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Review article: the diagnostic approach and current management of chylous ascites

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ABSTRACT

BACKGROUND:

Chylous ascites is rare, accounting for less than 1% of cases of ascites. An appropriate and stepwise approach to its diagnosis and management is of key importance.

AIM:

To review the current diagnostic approach and management of chylous ascites.

METHODS:

A literature search was conducted using PubMed using the key words ‘chylous’, ‘ascites’, ‘cirrhosis’, ‘pathophysiology’, ‘nutritional therapy’, ‘paracentesis”, “transjugular intrahepatic portosystemic shunt” and “TIPSS’. Only articles in English were included.

RESULTS:

Chylous ascites is caused by the traumatic or obstructive disruption of the lymphatic system that leads to extravasation of thoracic or intestinal lymph into the abdominal space and the accumulation of a milky fluid rich in triglycerides. The most common causes are malignancy, cirrhosis and trauma after abdominal surgery. This condition can lead to chyle depletion, which results in nutritional, immunologic and metabolic deficiencies. An ascitic triglyceride concentration above 200 mg/dl is consistent with chylous ascites. Treatment is based on management of the underlying cause and nutritional support.

CONCLUSION:

Chylous ascites is mostly due to malignancy and cirrhosis in adults and congenital lymphatic disorders in children. Treatment with nutritional optimization and treating the underlying etiology is the cornerstone of therapy. When conservative measures fail, other interventions such as ocreotide/somatostatin analogues, surgical ligation, embolization and transjugular intrahepatic portosystemic shunt in patients with cirrhosis can be considered.

Introduction

Chylous ascites is defined as a milky appearing, triglyceride-rich peritoneal fluid, characterized by the presence of thoracic or intestinal lymph in the abdominal cavity.[1] Abdominal malignancy, cirrhosis, lymphatic disruption after abdominal surgery, and infections represent the leading causes in adults.[2] In children, congenital lymphatic abnormalities and trauma are considered the most common etiologies.[3] Its incidence is not well established, however previous data from Press et al. published in 1984 indicates that it accounts for 1 per 20,000 hospital admissions overall, since then no further epidemiological studies have been performed, thus the current incidence is not well known.[4] Chylous ascites is rich in nutrients and immunoglobulins, which become no longer biologically available after accumulating in the peritoneum. This can lead to dehydration, malnutrition, electrolyte imbalance and immunosuppression.[5] Therefore, prompt diagnosis and treatment is warranted. Herein, we review best practices for diagnosis and conservative treatment as well as emerging therapeutic options for refractory cases of chylous ascites.

Methods

A literature search was conducted using PubMed using the key words ‘chylous’, ‘ascites’, ‘cirrhosis’, ‘pathophysiology’, ‘nutritional therapy’, ‘paracentesis” and “TIPSS’. Only articles in English were included.

Pathophysiology

The underlying cause of chylous ascites is the disruption of lymphatic flow. An interconnected network moves lymph – a complex mixture of proteins, lipids/chylomicra, and immune cells – from the body to the thoracic duct where it empties into the venous circulation at the union of the left internal jugular vein and the subclavian vein. Lymph is propelled through its circuit by the active, intrinsic contraction/relaxation of lymphatic vessels and passive, external compressive forces (skeletal muscles, central venous pressure variations, respiratory movement and pulsations of adjacent arteries).[6] Approximately half of the lymph originates in the intestine. After hydrolysis and emulsification, fatty acids and monoglycerides are converted into triglycerides, which are subsequently absorbed into the lymphatic system as chylomicrons. Hence, the milky appearance of the lymph is attributed to its high triglyceride and free fatty acid content.

Browse, et al[7] proposed three pathophysiologic mechanisms by which chylous ascites occurs (Table 1): acquired lymphatic disruption, fibrosis of the lymphatic system and congenital causes. Acquired lymphatic disruption from surgery or trauma, leads to dilation of the retroperitoneal lymphatics with subsequent drainage of lymph into the abdomen through a lymphoperitoneal fistula. This dilation of lymphatic vessels also occurs as a result of the increased lymph production and elevated hepatic venous pressure seen in patients with cirrhosis and constrictive pericarditis. Cardiac conditions such as right heart failure and dilated cardiomyopathy lead to an increased lymphatic pressure from disrupted lymphatic drainage, thereby causing lymph stasis, lymphatic dilation and chylous ascites. The caval and hepatic venous hypertension precipitates an increment in the production of hepatic lymph.[8] The second proposed mechanism is lymph node fibrosis, most commonly due to malignancy causing lymph flow obstruction from the gut into the cysterna chyli, resulting in leakage from the dilated subserosal lymphatics into the peritoneum. The chronic effects of a persistently elevated lymphatic pressure may lead to collagen deposition at the basement membrane of the lymphatics, impairing the intestinal mucosal absorptive capacity. This process can cause protein-losing enteropathy with malabsorption, chronic steatorrhea and malnutrition. Lastly, congenital causes like congenital lymphangiectasia lead to exudation and leakage of lymph through a fistula into the peritoneal cavity due to the absence of lymphatic valves.

