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THERAPEUTIC THORACIC DUCT DRAINAGE: A SYSTEMATIC REVIEW OF THE EASTERN EUROPEAN EXPERIENCE AND FUTURE POTENTIAL

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ABSTRACT

Thoracic duct drainage (TDD) is gaining renewed interest, largely due to accumulation of evidence supporting the gut-lymph model, where toxic mesenteric lymph from the intestine contributes to development of multi-organ failure in acute and critical illness (ACI). Advances in minimally invasive TDD have added to this growing interest. The English TDD literature has been previously reviewed, but the more extensive Eastern European literature has not been available to English readers. Therefore, we undertook a systematic search of Eastern European human TDD studies using Scopus and PubMed databases and Russian language websites. Indications for TDD, clinical outcomes, and complications were reviewed. 113 studies, published between 1965 and 2015, were reviewed. The most common indications for TDD were hepatic failure, acute pancreatitis, and peritonitis. It was often used late and when other treatment options had been exhausted. Human TDD appeared safe and probably effective, especially when combined with lymphosorption. The benefit appeared to correlate with the volume of lymph drained. A randomized controlled trial (and some case-control studies) showed reduced mortality in patients with ACI with TDD. Other benefits included rapid normalization of blood parameters and decreased organ edema. This review provides further support for the gut-lymph model and justification for high quality randomized controlled trials of TDD in ACI. It also highlights other potential indications for TDD, such as bridging patients with liver failure to surgery or transplant.

Keywords: thoracic duct drainage, critical illness, lymph, gut-lymph model, Eastern Europe

The thoracic duct (TD) drains lymph from the entire body except the right thorax, arm, head, and neck, which are drained by the right lymphatic duct. Although thoracic duct drainage (TDD) for diagnosis and treatment is no longer performed, there is renewed interest in this procedure by researchers and clinicians (1,2) because of the growing evidence support-

ing the gut-lymph model (3,4). In this paradigm, TD lymph has an important role in the pathogenesis of systemic inflammation and organ dysfunction/failure during acute and critical illness (ACI) (5,6). There is now a large number of animal studies of ACI showing that splanchnic vasoconstriction, secondary to systemic inflammation and hypotension, can lead to release of toxic mediators into mesenteric lymph (5,6). Mesenteric lymph flows into the cisterna chyli and makes up the majority of TD lymph (7,8). Unlike the venous drainage from the intestine, lymph drainage bypasses the liver and is released directly into the central veins of the neck via the lymphovenous junction (LVJ). This pro-inflammatory lymph enters the circulation immediately upstream of the heart, lungs, and kidneys, the organs that fail most often in ACI. The therapeutic implication of the gut-lymph model is that external drainage of TD lymph during the early phase of ACI will reduce the exposure of vital organs to the toxic lymph mediators to reduce organ dysfunction and improve clinical outcomes, and indeed this has been shown in preclinical studies (9-11). There is also evidence that this intervention can be of benefit in chronic disease states, including congestive heart failure (CHF) with renal dysfunction (12, 13), and ascites secondary to liver cirrhosis (1).

Cannulation of the TD for drainage has previously required an open surgical technique (1), which is susceptible to the inherent risks of open surgery, including infection and chylous fistula, and can be difficult because of anatomical variation of the terminal TD (14-16). However, a new percutaneous approach to TD cannulation has greatly diminished these risks and made it possible to reconsider TDD as a therapeutic option in the clinical setting (17,18). In this technique, intranodal lymphangiography is performed to image the TD (19). A guidewire is then inserted into the TD via a percutaneous transabdominal approach and advanced through the LVJ into the subclavian vein (20). This guidewire is then snared by another looped guidewire inserted from the left arm, withdrawn, and exteriorized at the arm. A catheter is inserted over this guidewire and advanced via the subclavian vein into and down the TD, followed by removal of the guidewire. This minimally invasive approach to TD cannulation and drainage does not divide the TD and is not associated with a chylous fistula (18). The main risk of prolonged drainage is immune suppression. To counter this risk previously, TDD was often combined with 'lymphosorption', a term used in the Eastern European literature for cleaning or detoxifying lymph, often by passing it slowly over an activated carbon sorbent, before reinfusing the cleaned lymph intravenously (21).

A review of the 71 English language publications describing TDD has previously been published (22), which showed a peak between 1965 and 1975 and none in the last 2-3 decades. There have been sporadic reports that TDD was widely used in Eastern Europe (mainly Russia), but this experience has yet to be reviewed. The aim of this study was to systematically review the literature on TDD published in Eastern European languages, with a specific focus on the indications, outcomes, and complications.

METHODS

Search Strategy

A search of Scopus and PubMed databases was performed by two independent reviewers (PR, SN) for all papers up to September 2021 on therapeutic TDD in humans. External TDD, internal drainage (lymphovenous anastomosis (LVA)), and right lymphatic duct drainage were included. Search terms were 'thoracic duct' OR 'lymph' AND 'drainage' OR 'lymphosorption' OR 'detoxification' OR 'lymphorrhoea' (a common term for external drainage of lymph). Languages were limited to Russian, Bulgarian, Czech, Hungarian, Polish, Romanian, Serbian, Slovak, and Ukrainian. Reviews, non-human studies, chylous leak/fistula, TD embolization or ligation, and publications that solely described techniques were excluded. Further searching of Eastern European language websites (see Supplementary Material available from author), theses databases, review articles, and patents was under-

taken by Russian-speaking investigators (CS, GG), and a secondary search of references from all included studies was performed.

Translation

Fifty articles were translated in full by medically-qualified Russian-speaking investigators (SN, CS). The remainder (63) were translated by Google Translate (Google, https://translate.google.com), with ambiguous terminology clarified by one or more of the translators (SN, CS, GG).

Data Extraction

Data were extracted from the articles onto a pro forma template. Extracted data included indication for TDD, study design, number of patients, inclusion of lymphosorption, LVA, lymphostimulation or endolymphatic antibiotics, primary and secondary endpoints, and complications. If patients could be included under multiple indications, the primary indication as stated by the author was used because the results were presented based on the patient groups they designated. For example, a study focused on hepatic failure would come under that category, even if the cause of hepatic failure was acute pancreatitis (AP) or peritonitis, and likewise, a study focused on AP would come under that category even if the patients had secondary hepatic failure (full details given in Supplementary Material). LVA was defined as any procedure that surgically joined the terminal TD to either the subclavian or internal jugular vein, bypassing the LVJ. Lymphostimulation was defined as any therapy designed to increase lymph flow from the TD.

Study Design

If the study was controlled, but considered to be non-randomized, it was referred to as a 'case-control study'. These included those that were clearly retrospective, and those where it was unclear if they were retrospective or prospective. Those that were clearly controlled and randomized were categorized as a 'randomized controlled trial' (RCT). If it was controlled, but unclear whether it was randomized, retrospective or prospective, it was referred to as a '(randomized?) controlled study'. Studies where therapeutic TDD was performed but the authors only presented results of a particular experimental investigation (as opposed to patient outcomes) were referred to as 'experimental' studies. 'Case series' were descriptive studies without a control group, and a 'case history' was a case series of only one patient. Study quality was assessed by randomization, a control group, prospective/retrospective, and presence of a power calculation.

