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REVIEW ARTICLE

Primary intestinal lymphangiectasia in children: A review

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Primary intestinal lymphangiectasia is an uncommon condition that usually presents early in childhood. This incurable condition is consequent to underlying lymphatic abnormalities that lead to loss of lymphatic contents into the intestinal lumen. This article outlines an approach to the assessment of children presenting with characteristic features and consideration of other conditions that could lead to enteric protein loss. An overview of the management of primary intestinal lymphangiectasia is outlined.

Key words: gastroenterology; lymphatic system; nutrition.

Protein-losing enteropathy (PLE) reflects increased enteric protein loss secondary to luminal, hepatic or other systemic diseases.[1] Clinical signs of the condition predominantly reflect the consequences of reduced serum albumin levels, and include peripheral oedema, ascites, pleural or pericardial effusions. PLE can be due to lymphatic dysfunction or loss of protein from the intestinal mucosa and is confirmed by elevated faecal α-1-antitrypsin levels.

Primary intestinal lymphangiectasia (PIL) is the most well characterised cause of lymphatic dysfunction leading to enteric protein loss in children.[2] Patients with PIL typically present with oedema, hypoproteinaemia, hypoalbuminaemia and hypogammaglobulinaemia.[3] PIL generally presents early in childhood: most diagnoses being made before the age of 3 years.[4] However, some individuals can present later in childhood or even as adults.

A number of other conditions can cause secondary intestinal lymphangiectasia (IL): these can be focal or generalised. These include intestinal volvulus, following repair of congenital heart disease, connective tissue disorders, sarcoidosis, inflammatory bowel disease, cancer and chromosomal abnormalities such as Turner Syndrome. Investigations are required to exclude secondary causes of intestinal lymphangiectasia, particularly in those who present later.

This review aims to highlight key aspects of the pathophysiology and management of PIL in children.

Key Points

1 Various conditions can lead to enteric protein loss, including primary intestinal lymphangiectasia (PIL).
2 PIL commonly presents with gut symptoms and features secondary to hypoalbuminaemia.
3 Dietary interventions are the most important management steps for PIL.

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Structure and Function of the Human Lymphatic System

The lymphatic system comprises a network of vessels that connect the interstitium, the vascular system, and lymphoid organs such as lymph nodes. Lymphatic channels coalesce to form a one-way system that collects lymph from the extremities and to propel it via a succession of individual lymphatic chambers that subsequently empty into the venous circulation.

The gastrointestinal (GI) tract has a particularly rich lymphatic supply, with its extensive network paralleling that of the adjacent vascular system.[5] Initial lymphatics are the entry conduit by which interstitial fluid, various cellular components and protein enter the lymphatic system. These non-fenestrated, single-layer endothelial-lined structures allow unidirectional flow of luminal contents towards collecting lymphatics.[6,7] Collecting lymphatic vessels are distinguished from initial lymphatics by the presence of smooth muscle cells[8] and they comprise functional units known as lymphatic chambers or lymphangiomas.[9]

Lymph nodes, within which adaptive immune responses are initiated, are located along the lymphatic network and are plentiful within the GI tract.[5] The GI mucosa also has additional lymphoid structures that augment host immune responses. Gut-associated lymphoid tissues (GALT) are present in the wall of the GI tract and are comprised of Peyer's patches and solitary lymphoid follicles. These local systems protect the host by inducing adaptive immune responses and lymphocyte proliferation and differentiation following exposure to luminal antigens.

The lymphatic system has three main functions: the maintenance of fluid homeostasis within tissues, immunological protection against foreign antigens, and the transport and distribution of digested lipids.[5] Lymph consists of a tenth of the fluid that

leaks out of capillary beds and enters initial lymphatics; the remaining 90% is absorbed into the venous circulation. Additionally, intestinal lymphatics also transport macromolecules synthesised within the GI tract as well as nutrients absorbed via the luminal mucosa, particularly chylomicrons. More than half of lymph is formed within the abdominal viscera, which then flows through mesenteric lymphatics before entering the thoracic duct and venous circulation. Lymphatic 'loading' of fluid and protein is directly proportional to interstitial fluid volume and solute content. Any disruption to this homeostasis can result in oedema.