Etiologies

Multiple etiologies have been described as causes of chylous ascites. Traditionally, the most common causes in western countries are abdominal malignancy and cirrhosis, accounting for two-thirds of atraumatic chylous ascites cases.[4] In developing and eastern countries, infections, such as tuberculosis and filariasis, are responsible for the majority of cases. However, Steinemann, et al[3] performed a systematic review of 190 patients with chylous ascites where a total of forty-one different etiologies were identified. The most common cause was lymphatic anomalies (32%), a condition more prevalent in the pediatric population. Malignant diseases were the second most frequent etiology (7%). Cirrhosis and mycobacterial infections were identified in 11% and 10% of the cases respectively.

Malignancy

Malignancy causes chylous ascites through the invasion and disruption of the normal lymph flow.[7] The most common malignancies reported to cause chylous ascites are lymphomas,

neuroendocrine tumors, sarcomas (Kaposi sarcoma) and leukemias (chronic lymphatic leukemias) in order of prevalence.[3]. Among the group of the abovementioned malignancies, lymphoma accounts for at least one-third of the cases[3] Solid malignancies can also cause chylous ascites.[9, 10]

Cirrhosis

Only 0.5%–1% of all cases of cirrhosis-related ascites are chylous in nature.[8, 11] Runyon, et al,[12] analyzed a total of 901 ascites samples where eleven were chylous ascites; ten of them were found to be secondary to cirrhosis and one due to malignancy. The underlying etiology is unclear but may be related to excessive hepatic and gastrointestinal lymph flow (up to 20 L/day) secondary to portal hypertension, leading to spontaneous rupture of the serosal lymphatic channels. Although data is limited, transjugular intrahepatic portosystemic shunt has proven effective for cases of refractory chylous ascites.[13, 14] The decompression of the portal vein has shown to relieve lymphatic hypertension.[15]

Infection

Mycobacterium tuberculosis and filariasis represent the most common causes of chylous ascites in third world countries.[3] Granulomatous lymphadenitis is thought to be the central cause of lymphatic obstruction and development of chylous ascites in *Mycobacterium tuberculosis* infection. It is important to also consider the diagnosis of tuberculosis in patients with alcohol abuse and malnutrition due to their relative immunocompromised state. Among patients with HIV, chylous ascites can occur in association with *Mycobacterium tuberculosis*, *Mycobacterium Avium Complex* and Kaposi sarcoma as a complication of immune reconstitution inflammatory syndrome.[16, 17] Filariasis, an infection caused by the parasite *Wuchereria bancrofti* in third world countries, causes a severe inflammatory reaction in the lymphatics that results in lymphedema and chylous ascites.

C*ongenital*

The congenital causes of chylous ascites are more commonly seen in the pediatric population. Steinemann, et al found lymphangiectasia as the most common cause of congenital anomaly in children (84%).[3] Lymphangiectasia or Waldmann's disease is characterized by the presence of dilated lymph vessels due to the lack of valves in the submucosa of the small bowel resulting in leakage of lymph. Waldmann first described this disorder in 1961 as a cause of protein-losing enteropathy, lymphopenia, hypoalbuminemia and hypogammaglobulinemia.[18] Lymphatic

anomalies account for only 8% of atraumatic cases of chylous ascites.[3]

Other lymphatic anomalies exist, but constitute a smaller percentage of cases of congenital chylous ascites. For example, yellow-nail syndrome causes chylous ascites due to hypoplastic lymphatics and consists of the triad of lymphedema, pleural effusion and/or chylous ascites, and yellow discoloration with nail dystrophy.[19] The Klippel-Trenaunay syndrome is an inherited autosomal dominant disorder that is characterized by capillary and lymphatic hypoplastic malformations that causes chylous ascites and is associated with soft tissue and bony hypertrophy.[20-22] Lymphangiomas arise from sequestration of lymphatic tissue, which fail to communicate with the lymphatic system, and can reside in the neck, intestine, pancreas or mesentery.[23, 24]