RESULTS

From the database search, 989 titles (in English) were screened, and an additional 47 were obtained from Eastern European language websites (*Fig. 1*). Of these, 261 full texts were sought, with 19 unavailable. After excluding a further 129, a total of 113 articles, published between 1965 and 2015, were included in the final analysis (*Fig. 1*). One hundred and five papers (93%) were written in Russian, four were in Czech, two were in Bulgarian, one was in Polish, and one was in Romanian. There were six theses, and the remainder were journal articles. The distribution of studies over time shows that the majority were published between 1975 and 1995 (*Fig. 2*). TDD was combined with lymphosorption (mostly using activated charcoal) in 66 studies, and with lymphostimulation (mostly using saline or mannitol infusion, or 'Trental', a drug with the active ingredient pentoxifylline that improves peripheral blood flow) in 15 studies. A comprehensive summary of all included studies is provided in Supplementary Material available from the author.

Study Designs in the Dataset

There was one RCT (23), one (randomized?) controlled study (24), 28 case-control studies, 78 case series, two experimental studies and three individual case histories. No studies specifically stated whether they were prospective or retrospective, and none

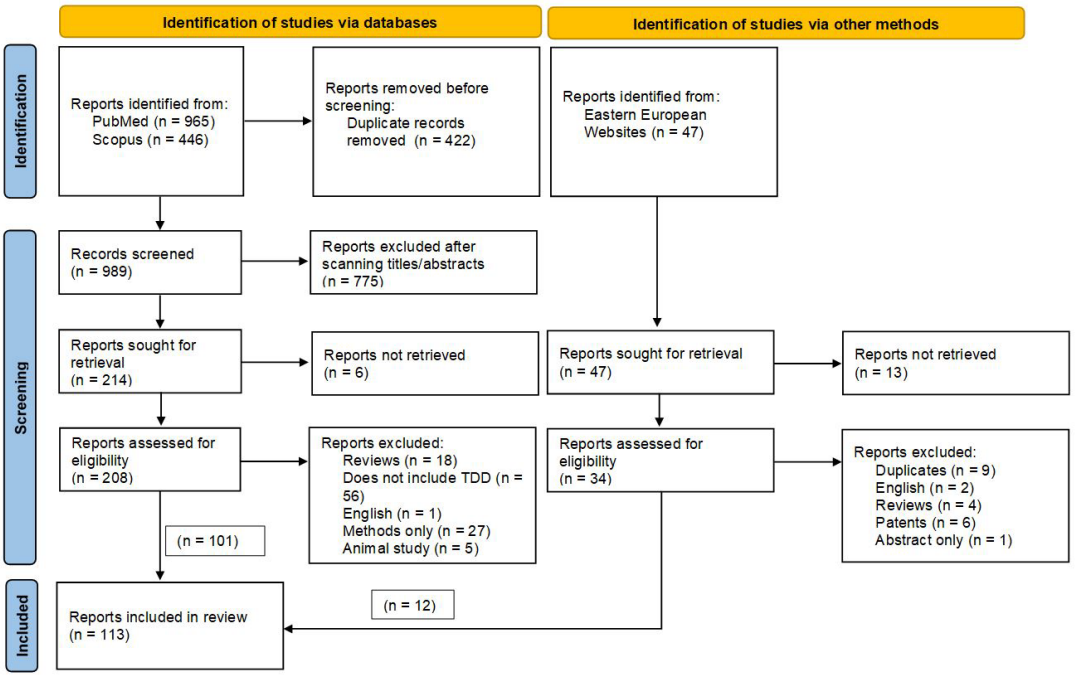

Fig. 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (ref. 136) flow chart showing the number of publications identified, screened, excluded, and selected.*

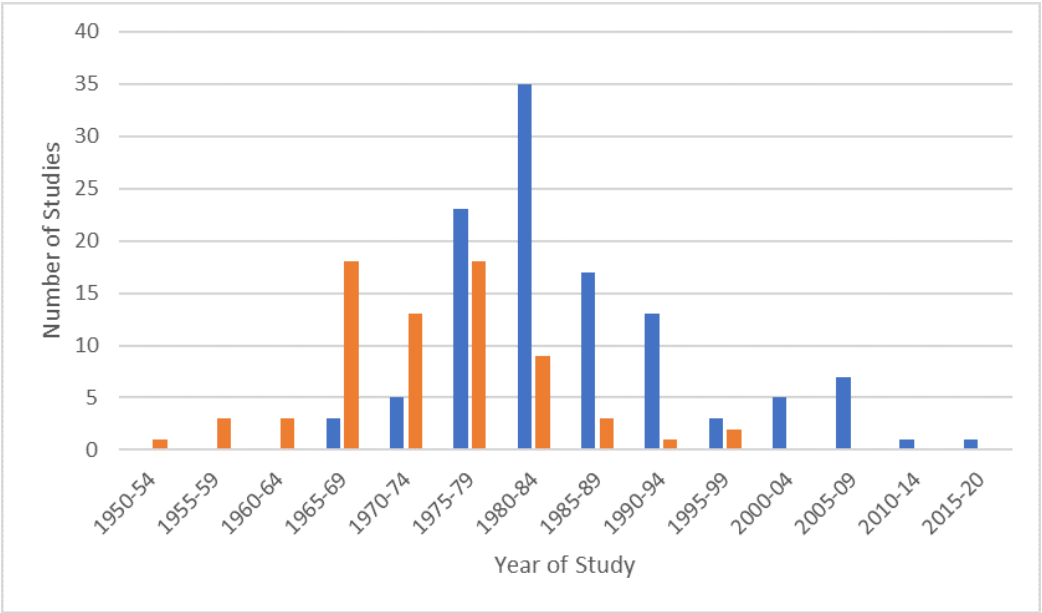

Fig. 2. *The frequency distribution of 113 publications in the Eastern European languages (blue) included in this review. Also included are a summary of the studies included in the recent review of English publications (orange) [extracted and modified from Wang et al. (22)].*

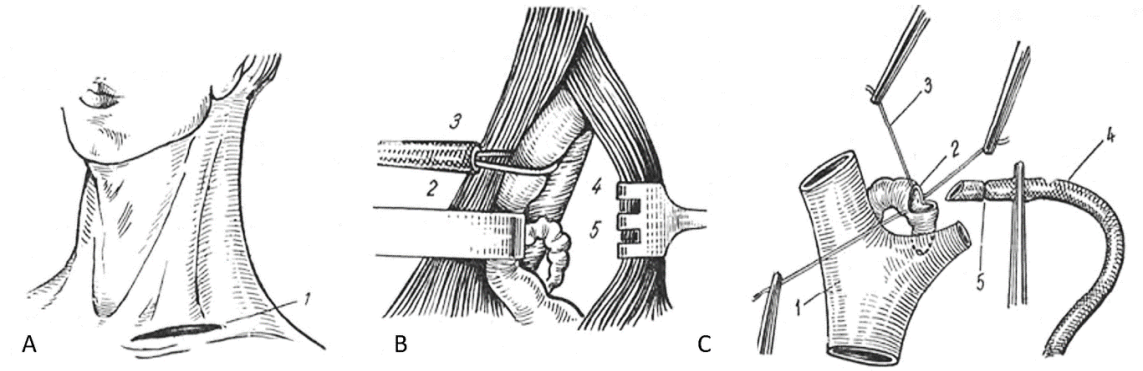

Fig. 3. *Schema of the technique of thoracic duct drainage. (A) Location of horizontal skin incision (1) above left clavicle. (B) Isolation of the cervical part of the thoracic duct. The clavicular head of the sternocleidomastoid muscle is retracted laterally. The internal jugular vein is brought forward and medially (2,3) to expose the carotid artery (4) and the thoracic duct (5). (C) Cannulation of the thoracic duct. (1) Left venous angle; (2) the lumen of the opened thoracic duct; (3) sutures retracting the thoracic duct; (4) drainage catheter; (5) grooved notch to hold the catheter in place. Modified from Pikovskiĭ and Alekseev (96).*