The lymphatic system also provides a molecular communication system, and transportation of antigens and their presenting cells. Antigens transported via afferent lymphatics and sequestered in lymphoid structures elicit immunological responses via activation of naïve T and B lymphocytes. Upon leaving the lymph nodes these activated cells re-enter the systemic circulation and defend against foreign antigens.

The lymphatic system within the GI tract plays a crucial role in the absorption of lipids, especially long-chain triglycerides (LCT). Intraluminal digestion of LCT involves emulsification by bile salts, enzymatic hydrolysis by lipase, and reconfiguration into chylomicrons. Chylomicrons then enter the lymphatic system via lacteals. The concentration of lipids within lymph, and its flow through intestinal lymphatics, correlates with dietary lipid intake.

A recent study delineated the importance of calcitonin receptor–like receptor (Calcrl) in lymphatic function. Deletion of this receptor in lymphatic tissues resulted in intestinal lymphangiectasia, characterised by PLE and dilated lacteals with consequent inability to absorb lipids.[10] In addition, Calcrl/adrenomedullin signalling was identified as an upstream regulator of the Notch pathway, previously identified to be important in intestinal lacteal maintenance and junctional integrity.[11] Further, integrity of lacteals is essential for the structural and functional maintenance of intestinal villi, underlining the pathophysiological relevance of these processes.[12]

Clinical Presentation of PIL

PIL most frequently develops early in childhood. However, presentation has been described in adolescence,[13–15] and rarely, in adulthood.[16–20] PIL can present with peripheral oedema, ascites, GI symptoms and impaired growth. Investigations typically show immunological deficiencies, lymphopenia and hypoalbuminaemia. The condition is characterised by the presence of abnormally dilated, distorted and obstructed lymphatic vasculature. Increased hydrostatic pressure within the GI lymphatic system leads to reversal of lymph flow, resulting in the rupture of intestinal lacteals with consequent leakage of their contents into the lumen of the GI tract.

Diagnosis of PIL

In a child with suggestive symptoms, initial testing would typically reveal hypoalbuminemia, lymphopenia and hypogammaglobulinemia. Serum levels of fat-soluble vitamins may also be low and should therefore be checked. Severe vitamin D deficiency leading to tetany or hypocalcaemia has been described as a presenting feature of PIL.[21,22] Elevated faecal levels of α-1-antitrypsin are reflective of increased protein loss from the small or large intestine. Secondary causes of intestinal lymphangiectasia should be excluded, depending on the clinical scenario.

Definitive diagnosis can be obtained by histological assessment of mucosal biopsies obtained endoscopically from the duodenum. Capsule endoscopy and double-balloon enteroscopy (enabling more extensive inspection of the small bowel) have also been employed for diagnosis.[14] The typical endoscopic appearance of lymphangiectasia is of multiple white-tipped villi in the duodenum resembling snowflakes. The administration of a fat-rich meal, for instance a meal containing full cream, prior to fasting, can enhance the appearance of the villi. Dilated lacteals would typically be seen on histological examination of small bowel biopsies.

The enteroscopic appearance in individuals with PIL may have prognostic relevance.[23] One group has shown that six patients with non-white tipped villi had lower serum albumin, higher stool α-1-antitrypsin levels, higher immunoglobulin A and M, but better response to corticosteroids compared to eight individuals with white tipped villi.

