Editorial

Pediatric chylothorax: where we've been and where we're going

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Chylothorax in children is associated with significantly increased rates of morbidities and mortality. As the prevalence of chylothorax increases over time (1), we are more frequently faced with the complications of chylothorax and its management. Since the initial identification of chylothorax 50 years ago, there is a paucity of evidence to drive the treatment of these patients. We appreciate this study by Ruangnapa *et al.*, who described the treatment and outcomes of chylothorax in children over the last 20 years at their institution (2).

Ruangnapa *et al.* reported 65 episodes of chylothorax over 20 years, with 80% (n=52) of cases occurring postoperatively (2). Conservative therapy [dietary modification, fasting/total parenteral nutrition (TPN), and/or octreotide] was effective in treating chylothorax in 89% (n=58) of cases, with dietary modification alone effective in 51% (n=33). Surgery was used to achieve resolution of chylothorax in 11% (n=7) of patients. Unfavorable outcomes (i.e., in-hospital death or prolonged hospitalization) were observed in 52% (n=34), with predictive factors including non-postoperative chylothorax, total TPN used >14 days, hypoalbuminemia, and ventilator-associated pneumonia.

In 2001, when Ruangnapa began enrolling patients, there were 9 manuscripts addressing pediatric chylothorax published that year (as identified by searching "chylothorax" and "pediatric" in PubMed), compared to 64 published in 2022. Despite this increase, delineating the etiology of chylothorax (e.g., congenital, operative injury, venous hypertension), and the association between current treatments and outcomes remains elusive. Given the lack of randomized controlled trials or multi-center efforts, the generalizability of treatment strategies is unknown. To address these challenges, a Chylothorax Quality Improvement Work Group (CWG) has been formed, which includes over 20 participating centers. In order to standardize treatment, a pediatric postoperative chylothorax management algorithm has been developed to reduce practice variation related to diagnosis and treatment (3). Initiatives of the work group include: standardizing diagnosis of chylothorax, using chest tube volume to drive management, decreasing fat-modified diet duration after resolving chylothorax, and understanding best practices for the treatment of refractory chylothorax.

Traditional diagnosis of chylothorax is based on milky appearing chest tube output or pleural fluid samples containing elevated triglycerides (>110 mg/dL), criteria derived from adult literature which have not been modified in over 50 years. Furthermore, these diagnostic criteria are dependent on enteral feeds containing long-chain triglycerides. In the case of patients unstable for feeds, these

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criteria may therefore delay the diagnosis of chylothorax, leading to a delay in treatment and presumably a delay in resolution. Ruangnapa *et al.* reported a milky appearance of chest tube output in only 45% of patients diagnosed with chylothorax (2). Alternative approaches to diagnosis may be helpful in identifying chylothorax regardless of feeding status and potentially earlier than the reported median time to diagnosis 4-9 days after surgery (4-6). Moza *et al.* used chest tube output of >15 mL/kg/day on the day after chest closure as a predictor for chylothorax and reported a c-statistic of 0.80 for the development cohort and 0.84 for the external validation cohort (7). Ongoing studies within the CWG are underway to determine if there is an association between earlier diagnosis and earlier resolution of chylothorax.

The predominant treatment for chylothorax is a fat-modified diet (medium-chain triglyceride formula, defatted/fortified human milk, or low-fat diet). Ruangnapa *et al.* reported a 71% success rate in resolving chylothorax with the use of medium-chain triglyceride formulas (2). However, when a fat-modified diet alone fails to resolve chylothorax, the next step is typically nothing by mouth (NPO) with TPN. Ruangnapa *et al.* found prolonged TPN use to be associated with unfavorable outcomes (2), which is unsurprising as these are typically patients with high and/or prolonged chest tube drainage and lack of optimal enteral nutrition due to illness severity.

