictors of death ($p = 0.028$ and $p = 0.043$, respectively). ALC was also found to be the only significant predictor of

Table 1
Study population characteristics and outcomes.

Baseline characteristics			Overall
Male			101 (57%)
Estimated gestational age (weeks)			37.7 ± 2.8
Birth weight (kg)			3.0 ± 0.7
Premature (<36 weeks EGA)			40 (22%)
Systemic syndrome/chromosomal anomaly			16 (9%)
Etiology			
Congenital			16 (9%)
Surgical			162 (91%)
Congenital heart disease			145 (82%)
Other surgical etiology			17 (9%)
Outcomes	**Congenital ($n = 16$)**	**Surgical ($n = 162$)**	**Overall ($n = 178$)**
NEC	2 (13%)	11 (7%)	13 (7%)
Sepsis	6 (38%)	25 (15%)	31 (17%)
Death	4 (25%)	29 (18%)	33 (19%)

EGA (estimated gestational age); NEC (necrotizing enterocolitis).