Other than endoscopic and histologic findings, imaging may also have a role. For instance, intestinal technetium-dextran lymphoscintigraphy to specify the location of intestinal protein loss was described many years ago.[24]

Management of Primary Intestinal Lymphangiectasia

Currently, PIL is incurable. In secondary IL, however, the lymphatic dysfunction may be resolved by appropriate management of the underlying cause. Surgical management may be curative in mechanical causes, such as volvulus. Optimal management of other conditions, such as sarcoidosis, may improve or resolve the concurrent lymphatic dysfunction. In addition, the management options considered for PIL, especially nutritional interventions, can also be considered for secondary causes.

There are three main components to the management of PIL: nutritional, medical and surgical. Nutritional treatments are based on our understanding of the underlying pathophysiology. The other interventions are supported by data from case reports and series, with no published randomised controlled data. Successful management of intestinal lymphangiectasia does require a multidisciplinary approach, including a paediatric gastroenterologist, an experienced paediatric dietitian, a coordinating nurse and psychological support.

Nutritional intervention in PIL

As noted, LCT absorption is an important aspect of lymphatic function (reviewed in references 25–28). Consequently, the first line of management of PIL comprises the restriction of dietary LCT and the concomitant use of medium chain triglyceride (MCT)-predominant formulae or supplements.[4] Together these changes reduce intestinal lymph flow and result in less intestinal losses. The absorption of MCT via the portal venous system (bypassing the intestinal lymphatics) provides adequate dietary fat and calories. As the complete exclusion of LCT also reduces intake of essential fatty acids, these may need to be supplemented (e.g. by the use of walnut oil).

Complete restriction of LCT is very difficult to achieve as small amounts of LCT are present in many foods. In addition, maintenance of rigorous restrictions is hard to maintain, requiring first acceptance on the part of the patient and parent, and then ongoing diligent adherence. Consequently, comprehensive education, training and ongoing support from an experienced dietitian is essential.

MCT can be provided within particular enteral formula products that have high proportions of this fat. Liquid MCT products can be added to supplement dietary intake and can also be used instead of fat in cooking. Fat-soluble vitamin measurement and supplementation is required in almost all instances.

Monitoring of outcomes of nutritional interventions

The outcome of these dietary interventions should be delineated and monitored by regular and ongoing review of symptoms, physical examination (e.g. extent of oedema), anthropometry and serial measurement of albumin, immunoglobulin (Ig) G and fat-soluble vitamins. Successful management of PIL should lead to normal levels of serum albumin and IgG, resolution of peripheral oedema (or other clinical findings), resolution of diarrhoea (or other symptoms) and resumption of expected growth.

Measurement of faecal α-1-anti-trypsin provides an additional assessment of the response to dietary interventions. Treatment should lead to reduced losses, but commonly does not lead to complete normalisation.

Short- and medium-term improvements with nutritional management alone have been documented in a number of cases series. One such report outlined the impact of nutritional intervention in six children with PIL over treatment periods of up to 8 years.[29] Dietary intervention in these children led to improved gut symptoms and normal growth patterns. However, symptoms recurred upon reduced adherence to strict dietary changes. Interestingly, although clinical and growth parameters improved satisfactorily, the children continued to have elevated faecal α-1-anti-trypsin levels, further indicating that the intervention was not curative.

More recently, the impact of diet was assessed in a combined group of 38 children with PIL.[30] Overall, benefits were noted in 24 (63%) of the 38 cases reviewed, with reduced benefit noted in the adult patients.

In the setting of incomplete or unsatisfactory response to initial dietary changes, a further option is to institute complete gut rest with delivery of all nutrition parenterally. While this enables further reduction in lymphatic losses, the provision of parenteral nutrition requires ongoing intravenous access (with associated potential complications), prolonged hospitalisation to facilitate training of the patient and family and large cost implications. Furthermore, this approach requires total adherence and significant social implications.

Intravenous administration of albumin and immunoglobulin

Hypoalbuminaemia can be corrected by the administration of intravenous albumin (in conjunction with frusemide). This should be based on clinical indications (such as significantly increased ascites) rather than just upon correction above a certain threshold. A single infusion of albumin would be expected to lead to transient improvement of the albumin level and will likely need to repeated periodically.