Inflammatory

Chylous ascites may occur due to radiotherapy, retroperitoneal fibrosis (Ormond' s disease), and autoimmune diseases like sarcoidosis, Behçet's disease, Henoch-Schönlein purpura and systemic lupus erythematous.[25, 26] Radiation has the same pathophysiological mechanism as retroperitoneal fibrosis; both cause fibrosis and obstruction of the lymphatics in the small bowel and mesentery with the development of chylous ascites.[27-29] Sarcoidosis can produce chylous ascites by producing intrathoracic nodal fibrosis and lymphatic obstruction. Chylous ascites from systemic lupus erythematous is more often seen in the elderly who have an insidious onset of disease, which is less commonly associated with the classic rheumatologic manifestations.[30, 31] It is proposed that the inflammation of the lymphatic vessels causes an increase in the endoluminal pressure disrupting permeability of the lymphatic walls and leading to extravasation of chyle.[32-34]

Traumatic and Postoperative

Any abdominal trauma that disrupts the lymphatic vessels can cause chylous ascites.[35] In children, battered child syndrome should be excluded in the presence of chylous ascites, as it accounts for 10% of cases in the pediatric population.[36, 37] Chylous ascites can occur early (around 1 week) after abdominal surgery due to disruption of the lymphatic vessels or late (weeks to months) due to adhesions or extrinsic compression of lymphatic vessels. Chylous ascites has been reported after many surgical procedures, including thoracic or abdominal aneurysm repair, retroperitoneal lymphadenectomy catheter placement for peritoneal dialysis, inferior vena cava resection, vagotomy, Nissen fundoplication, gastric bypass, pancreaticoduodenectomy and

gynecological surgery. Liver and kidney transplants have also been associated with postoperative chylous ascites.[38-40] Yilmaz, et al[41] reported a postoperative incidence of chylous ascites of 4.6% in a total of 516 liver transplant cases over a 9-year period. Low albumin, the presence of ascites before transplantation, and the use of LigaSure vessel sealing system instead of conventional suture were recognized as risk factors for developing chylous ascites.

Other Causes

Other less common causes include cardiac conditions, nephrotic syndrome, pancreatitis, celiac sprue, Whipple's disease and retractile mesenteritis.[42-47] Cardiac disease with increased right-venous pressures can lead to increased hepatic lymph production; causing impaired drainage, chyle stasis, lymphatic dilation and ultimately chylous ascites.[48-50] These include right heart failure, dilated cardiomyopathy and constrictive pericarditis. Chen, et al,[51] reported a case of chylous ascites secondary to cardiac amyloidosis, where the contributing factor was thought to be increased left subclavian venous pressure. Both acute necrotizing pancreatitis and chronic pancreatitis are associated with chylous ascites; the underlying mechanism remains unknown but is thought to be due to direct compression of lymphatic channels.[52, 53]

Evaluation and Diagnosis

The clinical evaluation of a patient that presents with ascites should start with a thorough history and physical examination. The detailed history must include family history, recent trauma or surgery, travel, social history, and past medical history, particularly looking for malignancy, liver or renal disease. The most common presenting symptoms in order of frequency are abdominal distension, abdominal pain, diarrhea, dysphagia and progressive peripheral edema.[3] Other features may include nausea, vomiting, early satiety, diarrhea, steatorrhea, malnutrition, edema, fever and night sweats. Shortness of breath, weight gain and increased abdominal girth due to increased abdominal pressure may be present. Physical examination may reveal cachexia, temporal wasting, evidence of pleural effusions or ascites, abdominal masses and hernias, stigmata of chronic liver disease, and lower extremity edema.