included power calculations. Only 20/113 studies provided any sort of statistical analysis. None of the case-control studies specifically stated that they were non-randomized, but it could be surmised that they were in all cases. No case-control studies provided adequate details on the inclusion/exclusion criteria for proceeding to TDD or not, although one study in patients with AP stated that only those with severe disease were offered TDD (25). Two other studies indicated that the two groups were matched at baseline (26,27). Primary and secondary outcomes were poorly defined in most cases. Only one study explicitly mentioned obtaining ethical approval (24), but omission of ethics statements for the other studies did not necessarily mean it was not obtained. Five studies [including the RCT (23)] were condensed versions of PhD theses and without the full text we were unable to determine if ethics approval was mentioned. The majority of the other studies were retrospective case studies, of an audit nature, where formal ethical approval was unlikely to have been obtained.

Technique of Thoracic Duct Drainage

The surgical technique of TDD was not formally reviewed but was very similar between different studies. A typical example is shown in *Fig. 3*. It was performed under either local anesthetic or general anesthetic during definitive surgery for the underlying condition and took 25-40 minutes (28). In most cases, a horizontal incision was made 1-2 cm above the medial half of the left clavicle (29,30). The surgeon then dissected down to the junction of the internal jugular and subclavian veins, either medially of the sternocleidomastoid muscle or between its two heads. The TD or one of its terminal branches was identified, and an incision was made through its wall between two sutures. A catheter was then inserted in a retrograde direction and sutured in place. The volume drained varied significantly [between 200 ml (31) and 8 L (32) per day]. The catheter was later removed by simply pulling it out (in the ward setting), followed by application of pressure. LVA was usually performed via an end-to-side anastomosis between the transected thoracic duct and the internal jugular vein (33).

Indications for Thoracic Duct Drainage

The indications for TDD were summarized to three broad categories: organ failure, inflammatory diseases, and miscellaneous (*Table 1*). Cross-over between these categories

TABLE 1
Indications for TDD by Disease, Including the Number of Studies and Patients. Expected Outcome of TDD from the Author's Point of View for Each Indication is Also Given.

Disease Process	Study (*n*)	Patients (*n*)	References	Outcome from TDD
Organ Failure				
Hepatic	26 [a]	1736	32-47,49,51,92,95,97,98,109,114,137,138	↓ serum liver enzymes/toxic metabolites, ascites, variceal bleeding, and hepatic encephalopathy
Hepatic + Renal	7 [b]	398	31,48,50,88,139-141	As above and below
Renal	5	7	29,82,91,109,142	↓ serum creatinine/urea/toxic metabolites
Inflammatory diseases				
Acute pancreatitis	32 [c]	887	23,25,27,28,52,53,56-58,66,89,92-94,96,98,109,117-120,138,141,143-151	↓ serum pancreatic enzymes/toxic metabolites, end-organ dysfunction, and mortality
Peritonitis	28 [d]	765	23,26,28,54,55,62-66,92,94,96,98,109,141,143,144,146,147,152-159	↓ bacterial/toxic metabolites, end-organ dysfunction, and mortality
Lung abscess	4	325	67-70	↓ bacterial/toxic metabolites, lung dysfunction/oedema, and mortality
Sepsis [e]	4	141	23,71,98,160	↓ bacterial/toxic metabolites, end-organ dysfunction, and mortality
Ulcerative colitis	3	61	72-74	Immunosuppression and resolution of disease
Other infections [f]	3	44	23,98,161	↓ bacterial/toxic metabolites, end-organ dysfunction, and mortality
Chronic pancreatitis	1	15	151	↓ pancreatic oedema and abdominal pain
Miscellaneous				
Obstructive jaundice	17 [g]	512	29,66,76-79,82,90,92,94,96,98,106,138,141,162,163	↓ serum bilirubin and liver enzymes, symptom improvement
Neoplasia [h]	10	213	29,30,80-83,90,91,93,96	Detection of cancer cells for diagnosis, ↓ chemotherapy side effects
Autoimmune disease [i]	5	36	84-87,91	Immunosuppression and resolution of disease
Poisoning [j]	6 [k]	87	31,96,98,99,107,164	↓ poison/toxic metabolites, end-organ dysfunction, and mortality
Vascular disease [l]	5	67	24,30,108,141,146	↓ oedema
Bowel obstruction	3	15	66,94,146	↓ bacterial/toxic metabolites from ischaemic bowel
Other [m]	6	330	30,31,60,61,75,96	Not applicable

Studies where individual patients could be classified in multiple categories are classified using the main category that the study uses, and further described below. Studies that include patients from different non-overlapping categories are listed under all relevant categories; therefore, there are more than 113 studies listed. Note that different studies from the same authors may include the same patients, who would then be counted twice or more, but this could not be confirmed.

[a] Includes 9 studies where underlying cause of hepatic failure could be classified in other categories for some patients, including obstructive jaundice, peritonitis, acute pancreatitis, pancreatic cancer and poisoning.

[b] Includes 5 studies where underlying cause of hepatorenal failure could be classified in other categories for some patients, including obstructive jaundice, peritonitis, acute pancreatitis, pancreatic tumor, crush syndrome, leptospirosis, lymphosarcoma, chronic alcoholism, liver cirrhosis, chronic renal insufficiency, and poisoning.

[c] Includes 1 study where some patients also had peritonitis and hepatorenal insufficiency

[d] Includes 1 study where all patients had post-operative peritonitis, where most were operated on for malignancy

[e] Defined as bacteremia and signs of sepsis without peritonitis or lung abscess

[f] Includes leptospirosis, viral hepatitis, hemorrhagic fever with renal syndrome, mediastinitis, liver abscess/purulent cholangitis, and scarlet fever

[g] Includes 5 studies where underlying cause of obstructive jaundice could be classified in other categories for some patients, including hepatic, bile duct and pancreatic cancer, and acute pancreatitis, and consequence of obstructive jaundice included
hepatic failure for some patients.
[h] Includes gastric, hepatic, rectal and breast cancer, and leukemia and lymphoma. Note that most pancreatic cancer has been classified under obstructive jaundice.
[i] Includes rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and vasculitis.
[j] Includes acetic acid, carbon tetrachloride, copper sulphate, barbiturates, phalloid mushrooms.
[k] Includes 3 studies where patients also had hepatorenal failure.
[l] Includes chronic lymphovenous insufficiency, acute arterial obstruction (mesentery, lower limb).
[m] Includes burns, positional compression syndrome, acute hemolysis, acute myolysis, respiratory disease NOS, diseases of esophagus/stomach/intestines NOS, liver/bile duct disease NOS, pancreatic diseases NOS, kidney/urinary tract disease NOS, hematological disease NOS, joint/bone disease NOS, uterine diseases NOS (NOS = not otherwise specified).

within studies was common (see footnote to *Table 1*). For example, of the 26 studies for hepatic failure, there were 9 studies where the primary disease process could be classified in another category. The most frequent indications for TDD were AP (32 studies), peritonitis (n=28), hepatic failure (n=26), obstructive jaundice (n=17), and neoplasia (n=10). The highest total number of patients were included in studies for hepatic failure (1736 patients), AP (n=887), peritonitis (n=765), and obstructive jaundice (n=512). Organ transplantation was not an indication in any publication.