Whilst hypogammaglobulineamia can also be partially corrected by the administration of intravenous immunoglobulin, this should only be considered in the setting of recurrent infections, as outlined in several case reports.[31,32] One such report described the benefits of subcutaneous intravenous immunoglobulin in one individual with PIL with ongoing severe hypogammaglobulinaemia.[33]

Pharmacological options for the management of PIL

Octreotide

Octreotide, a long-acting analogue of somatostatin, has been shown to be helpful in some cases of PIL.[19,34–42] The short- and longer-term response rates to octreotide have not been described. Furthermore, the precise mode of action of octreotide in the setting of PIL has not been defined: indeed, one group demonstrated that octreotide had no effect on lymphatic function in an animal model.[43]

Corticosteroids

Some individuals with PIL have had positive benefit with oral corticosteroids (prednisone or budesonide).[44–47] The main rationale for corticosteroids is due to their putative role in enteric protein losses in inflammatory conditions.

Anti-plasmin

Anti-plasmin therapy has been shown to be helpful in two individuals with PIL. The administration of tranexamic acid in an adolescent girl with PIL resistant to dietary changes and octreotide resulted in increased albumin levels and fever episodes of GI bleeding.[48] Tranexamic acid also lead to significant improvements in a young adult with PIL.[49] In this case, tranexamic acid was used after diet, octreotide and selective embolization had been tried unsuccessfully. The long-term benefits of tranexamic acid in these two cases was not clear. In addition, there are no other reports of this therapy.

Heparin

Various reports have shown reduced expression of heparin on the basolateral aspects of epithelial cells in the setting of secondary lymphangiectasia and demonstrated that supplementary heparin abrogated protein leak in *in vitro* models.[50–52] A small number of reports suggest that low dose heparin may be efficacious, particularly in secondary IL.[53–57]

Rapamycin and Everolimus

These two inhibitors of the kinase mammalian target of rapamycin have been demonstrated to be beneficial in PIL in two discrete cases. The introduction of everolimus in a 12-year child with refractory PIL resulted in resolution of diarrhoea and reduced enteric protein losses.[58] These improvements persisted over a 12-month period of treatment. Another case report outlined significant and prompt improvements in gut symptoms and enteric protein losses following the use of rapamycin in a child with concurrent tuberous sclerosis.[59]

A recent animal study provides some rationale for the use of these drugs. Rapamycin led to a reduction in lymphangiectasia in a neonatal mouse model of widespread airway lymphangiectasia, mediated by inhibition of mammalian target of rapamycin.[60]

Other medical interventions

In two separate cases, chemotherapy has been shown to result in long-term resolution of PIL. Both cases involved individuals with long-standing PIL complicated by the subsequent development of non-Hodgkin's lymphoma.[61,62] Chemotherapy for the non-Hodgkin's lymphoma in both cases resulted in ongoing resolution of enteric protein losses. The mechanism of these outcomes has not been elucidated.

Surgery

Intestinal resection has been described in some individuals with medically-intractable PIL.[63,64] As this appears to have been most useful in cases with restricted intestinal involvement rather than those with extensive or generalised changes, the role of surgical intervention is unclear. Further, the long-term outcomes of a limited resection are unclear.

Intestinal Lymphatic Hypoplasia

Intestinal lymphatic hypoplasia, characterised by the absence or marked reduction in intestinal lymphatics, can resemble PIL, but lymphopenia is not typically present.[65,66]

The advent of D2-40 antibody, which binds a sialoglycoprotein present on human lymphatic endothelium, has enabled the characterisation of this condition.[67,68] Among the patients included in an Australian cohort, the extent and severity of lymphatic hypoplasia varied, with some correlation to the severity of the clinical features.[68] The approach and management concepts for this entity are generally similar to those described for PIL.

