

REVIEW

Mesenteric Lymph: The Bridge to Future Management of Critical Illness

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Summary

Toxic factors released from the intestine have been implicated in the pathophysiology of severe acute illness, including acute pancreatitis, trauma and hemorrhagic shock, and burns. Toxic factors in mesenteric lymph may induce an inflammatory systemic response while bypassing the portal circulation and liver. This paper reviews current knowledge of the anatomy, physiology and pathophysiology of mesenteric lymph and focuses on factors influencing its composition and flow, and potential therapeutic interventions.

A search of the Ovid MEDLINE database up until the end of January 2006 yielded 1,761 relevant publications, the references of which were then searched manually to identify further related publications.

A wide range of factors potentially affecting mesenteric lymph flow and composition were identified. Targeted interventions have been similarly broad, including medical therapy, nutritional support and surgery. Of the available surgical interventions, thoracic duct external drainage has been the most widely studied.

This systematic review highlights significant gaps in our present understanding of the role of mesenteric lymph in health and disease. Further research is needed to identify factors responsible for the generation of biologically active mesenteric lymph, the role of agents

modulating its flow and composition, the importance of intrinsic pump activity, the potential therapeutic role of lipophilic antioxidant agents, the comparative effects of low-fat enteral nutrition and standard enteral nutrition, and the therapeutic outcomes of thoracic duct ligation *versus* thoracic duct external drainage.

Introduction

The intestine has been implicated in the pathophysiology of severe acute illness, including acute pancreatitis [1], trauma and hemorrhagic shock [2], and thermal injuries [3]. The orthodox view is that development of a systemic inflammatory response and multiple organ dysfunction in these contexts is due to a failure in the intestinal barrier, bacterial translocation, portal bacteremia and endotoxemia [4]. The potential for toxic intestinal factors to influence other splanchnic organs and induce a systemic response via mesenteric lymph while bypassing the portal circulation and liver is a more recent concept [2]. This paper reviews the current state of knowledge regarding the anatomy, physiology and pathophysiology of mesenteric lymph. Particular attention is given to factors that influence mesenteric lymph composition and flow in acute illness, and how these might lead to new therapeutic approaches.

Methods

A search of the Ovid MEDLINE database through to January 2005 was done using the following search terms: mesentery, pancreas, bowel, small intestine, lymphatic system, intestinal lymph, mesenteric lymph, structure, composition and physiology. The search yielded 1,761 potentially relevant papers. The "Related References" feature of PubMed was used to identify further references. A manual search of citations for all pertinent references was also done to identify older papers.

Historical Perspectives

The earliest known description of lymphatic vessels in the small intestine comes from the writings of the Alexandrian school (Herophilus, 335-280 BC and Erasistratus, 310-250 BC) [5, 6, 7]. Galen (129-199 AD) subsequently observed the intestinal lacteals when dissecting primates. Centuries later in 1622, Gasparo Aselli visualized the lacteals as "thin and beautiful white cords" in a well-fed dog and thought that he had discovered a fourth type of circulation. Aselli went on to demonstrate a relationship between lacteals and meals in unfed and fed dogs, and confirmed it in the human body by observing lacteals in a criminal executed after a large meal [7, 8, 9].

The earliest drawings of human lacteals appear in works by Johann Veslingius dated 1647 [6]. Four years later, Jean Pecquet demonstrated flow of lymph from the intestinal lacteals to the cisterna chyli and thoracic duct in dogs [9] and humans [6]. The term "lymphatics" was coined in 1653 by Bartholinus who, along with others, delineated the topography of lymphatics in various organs. In 1692, Anton Nück described the use of mercury injection to delineate fine lymphatic vessels and in 1787 Paolo Mascagni used this technique to map them, producing an elegant atlas of lymphatic anatomy. Philibert Sappey was possibly the first to count the valves of the lymphatics in 1874 [6].

These early anatomic studies paved the way for investigation of the physiologic function

of lymphatics in the nineteenth and twentieth centuries. In 1858 Carl Ludwig postulated that lymph was a filtrate derived from the blood via the capillary wall by intracapillary pressure. In 1891 Rudolf Heidenhain challenged this hypothesis, contending that lymph was an active secretion by the lymphatic endothelium [5]. Ernest Starling settled this debate by demonstrating that lymph is produced by the production of interstitial fluid due to the forces governing fluid movement across the capillary wall. These forces were the hydrostatic and colloid osmotic pressures both inside and outside the blood capillaries [8].

During the first half of the twentieth century, Drinker, Yoffey and Courtice [10] did a series of experiments on the lymphatic system using newly introduced electrophoretic techniques to investigate the protein fractions in plasma and lymph in different animal species. Moreover, they conducted experiments on the time-course of attaining equilibrium between plasma and lymph protein concentrations, and how this was affected by food intake and intravenous (i.v.) infusions of electrolyte solutions and vasoconstrictor drugs. They also estimated the daily bulk flow of lymph and extravascular protein in patients with thoracic duct fistulae.

Two developments in the second half of the twentieth century have further refined our understanding of mesenteric lymph. These were the development of organ transplantation and the evolving understanding that the intestine is not merely a passive bystander in critical illness, but may actually contribute to its severity. In transplantation research in the 1960s and 70s, there was an attempt to reduce the risk of organ rejection by depletion of lymphocytes using long term drainage of the thoracic duct [11, 12]. This approach found some acceptance in renal transplantation [13, 14]. Because thoracic duct drainage was typically performed three to four weeks before transplantation, there was the opportunity to study factors that influenced thoracic duct lymph volume and composition, including lymphocytes.