Organ Failure

In regard to primary organ failure, TDD was only used in patients with liver and/or renal failure (29 studies). A further nine reported on patients with organ failure from another primary indication. It was not used for heart failure or non-inflammatory respiratory failure. There were many studies that did not state organ failure as the primary indication for TDD but did include patients with secondary organ dysfunction (e.g., hepatic failure secondary to poisoning). If both primary and secondary organ failure are considered, the majority of patients in all indication categories (*Table 1*) had some degree of organ failure, which was usually respiratory, hepatic, or renal failure.

Most organ failure-only studies were case series, with only two case-control studies (34,35) and two experimental studies aimed at understanding lymph flow dynamics (36,37). In 65% of the studies (19/29) TDD with lymphosorption and reinfusion of lymph was performed, while in 24% (7/29) the procedure included lymphovenous anastomosis. Because the lymph was reinfused or recirculated in these studies, low rates of lymphopenia and hypoproteinemia were found, despite some patients undergoing TDD for up to 20 days (38). The longest duration of TDD was 64 days for a patient with renal failure secondary to glomerulonephritis (30) but the outcome for this patient was not reported.

Patients with hepatic failure had either chronic failure with cirrhosis or acute failure secondary to an underlying cause, such as obstructive jaundice, AP, peritonitis, or poisoning. The majority of studies included at least some patients in a severe or critical condition, including patients with life-threatening variceal bleeding (33,36,39,40) or patients with hepatic encephalopathy (41-47). Given the severity of disease in many patients, TDD in this cohort appears to be relatively effective overall (see Supplementary Material available from the author), although, as expected, it was less effective in patients in a more severe condition (42,44,47,48). Two studies reported a cessation in variceal bleeding with TDD (33,39) and three reported patients coming out of coma (41,43,46). Eleven studies reported increased TD pressure, diameter and lymph flow, and a correlation between these parameters and the efficacy of the procedure was noted in three (38-40). Similarly, two studies reported

decreased effectiveness in patients who had lower volumes of lymph drained [<200 ml (49) or <1.5 L (50)]. In patients with cirrhosis, one study noted failure of closure of the LVJ valve, which the authors attributed to an increased terminal TD diameter (40), and another noted functional insufficiency of the terminal TD with intraoperative ultrasound and sclerosis of the valve and thrombosis at autopsy (36), suggesting that TD lymph was not properly draining in these patients.

Findings of higher levels of bilirubin, ammonia, urea, and creatinine in TD lymph compared to blood were common (41,43,48, 50,51), especially in obstructive jaundice (49), and these levels, in both blood and lymph, consistently decreased with TDD. Both case-control studies noted a significant improvement in the volume of ascites in patients with cirrhosis (34,35). Of these, Viktorovich (35) found that patients who underwent LVA had long-term resolution of ascites (in 60-91% depending on the initial severity) and an improved 5-yr survival compared to conservative treatment ($p = 0.033$). However, no details were given as to the indications for TDD in these patients.

Inflammatory Conditions

The majority of studies investigated patients with inflammatory conditions, including 40 studies that only included patients with inflammatory conditions, and a further 17 that included patients with inflammatory conditions with other disease processes. Most patients had either AP or peritonitis, with four studies including patients with peritonitis secondary to AP (52-55). A larger proportion of these studies were case-control studies (17/40) compared to the studies on patients with organ failure (2/29). Most control groups were patients with the disease who did not undergo TDD, however, only one study detailed the criteria for performing TDD or not (25). In this study, patients who were critically unwell with unstable hemodynamic parameters were selected for TDD. Unlike studies on hepatic failure where patients often had chronic illness and many underwent LVA, no patients had LVA performed in this category.

Most studies (14/17) that only reported on AP patients described a rapid and significant improvement in pancreatic enzyme levels in the blood in most patients who underwent TDD, compared with those who did not. The level of pancreatic enzymes in TD lymph was found to be higher than in the blood for most patients in 10 studies (23 other studies that included patients with AP did not mention the level, and no studies recorded higher levels in the blood than the lymph) (*Fig. 4*). Similar to organ failure patients, there was a correlation between the volume of lymph drained and the time to normalization of blood parameters (amylase, lipase, trypsin, urea, ammonia) (52,56-58). Zatevakhin et al (52) found that drainage of more than 1 L/day for 4-5 days was necessary to achieve a good effect (systemic signs of inflammation, normalization of blood parameters, and lymph toxicity). Babichev et al (58) concluded that the optimum duration of TDD and lymphosorption was 5 days in patients with 'fatty pancreonecrosis' and 7-8 days in patients with 'hemorrhagic pancreonecrosis' with a lymph flow at least 1 L/day. Many studies detected enhanced toxicity of lymph drained from patients with AP, which decreased over the period of TDD. This toxicity was usually measured by the paramecium test (59), where paramecia (single-celled protists) were incubated with the lymph and the time to paramecium death was recorded (35-45 mins with healthy lymph and as low as 3-5 mins with toxic lymph) (60). Another study in patients with burns and shock measured lymph toxicity by the effect on chicken embryos (61).

In a case-control study, Rojkov et al (27) found that patients with AP who underwent TDD and lymphosorption had lower mortality and organ failure scores than patients without TDD. In this study, there was no difference in baseline sequential organ failure assessment (SOFA) score between groups (3.5 ± 0.9 without TDD vs. 3.4 ± 0.9 with TDD/lymphosorption vs. 3.6 ± 1.3 with TDD/lymphosorption and hemosorption), but there was a marked improvement after TDD on day 10 (7.5 ± 2.8 vs. 4.3 ± 2.1 vs. 3.9 ± 1.6, respectively). Morta-