Conclusion

PIL is a rare condition that mainly presents in early childhood. Multiple investigations are required to confirm the diagnosis and to characterise the impact of the condition. Although there is no high-level evidence to support specific therapies, the mainstay of management involves nutritional interventions with consideration of other supportive and therapeutic interventions.

References

1 Levitt DG, Levitt MD. Protein losing enteropathy: Comprehensive review of the mechanistic association with clinical and subclinical disease states. *Clin. Exp. Gastroenterol.* 2017; **10**: 147–68.
2 Walker-Smith JA, Murch S. *Disease of the Small Intestine in Childhood*, 4th edn. Oxford: ISIS; 1999.
3 Waldmann TA, Steinfeld JL, Dutcher TF, Davidson JD, Gordon RS Jr. The role of the gastrointestinal system in "idiopathic hypoproteinemia". *Gastroenterology* 1961; **41**: 197–207.
4 Vignes S, Bellanger J. Primary intestinal lymphangiectasia (Waldmann's disease). *Orphanet J. Rare Dis.* 2008; **3**: 5.
5 Von der Weid PY, Day AS. Pediatric lymphatic development and intestinal lymphangiectasia. In: Kuipers EJ, ed. *Encylopedia of Gastroenterology*, 2nd edn. USA: Elsevier; 2019; 158–69.
6 Azzali G, Arcari ML. Ultrastructural and three dimensional aspects of the lymphatic vessels of the absorbing peripheral lymphatic apparatus in Peyer's patches of the rabbit. *Anat. Rec.* 2000; **258**: 71–9.
7 Casley-Smith JR. The role of the endothelial intercellular junctions in the functioning of the initial lymphatics. *Angiologica* 1972; **9**: 106–31.
8 Baluk P, Fuxe J, Hashizume H *et al*. Functionally specialized junctions between endothelial cells of lymphatic vessels. *J. Exp. Med.* 2007; **204**: 2349–62.
9 Florey HW. Observations on the contractility of lacteals. Part I. *J. Physiol.* 1927; **62**: 267–72.
10 Davis RB, Kechele DO, Blakeney ES, Pawlak JB, Caron KM. Lymphatic deletion of calcitonin receptor-like receptor exacerbates intestinal inflammation. *JCI Insight* 2017; **2**: e92465.
11 Bernier-Latmani J, Cisarovsky C, Demir CS *et al*. DLL4 promotes continuous adult intestinal lacteal regeneration and dietary fat transport. *J. Clin. Invest.* 2015; **125**: 4572–86.
12 Jang JY, Koh YJ, Lee SH *et al*. Conditional ablation of LYVE-1+ cells unveils defensive roles of lymphatic vessels in intestine and lymph nodes. *Blood* 2013; **122**: 2151–61.
13 Wang X, Jin H, Wu W. Primary intestinal lymphangiectasia manifested as unusual edemas and effusions: A case report. *Medicine* 2016; **95**: e2849.