The putative role of the intestine in the development of multiorgan failure in critically ill patients has been the subject of considerable investigation and debate. The initial focus was on bacterial translocation [2], but recent studies have extended the gut hypothesis beyond that, implicating mesenteric lymph rather than portal vein blood [15], as the exit route of gut-derived nonbacterial inflammatory factors. Unlike thoracic duct lymph, mesenteric lymph comes solely from the bowel with no contribution from other organs. This has provided direct and compelling evidence that the intestine is the source of the injurious factors.

Deitch *et al.* suggested that the intestinal contribution to distant organ injury in severe acute illness is mediated by a number of events or “multiple hits” [16]. The first hit is intestinal ischemia, due to splanchnic vasoconstriction. This is followed by a reperfusion injury with resuscitation (second hit). The third hit arises from the interaction between pancreatic proteases and the ischemic bowel. The fourth hit results from translocation of intestinal bacteria and their products from the intestinal lumen into the gut wall where they can exacerbate the biological activity of mesenteric lymph.

Anatomy and Physiology

The central lacteal of the intestinal villus starts near the villus tip and courses axially down towards a network of submucosal lymphatic vessels. This network also receives tributaries from a plexus of lymphatic capillaries surrounding Peyer’s patches. The networks collectively form the efferent lymphatic trunks [5, 17] which then pass through mesenteric lymph nodes, often situated at the confluence of these trunks.

Mesenteric lymph nodes are small, bean-shaped structures lying along the course of lymphatic vessels. They act as a filter for particulate matter and micro-organisms, and are the site of antigen presentation. Mesenteric lymph nodes have three components: lymphatic sinuses, blood vessels and parenchyma (cortex, paracortex and medulla). They contain lymphocytes (B- and

T-cells), as well as macrophages and dendritic cells.

Mesenteric lymph nodes have been studied extensively in the context of bacterial translocation from the gastrointestinal tract, mainly in animals and *in vitro* models [18]. Recently, Reddy *et al.* confirmed the translocation of commensal bacteria to mesenteric lymph nodes in surgical patients [19], reporting that induction of IgA to commensal bacteria is confined to the mucosal immune system without systemic involvement, and that the extra-intestinal inflammatory response occurs when the host is immunocompromised or systemically ill.

In approximately two-thirds of patients the intestinal lymph trunk, which drains lymph from the stomach, intestines, pancreas, spleen and visceral surface of the liver, joins the right and left lumbar lymph trunks and smaller lymphatics from retroperitoneal structures to form the cisterna chyli. In a third of cases the intestinal trunk joins the left lumbar trunk and there is no cisterna chyli [20].

The cisterna chyli is located in front of the first and second lumbar vertebrae with the aorta on the left and the right crus of the diaphragm on the right [21]. The cisterna chyli is a thin-walled structure which collapses in cadavers, so it was initially difficult to define its shape. Heavy T2-weighted magnetic resonance cholangio-pancreatography images were used to define the shape and size of the cisterna chyli *in vivo*. The most common shapes were tubular (42.5%) plexiform (19.1%) and deltaic (12.5%). The mean (\pm standard deviation) longitudinal, anteroposterior, and transverse diameters were 33.45 ± 1.74 mm, 5.20 ± 0.13 mm and 5.23 ± 0.15 mm, respectively [22].

The thoracic duct, exiting from the cisterna chyli, ascends into the thorax via the aortic hiatus and through the posterior mediastinum between the azygos vein and the aorta, on the anterior surface of the vertebral bodies. At the level of the fifth thoracic vertebra it curves to the left, enters the superior mediastinum posterior to the arch of the aorta, and continues upwards on the left side of the

esophagus behind the left subclavian artery. At the root of the neck, the duct swings forward to drain into the neck veins, usually described as the junction of the left subclavian and internal jugular veins [21]. However, the termination of the thoracic duct varies extensively. Kinnaert dissected 529 cadavers and found that the most common terminations of the thoracic duct were the internal jugular vein in 36% of the cases, the jugulo-subclavian junction in 34%, and the subclavian vein in 17% [20]. He also reported that thoracic duct termination was multiple in 21% of cases and that the thoracic duct occasionally bifurcated high in the thorax, with the left branch terminating as discussed earlier and the right branch diverging to join one of the right lymph trunks or even the right lymphatic duct, and the combined vessels emptying into the right subclavian vein.

The mean diameter of the thoracic duct is 5 mm at its abdominal origin and 4 mm at its termination in the neck, and its length is approximately 45 cm. A study in 30 cadavers has shown that the thoracic duct contains an average of 14.7 valves [23]. This means that there is a valve every 3 cm along the length of the thoracic duct. At its termination there is a bicuspid valve to stop or diminish reflux of blood [20].

Valves allow the unidirectional transport of fluid from the interstitium into the initial lymphatics (irregular tissue cervices lined by a continuous attenuated endothelium) and then into the contractile lymphatics (containing a muscular wall capable of both tonic and phasic contraction). Schmid-Schonbein suggested that the initial lymphatics have a two-valve system, comprising a primary valve system at the level of the endothelium which prevents fluid escape into the interstitial space and a secondary intralymphatic valve system which prevents reflow along the lymphatic vessel [24].

The lymphangion is the morphologic-functional unit of the lymphatic vessels [6, 25, 26]. It consists of a segment of lymphatic vessel located between two valves; the peripheral one belongs to one lymphangion

and the central to the following one [26]. The presence of valves and ampullary dilatation between them gives larger lymph vessels a beaded appearance. These vessels have smooth muscle in the regions between valves, but at the origin of the valves the lymphatic wall has little or no smooth muscle [8].

