**Supplemental Table 3.** Review of ancillary medical therapies used to treat chylothorax

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| Ancillary medical therapy | Annotated summary |
| Antithrombin | Anthithrombin is a key regulator and natural inhibitor of the coagulation cascade, specifically Factors IIa (thrombin), Xa, XIIa, XIa, IXa and VIIa1. Antithrombin provides an estimated 80% of the body’s inherent anticoagulant effect against thrombin, and is considered essential for heparin to be efficacious, especially in children less than one year of age2. Plasma antithrombin levels can be decreased as soon as 2-4 days after chylous pleural losses, with more significant losses appreciated with higher volume chest tube output1. Antithrombin replacement often targets serum antithrombin activity levels of 80-120%, though no studies have evaluated the effect of antithrombin replacement on thrombosis burden, morbidity or mortality in the chylothorax population. While pleural chylous loss of pro-coagulant proteins such as fibrinogen and prothrombin has been reported, children with chylothorax are more prone to thrombotic rather than hemorrhagic complications 1,3,4. |
| Albumin | Albumin is a key protein in human blood which functions to modify inflammation, maintain vascular endothelial integrity and acid-base balance, ligate endogenous and exogenous compounds, and serve as a carrier molecule for the distribution and elimination of drugs 5,6. Half of the body’s total albumin is extravascular and transported via lymphatic vessels to the vascular compartment. Multiple studies have demonstrated univariate associations between pre- and postoperative hypoalbuminemia in the pediatric cardiac surgery patient and poor outcomes including increased postoperative infections, vasoactive infusion requirements, ICU length of stay and mortality 7-9. Retrospectively, a postoperative albumin level < 3 g/dl has been identified as a clinically significant risk factor, however, albumin replacement therapy has not demonstrated mortality benefit in the pediatric cardiac population7-9. Albumin replacement appears to benefit patients whose hypoalbuminemia is driven primarily by protein loss, rather than decreased synthesis, increased catabolism or altered distribution10. With regards to chylothorax, hypoalbuminemia can be multifactorial, due to ongoing chylous losses, capillary leak from inflammation or decreased synthesis from malnutrition. |
| Furosemide | Persistently elevated central venous pressure is known to cause prolonged chylothorax refractory to conventional therapy 11. While certain surgical and postoperative states portend a sustained elevation in central venous pressure, any reduction could potentially mitigate chylous drainage. Furosemide was associated with significant decreases in LOS and need for surgical intervention in a retrospective review 3503 children with chylothorax via the PHIS database. No such effect was appreciated for other diuretics such as chlorothiazide, bumetanide or acetazolamide. Independent of its diuretic effect, furosemide is known to increase venous capacitance and decrease venous pressure due to enhanced prostaglandin synthesis 12. |
| Intravenous Immunoglobulin | Intravenous immunoglobulin is a concentrate of pooled immunoglobulins derived from thousands of healthy donors to provide sufficient IgG antibodies for humoral adaptive immunity. Depletion of lymphatic fluid can lead to low serum levels of immune globulin and lymphopenia, concerning for a immunodeficient state13. This has led to the practice of immunoglobulin replacement, though the role for intravenous immunoglobulin in secondary immune deficiency is unclear. The response to infections for patients with chylothorax, does not appear to be affected by serum lymphocyte or immunoglobulin level, although the evidence is limited to small retrospective reviews 13,14. Orange, et al hypothesized that since only 2% of total body lymphocyte count is in the peripheral blood at any moment, chylous losses may not accurately reflect cellular immunity. Hoskote et al’s review of 37 chylothoraces after pediatric cardiac surgery demonstrated no benefit to intravenous immunoglobulin regarding infection rate or outcome. The 2006 AAAI guidelines for intravenous immunoglobulin administration in the setting of secondary immunodeficiency specify empiric therapy targeting a serum IgG > 500 mg/dl only for those with a history of significant infections 15. |
| Midodrine | Midodrine is a pro-drug hydrolyzed in the intestine and plasma which agonizes alpha-1 receptors producing arterial and venous vasoconstriction with a half-life of approximately 2.5 hours16. The smooth muscle contraction induced by alpha-1 agonism may reduce the diameter of lymphatic vessels and decrease chyle flow to promote healing and closure of lymphatic channels. Evidence of use in chylothorax is limited to case reports16-18. Side effects include urinary retention and systemic hypertension. |
| Octreotide | Octreotide, a somatostatin analogue, is a polypeptide hormone with effects throughout the gastrointestinal and endocrine systems including blocking growth hormone, insulin and glucagon release. With regards to chylothorax, octreotide is theorized to reduce hepatic, portal and splanchnic blood flow resulting in decreased lymphatic circulation to promote healing of lymphatic channels, though the exact mechanism of action is unclear19,20. While small, prospective studies in pediatric cardiac surgical patients suggest octreotide may be beneficial, a 2010 Cochrane review did not recommend routine use21,22. In reviewing their experience with 178 neonatal chylothorax patients, Church et al found octreotide to not improve outcomes and increased risks of complications compared to NPO and TPN therapy alone23,24. Known side effects of octreotide include hyperglycemia, hypothyroidism, diarrhea, renal impairment, liver dysfunction and necrotizing enterocolitis23-26. |
| Propranolol | Propranolol is a non-selective beta blocker with known ability to modulate vascular endothelial growth factor for the treatment of infantile hemangiomas27. This mechanism is thought to affect the lymphatic vasculature in similar fashion28. |
| Sildenafil | Sildenafil is a phosphodistersase-5 inhibitor promoting cyclic guanosine monophosphate and vasodilation29. The mechanism of action is thought to be due to the regulation of lymphatic endothelial cells by nitric oxide, the promotion of lymphatic vessel growth via the cGMP pathway, and relaxation of the lymphatic vasculature30,31. Sildenafil has shown promise in the treatment of children with lymphatic malformations 31. |
| Medical treatment failure | After medical treatment failure, surgical approaches are often considered, though the timeline of intervention and definition of “medical treatment failure” is left to the individual providers, as is the added challenge of deciding which available imaging and procedural options are most appropriate for a given patients (MR lymphangiogram, cardiac catheterization, CT lymphatic studies, thoracic duct ligation, lymphatic embolization, pleurodesis, pleuro-peritoneal shunt). Interventions such as thoracic duct ligation, pleurodesis and pleuro-peritoneal shunt placement have reported success rates ranging from 25-95%, yet with peri-operative mortality as high as 25% 32-34. Newer interventional radiological treatments such as percutaneous thoracic duct or lymphatic vessel embolization have reported success rates as high as 70-80% in specialized centers, even after unsuccessful surgery 32,34-36. |