14 Oh TG, Chung JW, Kim HM *et al*. Primary intestinal lymphangiectasia diagnosed by capsule endoscopy and double balloon enteroscopy. *World J. Gastrointest. Endosc.* 2011; **3**: 235–40.
15 Surampalli V, Ramaswamy S, Surendran D, Bammigatti C, Swaminathan RP. Primary intestinal lymphangiectasia (Waldmann's disease) presenting with chylous effusions in a 15-year-old. *J. Clin. Diagn. Res.* 2017; **11**: OD17–OD8.
16 Lu J, Zhai H. Exacerbation of primary intestinal lymphangiectasia during late pregnancy and recovery after delivery: A case report and literature review. *Medicine* 2017; **96**: e7928.
17 Freeman HJ, Nimmo M. Intestinal lymphangiectasia in adults. *World J. Gastrointest. Oncol.* 2011; **3**: 19–23.
18 Huber X, Degen L, Muenst S, Trendelenburg M. Primary intestinal lymphangiectasia in an elderly female patient: A case report on a rare cause of secondary immunodeficiency. *Medicine* 2017; **96**: e7729.
19 Filik L, Oguz P, Koksal A, Koklu S, Sahin B. A case with intestinal lymphangiectasia successfully treated with slow-release octreotide. *Dig. Liver Dis.* 2004; **36**: 687–90.
20 Herfarth H, Hofstadter F, Feuerbach S *et al*. A case of recurrent gastrointestinal bleeding and protein-losing gastroenteropathy. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 2007; **4**: 288–93.
21 Lu YY, Wu JF, Ni YH *et al*. Hypocalcemia and tetany caused by vitamin D deficiency in a child with intestinal lymphangiectasia. *J. Formos. Med. Assoc.* 2009; **108**: 814–8.
22 Van Biervliet S, Velde SV, Robberecht E, Van Winckel M. Hypocalcaemic seizures: Sign of intestinal disease? *Acta Gastroenterol. Belg.* 2007; **70**: 243–4.
23 Ohmiya N, Nakamura M, Yamamura T *et al*. Classification of intestinal lymphangiectasia with protein-losing enteropathy: White villi type and non-white villi type. *Digestion* 2014; **90**: 155–66.
24 Bhatnagar A, Lahoti D, Singh AK, Shankar LR, Sharma B, Singh T. Scintigraphic diagnosis of protein losing enteropathy using Tc-99m dextran. *Clin. Nucl. Med.* 1995; **20**: 1070–3.
25 Tso P, Balint JA. Formation and transport of chylomicrons by enterocytes to the lymphatics. *Am. J. Physiol.* 1986; **250** (6 Pt 1): G715–26.
26 Phan CT, Tso P. Intestinal lipid absorption and transport. *Front. Biosci.* 2001; **6**: D299–319.
27 Nordskog BK, Phan CT, Nutting DF, Tso P. An examination of the factors affecting intestinal lymphatic transport of dietary lipids. *Adv. Drug Deliv. Rev.* 2001; **50**: 21–44.
28 Tso P, Nauli A, Lo CM. Enterocyte fatty acid uptake and intestinal fatty acid-binding protein. *Biochem. Soc. Trans.* 2004; **32** (Pt 1): 75–8.