Anastomoses between the lymphatic vessels and veins have been described in various animal species [27, 28, 29] and are of potential physiologic and pathologic significance. Some studies have suggested that such communications only occur when there is obstruction to lymphatic flow [30, 31, 32, 33, 34]. Human studies have been limited to cancer patients and cadavers [35, 36, 37]. In his review of these studies, Barrowman concluded that lymphovenous communications do exist but only function with elevated lymphatic pressure [8]. It has further been suggested that these lymphovenous shunts are also located within the lymph nodes [38, 39, 40], but their pathophysiological significance has not been explored.

Mesenteric lymph vessels and nodes are innervated by autonomic nerves [41, 42]. There is evidence of a dual (cholinergic and adrenergic) supply [41] but the innervation is less dense in lymphatics than in veins and arteries, lower in colon than in small bowel [43], and lower in mesenteric nodes than other lymph nodes [44]. Adrenergic innervation of bovine mesenteric lymph has been shown to be capable of modulating lymphatic vasomotion as well as controlling lymph flow [45].

Mesenteric Lymph Composition

Studies of mesenteric lymph composition have been in the context of lymphatic leaks and chylomas [46, 47]. Changes in mesenteric lymph composition reflect its functions of maintaining fluid homeostasis [25] and blood pressure [48] by returning interstitial fluid to the systemic circulation. Mesenteric lymph also transports macromolecules and lipids [49], fat soluble vitamins [50] and water insoluble compounds [51]. In addition, mesenteric lymph has an important role in the immune response [52]. The composition of

mesenteric lymph will be discussed with reference to its non-protein (electrolytes and lipids), protein (enzymes, hormones, iron, coagulation factors) and cellular components.

Electrolytes

The electrolyte composition of thoracic duct lymph has been meticulously studied by Yoffey and Courtice [5] who presented the average values in fasting human subjects [53, 54, 55]. Total cations were marginally lower and total anions (chloride and bicarbonate) were higher in lymph than in plasma. These differences in ion concentration probably reflect the differences in protein composition between plasma and lymph, and are governed by the Gibbs-Donnan equilibrium. Calcium and magnesium concentrations are affected by their binding to proteins. Urea and creatinine concentration in lymph is similar to that in plasma [5]. Iron concentration in mesenteric lymph is increased by oral [56, 57, 58] and i.v. [59] administration of iron and is probably bound to transferrin, as in plasma.

Lipids

The lipid composition of mesenteric lymph has been studied extensively, particularly in relation to fat absorption or chylous effusion. The lipid content of intestinal lymph fluctuates widely depending on the type, extent and timing of fat ingestion. Chyle is a complex mixture of lymph and chylomicrons. Chylomicrons are the largest (1,000 nm) and the least dense (less than 0.95) of the lipoproteins. They are made up of 85 to 88% triglycerides, and approximately 8% phospholipids, 3% cholesterol esters, 1 to 2% proteins and 1% cholesterol. Chylomicrons contain several types of apolipoproteins including apo-AI, II and IV, apo-B48, apo-CI, II and III, apo-E and apo H. In chylous effusion cholesterol to triglyceride ratios are typically less than one. Fluid to serum triglyceride ratios greater than 2-3:1 are diagnostic for chylous effusion; ratios of 10-20:1 are commonly encountered [60].

Proteins

The protein and amino acid content of mesenteric lymph is relatively high but less

than hepatic lymph [61, 62] and is usually around half the protein concentration of plasma [5]. Yoffey and Courtice measured the protein content of lymph from various body regions in different animal species. In dogs for example, the average protein content of lymph from small bowel, liver and plasma was 3.2, 4.8 and 6.18 g/100 mL, respectively [5]. This mesenteric lymph protein is derived from the plasma proteins, all of which are present in different proportions. Another important class of proteins are the immunoglobulins derived from the plasma cells of the lamina propria in the intestinal mucosa and mesenteric lymph nodes [8, 62]. Lymph clots, but less readily than plasma. The concentrations of fibrinogen and prothrombin in lymph vary, but are generally lower than the plasma concentration [5]. Most investigators have studied the coagulation factors of thoracic duct lymph rather than mesenteric lymph. Mann *et al.* reported profound hypoprothrombinemia following drainage of mesenteric lymph in rats for 24 hours, which was corrected by i.v. administration of vitamin K despite the ongoing lymph loss [63]. Hanley *et al.* measured activated partial thromboplastin time and prothrombin times in sheep mesenteric lymph and found that both were more prolonged in mesenteric lymph than in plasma [64].

Enzymes

A wide range of enzymes has been described in mesenteric lymph and thoracic duct lymph. The concentration of many enzymes is higher in lymph than in plasma. Lindena *et al.* summarized these studies in man and in four different animal species [65]. They examined the concentrations of 16 enzymes in thoracic duct lymph and mesenteric lymph and concluded that these enzymes are primarily released from tissue cells into the interstitial space.

Alkaline phosphatase catalyzes hydrolysis of phosphoric esters and is a good example of an enzyme released by cells primarily into the interstitial space. The intestinal mucosa has a high concentration of alkaline phosphatase

[66] which accounts for the higher concentration of alkaline phosphatase in mesenteric lymph than in plasma. The activity of alkaline phosphatase in plasma is greatly diminished following draining of mesenteric lymph, suggesting that mesenteric lymph is an important source of alkaline phosphatase [67]. It has been found that alkaline phosphatase concentration in both plasma and mesenteric lymph increases after meals containing fat. This increased alkaline phosphatase activity in mesenteric lymph is greatly reduced or abolished if bile is excluded from the intestine [68].