Laboratory Findings

Obtaining laboratory parameters in the blood and ascites is central in the diagnosis and evaluation of chylous ascites. Standard blood tests are required and should include complete blood count, basic metabolic panel, liver function tests, total protein, albumin, lactate dehydrogenase (LDH),

lipid panel, amylase and lipase. A paracentesis is mandatory and is the diagnostic tool of choice in evaluating patients with ascites (Figure 1). If the appearance of the ascites is milky and chylous ascites is suspected, a triglyceride level should be measured in the ascitic fluid. A triglyceride concentration above 200 mg/dL supports the diagnosis of chylous ascites, while a level less than 50 mg/dL excludes it.[1, 4] The macroscopic appearance of chylous ascites is turbid and thick compared to the straw-colored, transparent ascitic fluid seen in portal hypertension.[54] Microscopic examination of the fluid stained with Sudan III shows fat globules and leukocytes with a lymphocytic predominance. Ascitic fluid should be sent for cytology, cell count, Gram's stain, culture, total protein concentration, albumin, LDH, glucose, triglyceride and amylase.[55] If tuberculosis is suspected, tuberculosis smear, adenosine deaminase and culture should be performed. Adenosine deaminase is a sensitive (93%) and specific (94%) method to diagnose peritoneal tuberculosis, but peritoneal biopsy is required in some cases. The diagnostic accuracy of adenosine deaminase is not influenced by different study settings, adenosine deaminase cut-off or methodological quality.[56] The total protein content ranges between 2.5 to 7.0 g/dl and will vary according to the underlying etiology.[12] Typically, hepatic cirrhosis is associated with a total protein concentration in the ascites of less than 2.5 g/dl. Additionally, the serum to ascites albumin gradient can be used to identify the presence of portal hypertension in the setting of liver-related disease.[57] A serum to ascites albumin gradient below 1.1 g/dl rules out portal hypertension and suggests other etiologies. In patients with chylous ascites secondary to cirrhosis, the serum to ascites albumin gradient is normally above 1.1 g/dl. [58, 59] Interestingly, CA-125 has been reported to be particularly elevated in cirrhotic patients with chylous ascites.[60] (Figure 2)

Radiology

Radiological assessment also plays an important role in the evaluation of chylous ascites. Lymphangiography is the gold standard diagnostic tool in cases of lymphatic obstruction. Lymphangiography and lymphoscintigraphy are useful in detecting abnormal retroperitoneal nodes, leakage, fistulization and patency of the thoracic duct. These techniques are also effective for selecting patients for surgery and assessing the effects of treatment.[61, 62] Computed tomography (CT) and magnetic resonance imaging are not specific to chylous ascites, however they are useful in identifying intraabdominal masses, fluid collections or lymph nodes. The CT density of chylous ascites resembles that of water and is indistinguishable from urine, bile, bowel secretions or simple ascites.[63]

Treatment

The management of chylous ascites is a multifaceted process with limited therapeutic options available. The cornerstone of therapy revolves around correcting the underlying cause and applying conservative measures to improve patient comfort, reduce recurrence and optimize outcomes. Treatment should be individualized and adjusted for the severity of chylous ascites. Conservative measures are centered on maintaining an optimum nutritional balance and administering therapies in order to reduce the production and flow of lymph (Table. 2).

The key initial step in management of chylous ascites is to optimize the patient's nutritional status. Nutritional support includes a high-protein, low fat diet supplemented with medium-chain triglycerides.[64] Medium-chain triglycerides are absorbed by the enterocytes and transported as free fatty acids and glycerol directly into the liver through the portal vein, sparing the lymphatic system. This is in contrast to long-chained triglycerides, which are converted to free fatty acids and monoglycerides that are then transported as chylomicrons to the intestinal lymph ducts contributing to the overall lymphatic pool. Capric, caprylic and lauric acid are medium-chain triglycerides found in coconut oil, palm kernel oil, whole milk, butter and cheese. Most oils and fats, including nuts, fish, meat, olive oil and avocado contain long-chained triglycerides and should be avoided in chylous ascites.[65] Orlistat, a gastric and pancreatic lipase inhibitor, has shown to reduce the triglyceride concentration in ascites and can be used adjunctively to a low-fat diet with medium-chain triglycerides, although data is limited [66]