29 Tift WL, Lloyd JK. Intestinal lymphangiectasia long-term results with MCT diet. *Arch. Dis. Child.* 1975; **50**: 269–76.
30 Wen J, Tang Q, Wu J, Wang Y, Cai W. Primary intestinal lymphangiectasia: Four case reports and a review of the literature. *Dig. Dis. Sci.* 2010; **55**: 3466–72.
31 Kagiyama Y, Kishimoto S, Yoshimoto H, Kudo Y, Gotoh K, Suda K. Successful combined intravenous and subcutaneous immunoglobulin treatment for intractable protein-losing enteropathy in a patient long after Fontan-type operation. *J. Cardiol. Cases* 2018; **17**: 52–5.
32 Lan J, Eshun J, Lieberman JA. Identical twins with XLA requiring differing amounts of 20% subcutaneous immunoglobulin secondary to protein-losing enteropathy. *J. Allergy Clin. Immunol.* 2018; **6**: 1073–4.
33 Patuzzo G, Tinazzi E, Micheletti M, Puccetti A, Lunardi C. Secondary hypogammaglobulinemia in Waldmann's disease treated with subcutaneous immunoglobulins. *Eur. Ann. Allergy Clin. Immunol.* 2016; **48**: 55–7.
34 Suehiro K, Morikage N, Murakami M, Yamashita O, Hamano K. Late-onset primary intestinal lymphangiectasia successfully managed with octreotide: A case report. *Ann. Vasc. Dis.* 2012; **5**: 96–9.
35 Bac DJ, Van Hagen PM, Postema PTE, Zondervan PE, van Blankenstein M. Octreotide for protein-losing enteropathy with intestinal lymphangiectasia. *Lancet* 1995; **345**: 1639.
36 Al Sinani S, Rawahi YA, Abdoon H. Octreotide in Hennekam syndrome-associated intestinal lymphangiectasia. *World J. Gastroenterol.* 2012; **18**: 6333–7.
37 Altit G, Patel H, Morinville VD. Octreotide management of intestinal lymphangiectasia in a teenage heart transplant patient. *J. Pediatr. Gastroenterol. Nutr.* 2012; **54**: 824–7.
38 Kuroiwa G, Takayama T, Sato Y *et al*. Primary intestinal lymphangiectasia successfully treated with octreotide. *J. Gastroenterol.* 2001; **36**: 129–32.
39 Lee HL, Han DS, Kim JB, Jeon YC, Sohn JH, Hahm JS. Successful treatment of protein-losing enteropathy induced by intestinal lymphangiectasia in a liver cirrhosis patient with octreotide: A case report. *J. Korean Med. Sci.* 2004; **19**: 466–9.
40 Klingenberg RD, Homann N, Ludwig D. Type I intestinal lymphangiectasia treated successfully with slow-release octreotide. *Dig. Dis. Sci.* 2003; **48**: 1506–9.
41 John AS, Phillips SD, Driscoll DJ, Warnes CA, Cetta F. The use of Octreotide to successfully treat protein-losing enteropathy following the Fontan operation. *Congenit. Heart Dis.* 2011; **6**: 653–6.
42 Sari S, Baris Z, Dalgic B. Primary intestinal lymphangiectasia in children: Is octreotide an effective and safe option in the treatment? *J. Pediatr. Gastroenterol. Nutr.* 2010; **51**: 454–7.
43 Makhija S, von der Weid PY, Meddings J, Urbanski SJ, Beck PL. Octreotide in intestinal lymphangiectasia: Lack of a clinical response and failure to alter lymphatic function in a guinea pig model. *Can. J. Gastroenterol.* 2004; **18**: 681–5.
44 Fleisher TA, Strober W, Muchmore AV, Broder S, Krawitt EL, Waldmann TA. Corticosteroid-responsive intestinal lymphangiectasia secondary to an inflammatory process. *N. Engl. J. Med.* 1979; **300**: 605–6.
45 Hoashi T, Ichikawa H, Ueno T, Kogaki S, Sawa Y. Steroid pulse therapy for protein-losing enteropathy after the Fontan operation. *Congenit. Heart Dis.* 2009; **4**: 284–7.
46 Thacker D, Patel A, Dodds K, Goldberg DJ, Semeao E, Rychik J. Use of oral budesonide in the management of protein-losing enteropathy after the Fontan operation. *Ann. Thorac. Surg.* 2010; **89**: 837–42.
47 Schumacher KR, Cools M, Goldstein BH *et al*. Oral budesonide treatment for protein-losing enteropathy in Fontan-palliated patients. *Pediatr. Cardiol.* 2011; **32**: 966–71.
48 MacLean JE, Cohen E, Weinstein M. Primary intestinal and thoracic lymphangiectasia: A response to antiplasmin therapy. *Pediatrics* 2002; **109**: 1177–80.