Another example is pancreatic amylase which is secreted into the pancreatic duct then enters the intestinal lumen. To a much lesser extent this enzyme enters the pancreatic interstitial fluid and reaches the circulation via thoracic duct lymph. Amylase was found to be always present in the thoracic duct lymph of normal subjects [69] and its concentration to vary with fasting and feeding status [66]. Although it has been suggested that the amylase in thoracic duct lymph could come from sources other than the pancreas, several investigators have shown that this amylase is pancreatic in origin. Dumont *et al.* studied human thoracic duct lymph amylase levels in both the resting and stimulated pancreas and found that i.v. secretin produced a marked increase in thoracic duct lymph amylase concentration without significant changes in serum amylase levels [70]. They also reported that morphine co-administered with secretin augmented this effect and that a sharp rise in thoracic duct lymph amylase levels occurred during gentle handling of the pancreas.

Bartos *et al.* studied 40 fasting patients with a variety of gastrointestinal diseases, and reported that amylase levels in thoracic duct lymph exceeded those in blood when the pancreas was stimulated by administration of a combination of secretin and pancreozymin or secretin and morphine [71]. Following thoracic duct lymph diversion, the increase in serum amylase in response to pancreatic stimulation was markedly diminished.

Singh *et al.* suggested that the liver and the small intestine make no contribution to serum

amylase via the lymph, reporting that the increase of serum and lymph amylase following i.v. secretin is abolished by pancreatectomy in dogs [72].

Certain lysosomal enzymes appear in thoracic duct lymph in shock and have been implicated in the pathogenesis of distant organ failure. Details of relevant experiments are discussed later in this review.

Hormones

The hormonal composition of mesenteric lymph has been studied. Insulin levels have been found to be consistently lower in thoracic duct lymph than in plasma in both humans [73] and animal models [74, 75, 76]. This suggests that most lymphatic insulin is derived from the plasma by filtration. Another possible source of insulin in thoracic duct lymph is pancreatic lymph. Lymphatic transport of insulin bypasses the liver, which is known to clear 40 to 50% of insulin transported via portal blood. The i.v. administration of glucose did not produce increased insulin levels in cisterna chyli lymph in rats [74] or in thoracic duct lymph in dogs [77], confirming that insulin enters the circulation primarily by direct secretion rather than by lymphatic transport. Other intestinal hormones have been detected in thoracic duct lymph and are all present at low concentrations in the resting state. Svatos *et al.* reported that cholecystokinin levels were very low in fasting patients with gastrointestinal disease, but increased significantly after intraduodenal infusion of sorbitol [78]. Whether or not there is any physiologic role for hormones in mesenteric lymph has not been determined.

Cells

Gut-associated lymphoid tissue (GALT) is an important secondary lymphoid tissue. It makes a major contribution to the lymphocytes present in mesenteric lymph, thoracic duct lymph and the systemic circulation. It was first demonstrated in rabbits in 1940 by Erf, who showed that removal of the stomach and intestine produced lymphopenia which was not

Table 1. Factors affecting mesenteric lymph flow.

Factors	Decrease mesenteric lymph flow	Increase mesenteric lymph flow
Diet	Low fat diet [46, 219]	Lipids [190, 202]
Nutrition	Fasting [220]	Feeding [220, 221]
Absorption	Net fluid secretion [193]	Net fluid absorption [8, 222]
Fluids	Intra-arterial hypertonic glucose [223] Continuous plasma dilution [192, 193]	Saline infusion [193, 224] Ringer's [225] Plasma dilution [193]
Pressure	Arterial hypotension [226] Primary intra-abdominal hypertension [227] Increased neck vein pressure [225, 228]	Venous hypertension [229] Secondary intra-abdominal hypertension [227] Intra-enteric distension [230, 231] Massage [231]
Temperature	Hypothermia [232]	Rewarming [167, 232]
Oxygen	100% oxygen [233]	Hypoxia [79]
Hormones/ Peptides	Vasopressin [234] Glucagon-like peptide [235] Serotonin (high concentration) [236, 237] Vasointestinal peptide [238] Octreotide [239]	Cholecystokinin [240, 241] Glucagon [242] Serotonin (low concentration) [236] Secretin [243] Histamine [244] Prostaglandin E1 (PgE1) [245] Bradykinin [279]
Drugs	Acetylcholine [237] Theophylline [238] Sodium pentobarbital [236, 237]	Ether [120] Diuretics (mannitol > ethacrynic acid > furosemide) [180] Physostigmine [236, 246] Epinephrine (decrease then increase) [236] Norepinephrine (increase then decrease) [247] Ephedrine (prevented by atropine) [248] Methacholine (prevented by atropine) [248] Hydralazine [249]
Alcohol	Chronic alcohol intake [251]	Acute alcohol intake [250]
Diseases	Bile drainage [79]	Bile obstruction [79] Liver cirrhosis [251] Intestinal obstruction [252] Intestinal ischemia (after reperfusion) [253]

worsened by removal of other lymphatic tissue [5]. Reinhardt and Yoffey confirmed this in guinea pigs by showing a greater than 95% reduction in thoracic duct lymphocytes following enterectomy [79]. The output of lymphocytes in mesenteric lymph draining regions with Peyer patches is higher than that of lymphocytes draining areas without Peyer patches [80] and contains more newly formed T than B lymphocytes [81]. Mesenteric lymph contains lymphocytes as well as non-lymphoid cells such as veiled (dendritic) cells [82]. The lymphocytes consist of CD2⁺ cells (mainly CD8⁺ and CD4⁺), immunoglobulin-positive cells (IgM and IgA) and null cells

(unstimulated lymphocytes). Thielke *et al.* identified subsets of lymphocytes in female minipigs, showing that the approximate proportions of CD2⁺, immunoglobulin-positive cells and null cells were 80%, 10% and 10%, respectively [82]. CD4⁺ T helper cells (about 39.5%) outnumbered CD8⁺ T cytotoxic/suppressor cells (about 30.2%). IgM cells (about 9.2%) also outnumbered IgA cells (about 1.2%).