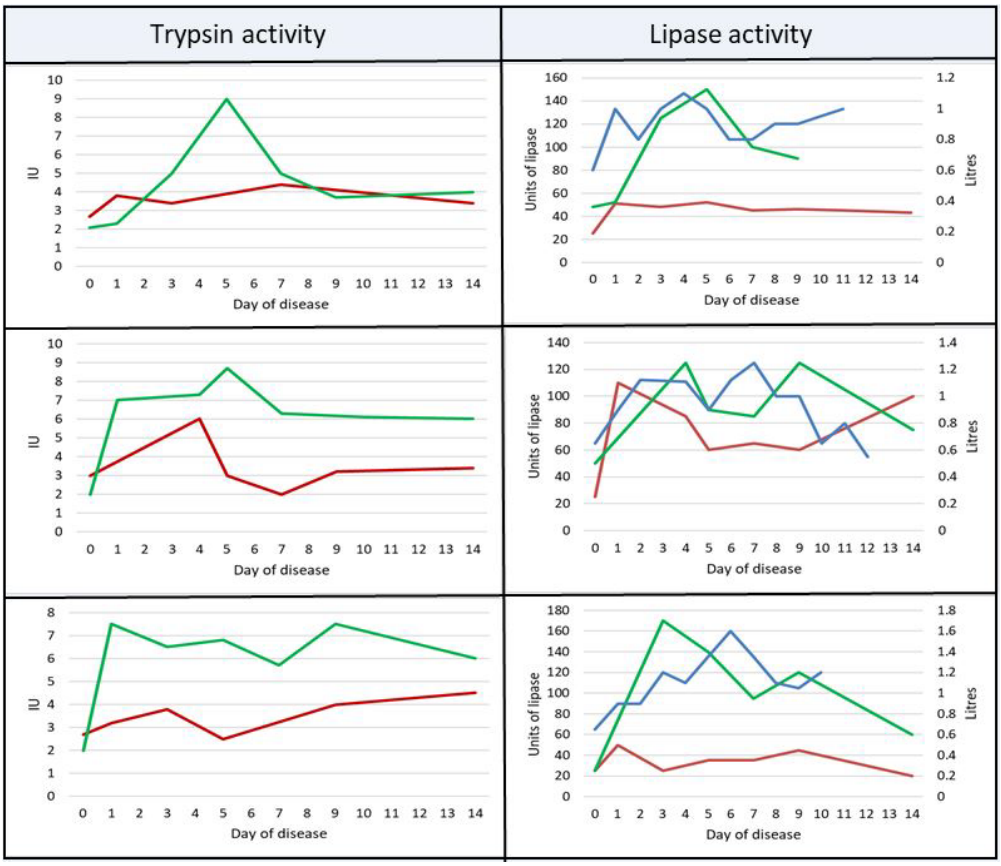

Fig. 4. *Lipase and trypsin activity in serum (red) and thoracic duct lymph (green) and drained lymph volume (blue) over 14 days in patients with edematous pancreatitis (top; n = 17), partial pancreatic necrosis (middle; n = 16) and total pancreatic necrosis (bottom; n = 15). Error bars/confidence intervals not available from source document. Modified from Savel'ev et al. (56).*

lity was 28/59 (47.5%) without TDD, 11/66 (16.7%) with TDD/lymphosorption, and 5/41 with (12.2%) with TDD/lymphosorption and hemosorption. Another case-controlled study on patients with either peritonitis with multi-organ failure (MOF) or AP with MOF showed reduced mortality (34.1% vs. 61.8% (control)) and complications (56.5% vs. 89.5% (control)) in patients who underwent TDD (28).

Similar to studies in AP patients, case-control studies on peritonitis suggested improved outcomes for patients that underwent TDD. These outcomes included time to normalization of blood parameters (55,62), bowel function (26,62), general clinical parameters (26,63,64), and mortality rates (62,64). It was not uncommon to find pathological bacteria in the lymph of patients with peritonitis (23,42, 43,62,65,66). In the only randomized controlled trial in this review (23), patients with either mediastinitis, AP, peritonitis, cholangitis, or sepsis were randomized to diuretics only (group 1), hemosorption (dialysis) (group 2), or TDD/lymphosorption (group 3). Group 3 showed a faster time to normalization of blood and clinical parameters and return of bowel function compared to group 1 (and marginally faster than group 2) (e.g., on day 5 post-TDD, decrease in respiratory rate by 39% in group 3 vs. 10.3% in group 1 and increase in urine output by 43% in group 3 vs. 39% in group 1, p values not given). Mortality was reported as

44% (group 1), 32% (group 2), and 29% (group 3) (p value not given but calculated as 0.3766 by Chi-square test).

Studies in patients with lung abscess included right lymphatic duct drainage, aided by radiolymphography, in patients with right sided disease (67,68). These studies also involved patients with TD drainage and so the results could not be separated. Case-control studies on lung abscess showed improved mortality in patients who underwent TDD [3.6% vs. 9.8% without TDD (69), and 3.2% vs. 9.8% without TDD (67)] and an increased proportion of patients who recovered without the need for surgery (67,69). These patients also displayed less lung edema after lymph drainage, determined through radionuclide methods (69,70). One case-control study (71) in patients with sepsis showed decreased complications (19% vs. 28%), length of stay (29% vs. 34% bed-days), and mortality (29% vs. 37%) in patients with TDD compared with those without TDD, respectively. Most patients with ulcerative colitis had a marked clinical benefit from TDD, including those with chronic disease (72-74), and some patients showed persistent remission up to 30 months following TDD (72).

Respiratory Dysfunction in the Context of Acute Inflammatory Conditions

There were 69 publications that included patients that had an acute inflammatory condition. Of these, 37 did not mention respiratory dysfunction. Of the remaining 32, six (30, 67-70,75) included patients with primary respiratory disease. The other 26 studies used various terms, without definitions, for describing respiratory dysfunction as a secondary complication of the underlying inflammatory condition but did not give details of the number of patients with respiratory dysfunction and the number that improved after TDD. The terms used included dyspnoea, tachypnoea, respiratory dysfunction, and respiratory failure. One study (38) specifically stated that 4/101 patients were ventilated but did not describe the effect of TDD for these patients. Similarly, other studies did not describe the effect of TDD on lung function specifically but rather included lung function in the general description of 'clinical improvement' with TDD.

Other Miscellaneous Conditions

Other indications for TDD included obstructive jaundice, neoplasia, autoimmune disease, poisoning, vascular disease, positional compression syndrome, burns, and asthma (*Table 1*). Many patients with obstructive jaundice could also have been included in other categories, such as those with secondary hepatic failure and hepatorenal syndrome, or those with obstructive jaundice secondary to pancreatic cancer or AP. Patients with non-neoplastic causes of obstructive jaundice had better outcomes (76,77), and again clinical improvement correlated with the volume of lymph drained (78,79). One case-control study of obstructive jaundice showed a marked improvement in mortality following TDD + lymphosorption compared to patients that did not have the procedure (9% vs. 30%, respectively), noting that some patients in the drainage group also had hemosorption (79).

A case-control study in patients with gastric cancer tested the effects of TDD in combination with endolymphatic chemotherapy (no details provided on this method), with the aim to deliver higher concentrations of chemotherapy to the tumor while decreasing the risk of serious side effects (80). This study found a decrease in relapse within 2 years (26% vs. 59%) and an improved 2-year survival (91.2% vs. 47.6%) in patients with TDD + endolymphatic chemotherapy compared with those who did not receive this, respectively. Three studies on gastric cancer also found cancer cells in the TD lymph (29,81,82) but the presence of these cells did not predict mortality (81). Another case study in patients with chronic lymphocytic leukemia showed improved lymphocytosis, splenomegaly, and lymphadenopathy in all patients who underwent TDD (83).