49 Balaban VD, Popp A, Grasu M, Vasilescu F, Jinga M. Severe refractory anemia in primary intestinal lymphangiectasia. A case report. *J. Gastrointestin. Liver Dis.* 2015; **24**: 369–73.
50 Bode L, Salvestrini C, Park PW *et al*. Heparan sulfate and syndecan-1 are essential in maintaining murine and human intestinal epithelial barrier function. *J. Clin. Invest.* 2008; **118**: 229–38.
51 Bode L, Eklund EA, Murch S, Freeze HH. Heparan sulfate depletion amplifies TNF-alpha-induced protein leakage in an in vitro model of protein-losing enteropathy. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2005; **288**: G1015–23.
52 Bode L, Murch S, Freeze HH. Heparan sulfate plays a central role in a dynamic in vitro model of protein-losing enteropathy. *J. Biol. Chem.* 2006; **281**: 7809–15.
53 Facchini M, Guldenschuh I, Turina J, Jenni R, Schalcher C, Attenhofer Jost CH. Resolution of protein-losing enteropathy with standard high molecular heparin and urokinase after Fontan repair in a patient with tricuspid atresia. *J. Cardiovasc. Surg.* 2000; **41**: 567–70.
54 Bendayan I, Casaldaliga J, Castello F, Miro L. Heparin therapy and reversal of protein-losing enteropathy in a case with congenital heart disease. *Pediatr. Cardiol.* 2000; **21**: 267–8.
55 Bhagirath KM, Tam JW. Resolution of protein-losing enteropathy with low-molecular weight heparin in an adult patient with Fontan palliation. *Ann. Thorac. Surg.* 2007; **84**: 2110–2.
56 Ryerson L, Goldberg C, Rosenthal A, Armstrong A. Usefulness of heparin therapy in protein-losing enteropathy associated with single ventricle palliation. *Am. J. Cardiol.* 2008; **101**: 248–51.
57 Liem YS, Bode L, Freeze HH, Leebeek FW, Zandbergen AA, Paul WJ. Using heparin therapy to reverse protein-losing enteropathy in a patient with CDG-Ib. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 2008; **5**: 220–4.
58 Ozeki M, Hori T, Kanda K *et al*. Everolimus for primary intestinal lymphangiectasia with protein-losing enteropathy. *Pediatrics* 2016; **137**: e20152562.
59 Pollack SF, Geffrey AL, Thiele EA, Shah U. Primary intestinal lymphangiectasia treated with rapamycin in a child with tuberous sclerosis complex (TSC). *Am. J. Med. Genet. A* 2015; **167A**: 2209–12.
60 Baluk P, Yao LC, Flores JC, Choi D, Hong YK, McDonald DM. Rapamycin reversal of VEGF-C-driven lymphatic anomalies in the respiratory tract. *JCI Insight* 2017; **2**: e90103.
61 Shpilberg O, Shimon I, Bujanover Y, Ben-Bassat I. Remission of malabsorption in congenital intestinal lymphangiectasia following chemotherapy for lymphoma. *Leuk. Lymphoma* 1993; **11**: 147–8.
62 Broder S, Callihan TR, Jaffe ES *et al*. Resolution of longstanding protein-losing enteropathy in a patient with intestinal lymphangiectasia after treatment for malignant lymphoma. *Gastroenterology* 1981; **80**: 166–8.
63 Kim NR, Lee SK, Suh YL. Primary intestinal lymphangiectasia successfully treated by segmental resections of small bowel. *J. Pediatr. Surg.* 2009; **44**: e13–7.
64 Connor FL, Angelides S, Gibson M *et al*. Successful resection of localized intestinal lymphangiectasia post-Fontan: Role of (99m)technetium-dextran scintigraphy. *Pediatrics* 2003; **112**: e242–7.
65 Hardikar W, Smith AL, Chow CW. Neonatal protein-losing enteropathy caused by intestinal lymphatic hypoplasia in siblings. *J. Pediatr. Gastroenterol. Nutr.* 1997; **25**: 217–21.
66 Stormon MO, Mitchell JD, Smoleniec JS, Tobias V, Day AS. Congenital intestinal lymphatic hypoplasia presenting as non-immune hydrops in utero, and subsequent neonatal protein-losing enteropathy. *J. Pediatr. Gastroenterol. Nutr.* 2002; **35**: 691–4.
67 Kahn HJ, Marks A. A new monoclonal antibody, D2-40, for detection of lymphatic invasion in primary tumors. *Lab. Invest.* 2002; **82**: 1255–7.
68 Zeng Y, Wang F, Williams ED, Chow CW. Lymphatics in the alimentary tract of children in health and disease: Study on mucosal biopsies using the monoclonal antibody d2-40. *Pediatr. Dev. Pathol.* 2005; **8**: 541–9.