Lemaire *et al.* identified leucocytes in both thoracic duct lymph and peripheral blood in patients undergoing resection of esophageal or gastro-esophageal cancers, and found comparable proportions of B lymphocytes

(14.5% vs. 11.9% for thoracic duct lymph and peripheral blood, respectively), T lymphocytes (78.1% vs. 78.2%) and CD8⁺ cells (23% vs. 25.2%) [83]. Compared with peripheral blood, thoracic duct lymph contained proportionately more CD4⁺ cells (59.6% vs. 40.3%, respectively) and more CD4⁺CD45RO⁺ and CD8⁺CD45RO⁺ expressing alpha4beta7 cells (41.6% vs. 17.7% and 59.5% vs. 33.3%, respectively). These data suggest an equivalent B and T lymphocyte recirculation rate, and a more active recirculation of CD4⁺ than CD8⁺ cells, and a more active recirculation of memory cells to the gut than to other extralymphoid sites.

Farstad *et al.* reported that human mesenteric lymph obtained from three organ donors contained naïve T and B lymphocytes (approximately 60% and 25%, respectively), memory T and B lymphocytes (about 10%) and B-cell blasts (about 2%) [84]. Other blood cells such as platelets are nearly or entirely absent, while erythrocytes are constantly present in chyle [5, 85].

Mesenteric Lymph Flow

Thoracic duct lymph comprises about 90% of total lymph flow [86] in anesthetized animals but probably about 50 to 70% in the conscious animal [65]. The daily thoracic duct lymph flow in humans is about 24 to 48 mL/kg [87] but increases up to 120 mL/kg in ruminants [5]. Under normal resting conditions thoracic duct lymph is derived largely from the abdominal viscera [88, 89], (mainly the intestine and liver) [88, 90, 91] with minor contributions from the trunk, lower extremities [92] and intrathoracic structures [5]. The relative contribution of mesenteric lymph to total thoracic duct lymph exceeds the liver contribution in cats [88], rats [50] and ruminants [93, 94].

Factors modulating mesenteric lymph as well as diseases reported to be associated with abnormal mesenteric lymph flow are summarized in Table 1. These factors might be used to alter the course of diseases in which mesenteric lymph has a role. The centripetal forces producing lymph flow can

be classified as extrinsic (passive lymph pump) or intrinsic (active lymph pump). Extrinsic forces include skeletal muscle activity, central venous pressure, gastrointestinal peristalsis, pulsation of blood vessels, gravity and respiration [5]. Intrinsic forces are the coordinated contraction of a chain of lymphangions. These contractions are initiated by pacemaker activity in smooth muscle cells in the lymphangion wall. Factors which modulate this pacemaker activity can be broadly classified as neural, humoral, pharmacologic and mechanical. In certain conditions, such as hemorrhage, more than one factor can influence intrinsic pump activity. The mechanisms by which these factors exert their effects on the intrinsic pump are not well defined, but appear to differ between different animals and humans. There are also profound differences between the pressure and flow sensitivities of different lymphatic vessels, including the thoracic duct and mesenteric lymphatics [95]. Factors affecting the intrinsic pump are listed in Table 2.

Mesenteric Lymph and Disease

The literature contains many studies that have investigated changes in thoracic duct lymph and mesenteric lymph flow and composition in a variety of diseases. There is now evidence to show that mesenteric lymph plays a key role in the pathogenesis of multiorgan dysfunction in trauma/hemorrhagic shock [2, 15, 96, 97, 98], burn [99, 100], surgical stress [101, 102] and reperfusion injury [103, 104, 105].

The mesenteric lymph factors active in these diseases and the way in which they exert their effects are poorly understood. They include serine protease [106], oxidative stress [107], phospholipase A2 [108, 109] and apoptotic factors [110]. The lack of understanding is highlighted by the range of opinions that the active factor is in the lipid fraction [111, 112], in the protein-aqueous fraction [113], is a modified form of albumin [114, 115], is greater than 100 kD [116], and could be a 24-amino acid peptide [114]. Other studies have

Table 2. Factors influencing the intrinsic pump.

Type	Inhibitors of intrinsic pump	Stimulants of intrinsic pump
Neural	Autonomic nerves [42]	Autonomic nerves [42, 255]
Humoral	5-HT [256, 257, 258] PGI ₂ , PGE ₂ [261] Cyclooxygenase inhibitors [262] Aspirin [263] Acetylcholine [264] Histamine (low concentrations) [265] Endotoxin [266, 267] Nitric oxide [269, 270] Vasoactive intestinal peptide(VIP) [272] Atrial natriuretic peptide (ANP) [275] Free radicals [278] Halothane [280, 281] Phenobarbitone [281] Propofol, sevoflurane [282]	5-HT [259, 260] PGF ₂ alpha, PGA ₂ , PGB ₂ [259, 261] Phenylephrine and noradrenaline [254] Histamine high concentration [259, 265] Endotoxin [268] Endothelin [271] ATP [273, 274] Substance P [276, 277] Bradykinin [279] Dopamine [259]
Mechanical	Elevated transmural pressure [95] Vibration [284]	Low transmural pressure [283] Vibration [284] Radiation [285]
Multifactorial	Haemorrhage to 50% blood volume [286, 287]	Haemorrhage 25% blood loss [286, 287, 288]

suggested that the effect of toxic mesenteric lymph is not due to its cellular component [96], translocating bacteria, endotoxin, cytokines or xanthine oxidase [2, 117]. It is likely that the effect of toxic mesenteric lymph is mediated by a combination of factors, and they may or may not be different in various disease states.