Likewise, all case studies in patients with chronic autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, multiple

sclerosis, and vasculitis) found a clinical improvement in most patients, including some examples of long-term remission (up to 2 years) (84-87). In a controlled trial (randomization not stated) in patients with lower limb chronic venous insufficiency who either underwent TDD + traditional therapy (compression therapy, physiotherapy, phlebotonics, non-steroidal anti-inflammatory drugs, antiplatelet agents, phlebectomy) or traditional therapy alone, there was a ultrasound-proven rapid decrease in leg edema in 72% of patients who underwent TDD (vs. 10% in control patients) and medium-term improvement in 86% of patients who underwent TDD (vs. 31% in control patients) (24). Other case series on patients with positional compression syndrome (60) and severe, treatment-resistant asthma (75) showed a clinical improvement in 30/32 patients. A case series of 12 patients in shock following burn injuries showed temporary clinical improvement in all patients following TDD but then later deterioration (61).

Adverse Effects

There were no reported adverse effects for the significant majority of patients who had TDD ± lymphosorption; 73/113 studies reported no adverse effects, and for the remaining studies that provided the number of patients with adverse effects, it was usually no more than 1-10% of patients. The most common adverse effects were hypoproteinaemia (52,58,60,78,88-90), lymphocytopenia (25,47, 52,58,61,74, 75,78,89,91-94), or hypogammaglobulinaemia (79), although these were generally anticipated by the investigators who prescribed intravenous protein infusion or reinfusion of lymph after lymphosorption. Other adverse events included tube displacement (42-45,76,78,95,96), lymph clot occlusion (31,33, 38,40,42-45,52,75), lymph leak (29,30,32,38,44, 73,76,96) and failure to cannulate the TD due to anatomical variation (29-32,54,56,78,82,83, 96-99). Four papers described fevers at the time of lymph reinfusion into a peripheral vein (31,44,52,78). Other uncommon complications included wound infection (30,38,44, 96), wound haematoma (38,76), pneumothorax (38), vagus nerve paresis (38), and venous injury (38,52,76,96).

DISCUSSION

Therapeutic TDD was introduced by various Eastern European institutions to remove toxic mediators or reduce lymphatic pressure and with generally positive results its use became relatively widespread (100). There is now renewed interest in TDD because of the gut-lymph model which states that toxic lymph arising from gut injury in ACI promotes the systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS) (2,101). Given that the common mechanism driving SIRS/MODS/MOF is unknown (102), this model provides new mechanistic and treatment paradigms, including TDD (2,103). This review examined 113 studies published from Eastern Europe between 1965 and 2015, with the peak a decade later than the 71 studies published in English (22). In contrast to the English literature (with no publications since 2000), there have been 14 published studies since 2000 in the Eastern European literature (*Fig. 2*). TDD was frequently combined with lymphosorption (66/113), whereas this was uncommon in the English literature (5/71). Open TDD was safe and probably effective. Improved outcomes included reduced mortality, rapid normalization of blood parameters and decreased organ edema. Combined, these studies provide a substantial experience of therapeutic TDD that is worth considering given the renewed interest in this intervention for the prevention and treatment of the systemic complications of ACI.

Indications for TDD

A striking feature of this review is the wide range of indications for therapeutic TDD. The majority were hepatic failure, AP, and peritonitis; less common indications were highly varied and included conditions such as asthma, burns, multiple sclerosis, and bowel obstruction. Chronic and acute conditions were roughly equally represented. The wide range of indications was paralleled, although

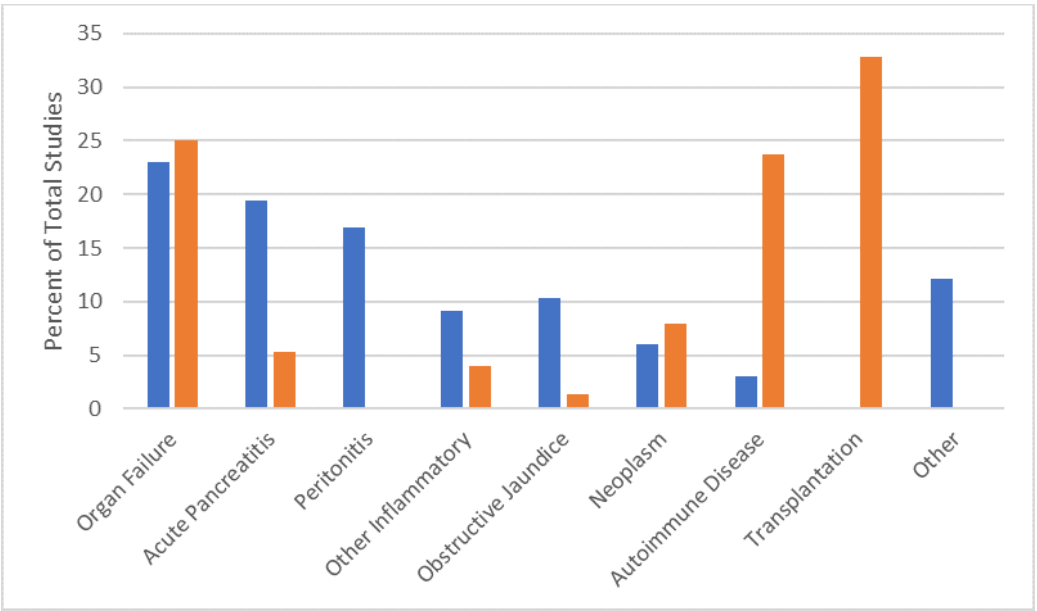

Fig. 5. *Comparison of the range of indications for TDD between the Eastern European literature (blue) and the English literature (orange) [extracted and modified from Wang et al. (22)]. Percent of total studies was calculated as the number of studies with a particular indication divided by the total number of studies (where studies with multiple indications were counted more than once, giving 165 Eastern European studies and 76 English studies as the denominators).*

to a lesser extent, by the English literature (22). However, there was a notable difference in the indications themselves (*Fig. 5*). The most common indication in the English literature was transplantation, mainly renal transplantation (23/71 studies), whereas no studies on transplantation were identified in this Eastern European literature review. Similarly, TDD was performed more commonly for autoimmune conditions in the English literature. This discrepancy may be partly due to the difference in the years of peak use of TDD (1975-1995, compared to 1965-1985 in the West; *Fig. 2*) and the introduction of cyclosporin in 1983 (104), but this does not explain the absence of transplantation as an indication in Eastern European literature prior to this time. The English literature also included on four studies on AP and two studies on heart failure, which was not found in the present review (22). The Eastern European experience of TDD in inflammatory conditions, particularly AP and peritonitis, was much more extensive. Apart from six studies on primary respiratory conditions (e.g., lung abscess), only 26/64 studies on acute inflammatory conditions reported respiratory dysfunction as a secondary consequence. This is surprising given that the lungs are the most common organ to become dysfunctional in MODS and it contrasts with the English literature (22), where respiratory function was described in the context of AP.

Study Quality

Similar to the English literature (22), the quality of evidence in this review was generally poor, with nearly all studies being non-randomized and retrospective. Only 12/28 case-control studies gave p values, which were generally significant. The (randomized?) controlled study provided p values and appeared adequately powered (24). Only one definite RCT from 2005 was identified in this review, where TDD in patients with a range of inflam-

matory conditions was shown to be beneficial compared to diuretics only, but only marginally better than hemosorption (23). However, the p values given, while significant, only compared within-group differences over time. This study appeared underpowered to detect between-group differences. The English literature also only identified a single RCT in patients with AP (105) from the 1960s. That study compared five patients that had TDD with six patients that had peritoneal drainage of ascites. The study was terminated early due to increased mortality in the patients with TDD, where three patients in the TDD group died compared to one in the peritoneal dialysis group, but the causes of death were not provided.