Complications related to chylothorax are often a result of pleural fluid losses, including volume, albumin, immunoglobulins, fat-soluble vitamins, and antithrombin, putting patients at risk for malnutrition, dehydration, infection and thrombus (8). The treatment goal of chylothorax is to decrease chest tube duration and expedite return to a regular diet. Therefore, based on the algorithm developed by the CWG, NPO duration is not a prescribed number of days. Instead, whenever chest tube volume is <10 mL/kg/day, a fat-modified diet is resumed, regardless of the NPO duration (3). If chest tube output remains high (>10–20 mL/kg/day) and/or prolonged (>7 days), secondary invasive interventions should be considered, thus minimizing NPO/TPN days and prolonged drainage.

Adjunctive conservative therapies are also frequently employed in an effort to resolve chylothorax in patients unresponsive to fat-modified diet alone. Ruangnapa *et al.* report the use of octreotide for treatment of chylothorax when dietary modification alone has failed, with an increase in use over time without a change in outcomes (2). Historically, octreotide is the most commonly utilized medication for treatment of chylothorax. As described by Ruangnapa *et al.*, the effect of octreotide is varied, and without controlled studies, it is difficult to make an association between the use of octreotide and earlier resolution. In a survey of 17 pediatric centers, 76% of respondents (n=13) reported using octreotide for chylothorax management, demonstrating its use is still more prevalent than any other medical option (9). Despite the common use of octreotide, a variety of other secondary medical management strategies have been reported. Loomba, *et al.*, in a Pediatric Health Information System (PHIS) database study, found octreotide was not associated with improved outcomes; however, steroids and furosemide were associated with shortened lengths of stay and decreased cost, and steroids were associated with fewer surgical interventions for chylothorax and decreased mortality (10).

In refractory chylothorax unresponsive to conservative therapy (chest tube drainage persists at least 10 days after diagnosis despite dietary modification and/or medications), secondary invasive interventions may be required to bring about chylothorax resolution. The gold standard for invasive intervention has become directed lymphatic interventions performed through MRI guidance. However, this option is only available at a handful of institutions worldwide. In a survey of Pediatric Cardiac Critical Care Consortium (PC4) centers, 15 of 17 respondents utilize thoracic duct ligation for refractory chylothorax, with only 8 employing lymphatic imaging/directed lymphatic interventions, which may even be an overestimate of availability of lymphatic interventions based on the centers that chose to complete the survey (8). In institutions such as Ruangnapa *et al.*'s, when thoracic duct embolization is not an option, medical options and thoracic duct ligation are often successful in treating refractory chylothorax, though resolution may be delayed.

Traditionally, patients with chylothorax will stay on a fat-modified diet for 4–6 weeks once chylothorax is resolving (chest tube output is <10 mL/kg/day) to prevent recurrence (6-8,11-15). Lengthy duration of a fat-modified diet can lead to altered nutrition, risk for poor neurodevelopmental outcomes, and parental dissatisfaction (difficulty sourcing and cost of specialty formulas, inability to breastfeed, follow-up appointments, etc.) (16-18). Optimal treatment duration must be balanced with the adverse effects of a fat-modified diet. Winder *et al.* found that 32 patients treated with a 2-week fat-modified diet after chylothorax was resolving had no recurrence of chylothorax within 30 days of resuming a regular diet, regardless of surgical complexity of chylothorax severity (19). These results were sustained across an additional 62 patients treated with a

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2-week fat-modified diet at their center, with no recurrence of chylothorax (20,21). An evaluation of shortened fat-modified diet durations across six centers in the CWG is underway.

Reported rates of postoperative chylothorax in the PC4 registry range between 0 to 10.1% (22), suggesting there are modifiable factors that may reduce the prevalence of chylothorax. Historically treatment of chylothorax has been the focus, but perhaps there are opportunities for prevention in the pre-, intra-, and early post-operative periods. The single center study provided by Ruangnapa *et al.* is a step in the right direction towards a more granular and longitudinal approach to chylothorax research.

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