Studies in Hemorrhagic Shock and Trauma

Experiments from around 1940 suggested the “shock-delaying” action of barbiturates [118] in contrast with ether anesthesia, which was associated with a more rapid onset of shock [119] in the context of intestinal injury. It appears that these different effects are attributable to the known actions of these agents with regard to mesenteric lymph flow. Ether causes an increase and barbiturates causes a decrease in lymph flow (see Table 1) [120].

Segmental intestinal resection has been reported to have a favourable impact on the outcome from endotoxic [121] and hemorrhagic shock [122]. This was in contrast with the finding that segmental exclusion of the small intestine (by jejunal or ileal stoma) did not improve survival in hemorrhagic shock [123, 124]. Segmental resection, unlike

segmental exclusion, appeared to reduce mesenteric lymph volume and flow. Total intestinal exclusion/excision was associated with an adverse outcome secondary to malnutrition [125]. In a more recent study, the influence of malnutrition was negated in rats by performing a total enterectomy, i.e. resection of both the small and large intestine, and simultaneous induction of hemorrhagic shock. Enterectomized rats were found to have a significant improvement in survival [125].

Other potential lymphatic mediators of distant organ injuries have been studied, including lysosomal enzymes. Dumont and Weissmann found that there was a significant increase in thoracic duct lymph beta glucuronidase in dogs that were bled to death, which was not found with diversion of thoracic duct lymph [126]. This finding could not be confirmed in a study of less severe hemorrhagic shock, in which the levels of three lysosomal enzymes (beta glucuronidase, acid phosphatase, leucine aminopeptidase) were higher in plasma than in thoracic duct lymph and thoracic duct diversion did not prevent this [127].

Diversion of thoracic duct lymph has been shown in a feline model to have a beneficial effect on the outcome of hemorrhagic shock [128]. There was a three-fold increase in

survival duration in animals with thoracic duct lymph diversion (156 ± 12.8 min) compared with controls (52 ± 4.1 min).

Ligation of the mesenteric duct also appears to have a protective effect. Deitch *et al.* have identified a number of changes that occur in this context, and in a variety of models. The relative contributions of these to outcome have not been determined. They include activation of neutrophils, cytotoxicity to endothelial cells with increased permeability and apoptosis, and upregulation of endothelial adhesion molecules [113, 129, 130, 131, 132, 133], decreased red cell deformability [134], hematopoietic failure [135] and impaired cardiac contractility [136].

Studies of Intestinal Ischemia

The intestine is particularly susceptible to ischemia because of the anatomy of the villus microcirculation. The countercurrent arrangement of veins around a central arteriole allows for arteriovenous shunting of oxygen and causes anoxia of the villus tip [137]. During ischemia, mucosal acidosis and ATP depletion [138] develop quickly and epithelial cells separate from the villi [139]. Reperfusion of the intestine exacerbates injury due to production of oxygen free radicals [140], nitric oxide derived radicals [141], cytokines [142], and activation of the complement system [143]. These factors lead to local injury and recruitment of leukocytes that exacerbate the injury. Ischemic damage to the intestine has at least two major effects. The first effect is that the intestinal barrier integrity becomes compromised, allowing bacterial translocation [144]. With breakdown of the intestinal barrier, bacteria and toxins translocate to mesenteric lymph nodes [145] causing generation of more cytokines and activated leukocytes. As a result, the intestinal interstitial fluid is awash with cellular debris, cytokines, bacteria, activated leukocytes and oxygen radicals. The second effect is that the intestine, an "endocrine organ" in its own right, is stimulated to release a large number of pro-inflammatory mediators [146]. These effects on the intestine drive the development

of multiple organ dysfunction syndrome (MODS) [147, 148].

In order to study the effect of intestinal ischemic injury on other diseases it is necessary to use an animal model that maintains perfusion of other organs. Kozar *et al.* compared three animal models of intestinal ischemia/reperfusion, i.e. controlled hemorrhage, uncontrolled hemorrhage and superior mesenteric artery occlusion (SMAO) [149]. They concluded that superior mesenteric artery occlusion is a simple and reproducible model, and a clinically relevant one for shock-induced intestinal ischemia/reperfusion. Using the superior mesenteric artery occlusion model of intestinal ischemia reperfusion in rats, Cavriani *et al.* [150] reported that the resulting intestinal and lung injuries were partially mediated by tumor necrosis factor and that they were prevented by ligation of the thoracic duct. The concentration of leukotriene B4 has been shown to increase in mesenteric lymph (but not portal blood) following occlusion of the descending aorta in a feline model. Leukotriene B4 is known to sensitize afferent nerve endings, but it is unknown whether it has any role in mediation of the adverse effects of intestinal ischaemia [151].

Studies of Acute Pancreatitis

Thoracic duct lymph contains amylase in normal subjects and the concentration increases dramatically in acute pancreatitis [70]. Furthermore, Brzek and Bartos found that amylase levels were higher in thoracic duct lymph than in blood during acute pancreatitis [152]. It is not known whether this increase in pancreatic enzymes in thoracic duct lymph has an adverse effect on the outcome of acute pancreatitis.