Overall Efficacy of TDD

In general, the efficacy of TDD in the Eastern European literature was more positive than the English literature. The discrepancy in the indications for TDD between the two reviews may partially explain this if TDD is more beneficial in inflammatory conditions, although the data and quality of the studies do not allow a definitive conclusion. Information on the efficacy of TDD is best gleaned by controlled studies but the vast majority of these in the Eastern European literature were retrospective case-controlled studies. While most of these studies did not give details on the criteria for TDD, one study (76) on patients with obstructive jaundice explicitly stated that TDD was used in the most severe patients admitted to intensive care and, despite this imbalance between the two groups, patients that underwent TDD had a lower mortality rate. Other retrospective case-controlled studies are unlikely to have only performed TDD in patients with mild illness, as it is invasive and in multiple case series (51,85,86,106-108) was reserved for patients with severe illness that had failed other therapies. Taken overall and given the multiple examples from many case-controlled studies with a majority showing improved outcomes from TDD, it is considered that the benefits are likely to be genuine. This data justifies appropriate randomized controlled studies.

Studies of TDD for chronic diseases allowed before and after comparisons. There were notable improvements after TDD reported in patients with chronic ulcerative colitis (72-74), chronic lymphocytic leukemia (83), and multiple sclerosis (86) who had often failed standard or best available treatment.

Five studies (in liver failure, obstructive jaundice, and AP) found that the clinical benefit from TDD correlated with the volume of lymph drained, although more data could have been provided (38,57,58,78,109). While not conclusive, this suggests a dose effect of TDD with more benefit from greater drained volumes. Other studies found that any clinical benefit was only seen in patients that had more than a certain amount of volume drained. Studies in AP indicated that more than 1 L /day is necessary to achieve a good clinical effect (52-58), but the volume drained reached as high as 8 L/day in patients with cirrhosis and ascites (32). Other studies noted beneficial effects of TDD only after 2-3 L in total were removed (50,51,66). This relationship between the clinical effect and the volume drained was noted by some authors who used the technique of lymphostimulation to increase the volume of drained lymph. The relationship between the volume drained and the clinical effect was also noted in two non-randomized studies on AP from the English literature (110,111).

Efficacy in Liver Failure

The most common indication for TDD in this review was liver failure. The efficacy of TDD in hepatic failure was striking in some instances where it seemed to immediately halt variceal bleeding (33,39) [also seen in some English-language studies, e.g., Rigas and Tsardakas (112)], significantly improve ascites (34,40), or bring patients out of coma (41,43, 46). Performing LVA also resulted in long-term improvement in some patients (35). In most cases, TDD improved the blood parameters (ammonium, urea, non-protein nitrogen, bilirubin), and where TD fluid dynamics were altered (e.g., increased TD pressure),

TDD was able to normalize these parameters. This is possibly because hepatic lymph flow increases in all forms of chronic liver disease (113), which potentially contributed to the raised TD pressure or diameter or lymph flow seen in many studies [e.g., 39,40,43,46,51,95, 114)]. Increased lymph flow is due to portal hypertension and splanchnic arterial vasodilation, both consequences of cirrhosis, which increase splanchnic capillary hydrostatic pressure, leading to increased interstitial volume and pressure (115). Cirrhosis is also known to lead to hyperammonemia, which contributes to the development of hepatic encephalopathy (116). In this review, ammonia and other toxic factors were present in TD lymph in chronic liver disease, often in greater concentration than the blood (41,50,51,114). These aspects of the pathophysiology of chronic liver disease can explain why TDD offers symptomatic improvement. However, because TDD is unlikely to address the underlying cause of hepatic failure, any beneficial effects are likely to be temporary. If the observed beneficial effects of TDD in hepatic failure are con-firmed, there may be an opportunity to use the procedure to bridge patients to transplantation or surgery to address the underlying cause.

Efficacy in Inflammatory Conditions

In this review, there appeared to be positive benefits from TDD in patients with AP or peritonitis. Pancreatic enzymes and other potentially toxic factors such as ammonia and urea were usually higher in the lymph than the blood (25,57,71,117-120). Human experiments dating back to the 1960s noted a dramatic increase in pancreatic enzymes in the TD, not seen in the blood, following pancreatic duct obstruction and administration of the pancreatic stimulatory hormone secretin (121-123). Proteomic analysis of TD lymph in a rodent model of AP has also shown markedly elevated pancreatic proteases and lipases (124). External TDD will divert pancreatic enzymes from entering the blood stream, resulting in faster normalization of serum pancreatic enzymes, which was seen in many studies in this review (57,117,119). However, as well as normalization of blood parameters, many studies also showed a clinical benefit from TDD [e.g., reduced SOFA score (27), improved SIRS criteria (93)]. Serum levels of pancreatic enzymes often do not correlate with severity in AP (125) [more so for amylase than lipase (126)] and therefore the beneficial effects of TDD were likely due to removal of other toxic factors from the lymph. This is in line with the gut-lymph model outlined above, where toxic factors released from the gut are transported via the TD and contribute to the development of SIRS and MODS (4,5). This would also explain the clinical benefit seen in patients with peritonitis and other inflammatory diseases, where gut ischemia-reperfusion injury is likely to occur in patients with SIRS. Many other potentially toxic factors released into the TD lymph from injured bowel in ACI have been identified. These include tryptophan catabolites (127), inflammatory cytokines (e.g., TNFα, IL-6, IL-4, ICAM-1) (10), modified albumin (128), and gut-derived exosomes (129). Furthermore, pancreatic lipase elevation without a commensurate increase in anti-lipase activity results in an increased production of free fatty acids, some of which are pro-inflammatory and injurious to end-organs (130). This review adds to the body of evidence that removal of these toxic factors through external TDD is likely to have a clinical benefit.

Safety of TDD and Potential Reasons for the Decline in Therapeutic TDD

This review highlighted the relative safety of open TDD as no studies reported mortality or significant, life-threatening, adverse effects from the procedure. Open TDD was also found to be a safe procedure on review of the English literature, where the most common complication was wound infection (22). However, surprisingly, there have been only two publications on the use of TDD in the clinical setting over the last decade, signifying a decline that is apparent in both English-language and Eastern European studies (*Fig. 2*). This decline does not align with the majority of studies suggesting that TDD has clinical benefits. Reasons for this decline are not clear

but almost certainly include the lack of definitive (Level 1) evidence. Wang et al (22) pointed out that the decline in published experience with TDD in the West was likely due to the advent of less invasive and more specific treatments, such as immunosuppression in transplantation, monoclonal antibodies for autoimmune conditions, and interferon therapy in viral hepatitis. It is possible that these treatments were not available in Eastern Europe until later. In addition, there may not have been centers of excellence with sufficient experience to drive the change in practice. Of note however, the majority of the studies in this review included patients with SIRS and MODS, for which there remains no specific treatment despite the advances in intensive care (102).

Short term (less than 10 days) use of TDD appears to be safe and associated with therapeutic benefit (49,52,58). The long-term use of TDD has also been reported but can be associated with hypoproteinemia and immune suppression. If long term drainage is required, these complications appear to be satisfactorily attenuated with the use of 'lymphosorption' or lymph dialysis, which was reported more frequently in the Eastern European experience than in the West. Ivanovich (28) suggested that the reason for the decline in the use of lymphosorption in the 1990s was because of the issues of poor or no lymph flow (presumably due to clots) and high labor costs. Other possible reasons for the decline in TDD include infection, chylous leak, cosmetic (scar on neck), and the challenges of anatomical variation (resulting in cannulation failure). These issues are in the main related to the open nature of the techniques, and the more recently introduced minimally invasive techniques appear to overcome these issues (18).

Future Potential of Therapeutic TDD

Only one institution, based in the Ukraine (131), was found that currently performs therapeutic TDD, but it appears that it is only offered for TD outlet obstruction secondary to metastatic disease. This review points to a likely overall positive clinical benefit, so it is worth considering the requirements for the design and conduct of high-quality clinical trials to provide definitive evidence (or not) of efficacy. There would appear to be a number of pre-requisites for such trials:

1. Sufficient and compelling evidence base for the gut-lymph model (in particular the specific role of toxic lymph in the mediation of SIRS/MODS) to justify clinical trials. There is wide ranging and compelling preclinical experimental data to support this (2). While not exhaustive, the accumulating clinical data to support a TDD intervention, including this review and the review of the English literature (22), is in the authors' opinion sufficient to proceed to more definitive clinical trials.
2. The possibility of selecting patient groups that are most likely to benefit from TDD and therefore be prioritized for clinical trials. This review has suggested that patients with both acute and chronic liver failure, and systemic inflammatory diseases such as sepsis, AP, and peritonitis, are likely to benefit from TDD. Within these broad categories, this review has also highlighted several patient subgroups where TDI may be particularly effective. The first is patients with increased terminal TD pressures and diameters. This occurred most often in the context of acute or chronic liver failure, especially that complicated by portal hypertension, but was also seen in AP (25,58), peritonitis (65), sepsis (71), and even chronic lower limb lymphovenous insufficiency (24). Terminal TD pressure that is higher than central venous pressure indicates a relative functional and/or anatomical outflow obstruction at the LVJ. In this review, LVJ valve failure (40), sclerosis of the LVJ valve (36), and dynamic insufficiency of the LVJ when the TD diameter was increased (24) were all seen. Increased central venous pressure, which is commonly seen in ACI, may cause a functional outflow obstruction due to compression of the terminal TD as it traverses obliquely across the venous wall (14,132). Patients with terminal TD outflow obstruction and a chronic condition such as chronic liver failure or heart failure may be particularly suited to LVA, which provides permanent

internal TDD, without loss of protein or immune cells. Modern microsurgical techniques with pre-operative imaging have greatly decreased the risk of performing LVA, as seen in newborns with congenital TD outflow obstruction (133).

Another patient sub-group likely to benefit from TDD is those with documented lung, liver, or bowel edema. Edema, defined as excess fluid within the interstitial space, is usually resolved with lymphatic drainage. On the basis that TDD increases end-organ lymphatic drainage, TDD should decrease tissue and organ edema. Using radionuclide methods, Samsonov (69) showed that TDD significantly decreased pulmonary edema in patients with pneumonia compared to controls. Furthermore, this effect on edema was not seen in patients who underwent hemosorption (69). A marked decrease in dyspnoea and orthopnoea, peripheral edema, and ascites was also seen in an English-language study in 12 patients with severe congestive heart failure who underwent TDD (13). Olegovich (24) showed a dramatic reduction in lower limb edema after TDD. Furthermore, many studies (e.g., 26,62,64), including one RCT (23), showed a reduced time to return of bowel function after TDD. This deserves further investigation as bowel edema, a common occurrence in patients with ACI, is known to contribute to the development of ileus (134). Reduced bowel wall edema could therefore contribute to the resolution of ileus.

3. A reliable and minimally invasive technique for cannulating the TD for external drainage. The basis for such a technique has been published (18). This involves ultrasound-guided Lipiodol injection of groin nodes and then the transabdominal Seldinger technique for antegrade guidewire insertion via the cisterna chyli to the thoracic duct and subclavian vein. The wire is then retrieved via the basilic vein to allow reliable retrograde cannulation of the thoracic duct. This technique can be readily taught to experienced interventional radiologists. It has some advantages over open TDD, including overcoming anatomical variation of the terminal TD (14,132), removing the risk of chylous leak, and avoiding a scar on the neck.

4. Evidence of whether lymphosorption (21) needs to be combined with TDD to ensure maximum efficacy and minimize the biochemical and immunological impact.

Based on the above and the accumulating evidence supporting the gut-lymph model, an initial RCT of minimally invasive TDD in patients with sepsis is now underway (135). Based on this RCT and other evidence, including this review, clinical trials can be extended to other patient groups and other settings.

Limitations

This review is limited by the poor quality of evidence available, where key criteria such as randomization and prospective design were missing. The study quality and the heterogenous indications for TDD meant that proper systematic review techniques and meta-analysis were not possible. Furthermore, many studies did not provide objective detail on the efficacy and instead used general statements such as "improvement in the general condition," or "reduction of intoxication." This review is further limited by the age of some studies. There have been improvements in treatments and outcomes over time, and so the treatment effect is likely to be less with modern healthcare. We would note however that many of the indications for TDD in the included studies still do not have effective interventions targeting the underlying pathological mechanisms. Overall, these factors limit the ability to make any definitive conclusions on the efficacy of TDD from this review. Despite these limitations, the available clinical data suggests clinical benefit in certain patient groups, and when combined with the pre-clinical data supporting TDD, more definitive and adequately powered trials are now required.

CONCLUSIONS

This review has identified, translated, and analyzed for English speaking researchers, a 'hidden' literature comprising 113 publications from Eastern European centers

that have evaluated the impact of therapeutic TDD on a range of acute and chronic diseases. These studies are particularly relevant today where there is a growing interest in therapeutic TDD for acute and critical illnesses. In many of these illnesses, intensive care treatment is supportive, and we do not have a targeted intervention that addresses an underlying and treatable driver of severity. In this review, TDD was most often offered when other treatment options had been exhausted and the benefit often correlated with the volume of lymph drained. Overall, despite the generally poor quality of many studies, there appeared to be a positive benefit from TDD in particular when combined with lymphosorption. Furthermore, there were very few reported complications with this large number of patients that underwent the procedure, some of whom were in a critical condition, suggesting that TDD is safe. The apparent decline in the reported use of these open surgical TDD techniques is notable, but the likely underlying reasons can be addressed with the minimally invasive approach to TD cannulation and drainage (18). The available pre-clinical and clinical data along with improved TDD methods, means that it is now important to proceed to definitive randomized controlled trials to properly evaluate the clinical benefit of therapeutic TDD in a range of acute, critical, and chronic diseases.

SUPPLEMENTARY MATERIAL

Please contact the corresponding author for detailed summary tables of the included studies.

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CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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