Several studies have investigated the effect of small intestinal exclusion or small intestinal resection on the course of acute pancreatitis. Kiriakou *et al.* divided dogs into three groups; acute pancreatitis only, acute pancreatitis plus small bowel exclusion, and acute pancreatitis plus small bowel resection. The first two groups survived from 90 minutes to 12 hours,

while most of the third group survived for up to two weeks [153].

Recently, it has been shown that mesenteric lymph in acute pancreatitis is injurious to the red blood cells. The decrease in red blood cells deformability was partially prevented by mesenteric duct ligation [154].

Schmid-Schonbein and Hugli have published a hypothesis which could help to explain the mechanism by which biologically active lymph was generated in acute pancreatitis in the above experiment. They suggest that when the gut mucosal barrier is compromised, as in acute pancreatitis [155], pancreatic digestive enzymes which are not normally able to cross the mucosal barrier become able to penetrate the submucosal space of the small bowel and release inflammatory mediators via mesenteric lymph, the portal vein and the peritoneum [156].

Interventions Directed at Mesenteric Lymph

In the absence of any clear understanding of what is responsible for the toxicity of mesenteric lymph, it is not surprising that a broad range of interventions targeted towards mesenteric lymph has been investigated. In various animal models, these have included peripheral infusion of hypertonic saline [157, 158, 159], Ringer's ethyl pyruvate [160] and albumin [161]. Another approach has been to instil sodium pyruvate [162], L-arginine [163], serine protease inhibitors [106, 164, 165], and edaravone (a free radical scavenger) [166] within the intestinal lumen. The other broad approach taken has been of a more procedural nature, including global hypothermia [167], ligation of the pancreatic [16, 168, 169], mesenteric [15, 131, 132, 135, 170, 171, 172, 173, 174, 175, 176, 177, 178] and thoracic [150] ducts, and external drainage of thoracic duct lymph [135, 177].

The timing of intervention needs to be considered. Mesenteric lymph becomes biologically active during trauma/hemorrhagic shock prior to resuscitation, and persists for several hours after resuscitation [96]. Therefore, it is desirable to intervene as

early as possible to reduce the adverse effects of critical illness.

Medical Therapy

Lymphatic flow can be modulated by medical therapies, as shown in Table 1. Morphine and barbiturates reduce mesenteric lymph/thoracic duct lymph flow, while noradrenaline and dopamine increase mesenteric lymph/thoracic duct lymph flow. Sympathomimetic drugs, at certain doses, can cause spasm of the lymphatic vessels and decrease mesenteric lymph flow [42, 179]. Chlorthiazide 20 mg/kg produces either no change or a very modest increase in mesenteric lymph, while furosemide 10 mg/kg greatly enhances mesenteric lymph [180].

The intestine and mesenteric lymph have efficient and intrinsic anti-oxidant defenses [181] but these can be overwhelmed by oxidative stress [107]. Early antioxidant therapy during hemorrhagic shock has been shown to improve survival in rats [182]. The idea of using the available lipophilic antioxidants such as U-74500A, U-74389G and U-74006F in this setting is appealing. Transport of these drugs by mesenteric lymph is slower than in portal blood and hence the lymph is targeted directly and efficiently. These orally active antioxidants also bypass the hepatic first-pass mechanism [49], and can be administered with enteral nutrition. It has been reported that infusion of U-74006F into rats has a protective effect in ischemic reperfusion injury of the bowel caused by splanchnic artery occlusion [183].

This suggests that modulation of lymphatic flow by medical therapy is worth exploring. Some of the other factors listed in Table 1 that decrease mesenteric lymph flow might be examined more critically in this context, such as hypothermia and use of the reverse Trendelenberg position to increase central venous pressure.

Nutritional Support of the Intestine

Early enteral nutrition in the critical care setting has been shown to be superior to total

parenteral nutrition (TPN) [184, 185, 186, 187, 188, 189]. However, it should be recognized that enteral nutrition will increase mesenteric lymph flow [8, 190], especially the lipid component. This might explain why enteral nutrition did not ameliorate the inflammatory response in patients with prognostically severe acute pancreatitis [191]. Conversely, TPN in the absence of oral food intake will decrease mesenteric lymph flow by not providing enteral nutrients for absorption [192, 193]. Both fat free/low fat enteral nutrition and TPN have been shown to decrease lymph output in the treatment of chyle leak [194, 195, 196]. Enteral nutrition has also been shown to be superior to TPN in the context of critical illness, and further studies are required to compare the outcome of using low fat enteral nutrition and standard enteral nutrition in critical illness.

Whether immune-enhanced enteral nutrition is superior to standard enteral nutrition remains controversial [197, 198, 199]. L-arginine and glutamine regulate NO synthesis [200], so potentially could modulate the intrinsic lymphatic pump and mesenteric lymph flow. This mechanism warrants further investigation.

Surgical Therapy

There are three ways to prevent mesenteric lymph from entering the peripheral circulation: mesenteric duct ligation, thoracic duct ligation and thoracic duct external drainage.

Mesenteric Duct Ligation

There are numerous animal studies demonstrating that mesenteric duct ligation can prevent distant organ failure [131, 132, 170, 171, 172]. There appear to be five problems in applying their findings to the clinical setting. Firstly, humans do not always have a well-defined intestinal trunk to be ligated [201]. Secondly, mesenteric duct ligation results in steatorrhea. This can be mitigated by diverting the lymph into the urinary bladder, the peritoneum or pleural cavities [202]. Thirdly, timing of mesenteric

duct ligation in the animal experiments was before induction of hemorrhagic shock, which is prior to the therapeutic window in the clinical setting. Fourthly, some mesenteric lymph will reach the thoracic duct despite mesenteric duct ligation [203], possibly via lymphovenous communications (see earlier) [5] and the extent of this is impossible to predict. Fifthly, mesenteric duct ligation is not a durable approach, which may be therapeutically advantageous, because mesenteric lymph can reverse flow to bypass an obstruction [204] and regenerate [205, 206]. Unfortunately there are no clinical studies of this.

Thoracic Duct Ligation

Thoracic duct ligation is reasonably well tolerated in both humans and animals [32, 207]. It causes a type of intestinal atrophy which is morphologically similar to malabsorption syndrome but without any associated functional changes [208]. Thoracic duct ligation in patients with chylothorax is without major sequelae, and was recommended to be undertaken as a routine step in an esophagectomy for cancer [209]. A recent report suggests that thoracic duct ligation prior to induction of bowel ischemia/reperfusion in rats causes a reduction in lung injury in models of trauma and hemorrhagic shock [150].

Toxic mesenteric lymph in an acute pancreatitis rat model demonstrated pro-inflammatory properties [154], so it could be hypothesized that thoracic duct ligation should result in an improved outcome. However, this has not been found, and the evidence available suggests that thoracic duct ligation has a negative impact on the normal, stimulated pancreas and in acute pancreatitis. Blalock *et al.* showed that the normal pancreas in dogs developed lymphedema as a result of chronic lymphatic obstruction at the level of cisterna chyli or thoracic duct at the neck [210]. Dumont *et al.* used secretin and bethanechol to stimulate the pancreas in dogs. Subcutaneous injection of their thoracic duct lymph into rabbits resulted in acute inflammation of skin and subcutaneous

tissues. Thoracic duct ligation made the lymph more toxic and caused severe inflammation of the rabbit skin and subcutaneous tissues [211]. In a rat model of trypsin-induced pancreatitis thoracic duct ligation resulted in a significant increase in mortality [212, 213].

Thoracic Duct External Drainage

In contrast with thoracic duct ligation which has had limited application, external drainage of the thoracic duct [214] has been investigated in a variety of diseases, and mainly in Eastern Europe. These diseases are listed in Table 3. In 1989 Dugernier *et al.* reported that thoracic duct external drainage for up to 10 days resulted in a dramatic improvement in pulmonary gas exchange, circulatory status and survival in patients with severe acute pancreatitis and respiratory failure [215]. The relatively short period of drainage in this study avoided possible complications associated with long term thoracic duct external drainage (for one to three months), such as humoral and cell-mediated immune suppression. Bondarev *et*

al. used thoracic duct external drainage with further lymphosorption (extracorporeal purification and reinfusion of purified lymph) successfully in the treatment of acute pancreatitis [216].

Later in 2003 Dugernier *et al.* investigated compartmentalization of the cytokine response in 60 patients with severe acute pancreatitis [217]. The investigators measured levels of 11 pro- or anti-inflammatory cytokines in ascitic fluid, thoracic duct lymph and plasma, and found that thoracic duct external drainage over a period of 6 days had no effect on circulating cytokine levels. Their finding reinforced the view that thoracic duct external drainage is ineffective in the treatment of severe acute pancreatitis [218]. However, this study had two noteworthy shortcomings. Firstly, thoracic duct external drainage was done in patients with pre-existing involvement of at least one organ. This indicates that significant damage had already been done because mesenteric lymph has maximum biological activity in the first few hours of critical illness [96]. Secondly, it is not clear if thoracic duct external drainage

Table 3. Clinical studies of thoracic duct external drainage.

Organ system	Disorder
Cardiovascular	Cardiogenic shock [289, 290] Lower limb circulatory disorders [291]
Lymphatic	Chronic lymphocytic leukemia [292, 293] Lymphoma [294]
Pulmonary	Asthma [295] Lung abscess [296]
Gastrointestinal	Peritonitis [297, 298] Pancreatic cancer [299] Acute pancreatitis [300] Chronic recurrent pancreatitis [301] Hepatitis [302] Obstructive jaundice [303, 304] Tuberculous enteritis [305] Emergency abdominal surgery [306, 307] Ulcerative colitis [308]
Renal	Glomerulonephritis [309] Transplantation [310, 311, 312]
Musculoskeletal	Rheumatoid arthritis and other connective tissue disorders [313, 314]
Dermal	Thermal burns [315] Skin graft [316]
Miscellaneous	Phalloid mushroom poisoning [317]

was complete, given that the duct may bifurcate or have multiple terminal openings. A more definitive study evaluating thoracic duct external drainage as an early intervention in critically ill patients is warranted.

Conclusions

The role of mesenteric lymph in pathogenesis of distant organ failure in critically ill patients has been highlighted by a number of studies over the last two decades. This focused review of the early and recent literature was warranted to highlight the gaps in current understanding of the role of mesenteric lymph in health and disease. This review demonstrates a need for further investigations in several areas. Firstly, there is a need to identify the factors responsible for generating biologically active mesenteric lymph. Secondly, there is a need to clarify the role of drugs modulating mesenteric lymph flow/composition and that of intrinsic pump activity in preventing distant organ failure. Thirdly, the action of lipophilic antioxidant drugs in mesenteric lymph needs further investigation. Fourthly, the impact of low fat enteral nutrition should be compared with standard enteral nutrition. Fifthly, there is a need for studies comparing the effects of thoracic duct ligation with thoracic duct external drainage.

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Erratum Table 1 was modified on August 14th, 2007: 1) The reference 279 was applied to quote Bradykinin instead of reference 245; 2) Isoprenaline was deleted

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