Somatostatin, or its synthetic analogue, octreotide, have been used as well in the treatment of chylous ascites.[67] The exact mechanism of action of somatostatin or its analogue is not completely understood. However, it has shown to decrease portal pressure by inhibiting glucagon and other intestinal peptide-mediated splanchnic vasodilatation. It also diminishes peristalsis, intestinal absorption of fats, triglyceride concentration in the thoracic duct and attenuates the lymph flow in the major channels.[68] Somatostatin must be administered intravenously due to its short half-life of 1-3 minutes. Octreotide has a longer half-life of 2 hours and the advantage of subcutaneous administration. This somatostatin analogue has successfully been used in patients with chylous ascites secondary to pancreatitis, malignancy, post liver transplant, portal vein thrombosis and idiopathic cases.[69, 70] Berzigotti et al,[68] utilized it as a long-term medication during 6 months in a patient with refractory chylous ascites in the setting of cirrhosis with no

relapses after discontinuation. In addition to nutrition and somatostatin analogues, total parenteral nutrition (TPN) can be considered if other measures fail. However, emerging data has found enteral nutrition with medium-chain triglycerides superior to TPN.[71] Recently, Pan et al,[72] in a retrospective study of 58 patients with postoperative chylous ascites evaluated the clinical effect of somatostatin, enteral medium-chain triglycerides diet and TPN. The early initiation of somatostatin demonstrated better outcomes than its delayed initiation; and the use of enteral nutrition with medium-chain triglycerides was superior to TPN. Historically, TPN has also shown to have associated adverse effects, such as cholestasis, fatty liver and fungal infections, which may preclude its use.

Therapeutic paracentesis may be performed to provide temporary symptomatic relief. Repetitive drainage should be avoided as it can lead to electrolyte imbalance, malnutrition and infection.[73] Intravascular volume and albumin replacement to prevent post-paracentesis circulatory derangements is not necessary unless the patient has underlying cirrhosis.

The management of cirrhosis-related chylous ascites involves a stepwise management approach. Initially, treatment is centered on the use of diuretics and nutritional optimization with a low sodium, low fat, and high protein diet with medium-chain triglycerides. In patients who are refractory to medical therapy and maintain normal liver function, transjugular intrahepatic portosystemic shunt can be considered to help reduce portal pressures, although the data is limited.[13, 74] Even though the effects of transjugular intrahepatic portosystemic shunt on chylous ascites are still preliminary, it is believed that portal decompression reduces the flow of lymph and reduces the formation of chylous ascites.[14] The recurrence of symptoms after shunt dysfunction supports this theory.[13] Nonetheless, the benefit of transjugular intrahepatic portosystemic shunt placements should be weighed with its inherent risks.

A number of additional therapeutic strategies have been trialed for refractory chylous ascites including glue embolization, spleno-renal shunt, surgical ligation and embolization of disrupted lymphatic channels, but the data is preliminary.[75-77] Peritoneovenous shunting was used in the past, however it is rarely performed nowadays due to its high morbidity from sepsis, electrolyte imbalance, disseminated intravascular coagulopathy, small bowel obstruction and air embolism.[78] Despite the number of potential therapeutic options available for chylous ascites, conservative treatment remains the cornerstone of therapy in these patients until further data emerges.

Conclusion

Chylous ascites is an uncommon disorder characterized by the presence of a milky-appearing, triglyceride-rich fluid in the peritoneum. It is caused by the disruption of the lymphatic system with subsequent leakage of thoracic or intestinal lymph into the abdominal cavity. The most common etiologies are malignancy and cirrhosis in adults and congenital lymphatic disorders in children. Infectious causes are more prevalent in developing countries. Other pathologies associated with chylous ascites include pancreatitis, sarcoidosis, autoimmune diseases, post-surgical complications and other hereditary disorders. The diagnosis is still based on clinical history, paracentesis and ascitic fluid analysis. Perhaps the most relevant topic regarding chylous ascites is its treatment. Conservative treatment with nutritional optimization and treating the underlying etiology remains the cornerstone of therapy for chylous ascites. A high protein, low fat diet with medium-chain triglycerides has shown to be beneficial. When conservative measures fail, other interventions such as ocreotide/somatostatin analogues, surgical ligation, embolization and transjugular intrahepatic portosystemic shunt in cirrhotic patients can be considered. Further investigation on the optimal therapeutic management for refractory cases of chylous ascites is warranted.

Table 1. Chylous ascites etiologies, mechanisms and causes

Etiology	Mechanism	Causes
Acquired	Thoracic duct obstruction or disruption _____ Increased lymph production	Trauma/ surgery Infections (TB, filariasis), radiotherapy, autoimmune (SLE, sarcoidosis) _____ Cirrhosis Cardiovascular disease
Fibrosis	Invasion and disruption of the normal lymph flow	Lymphomas Neuroendocrine tumors Sarcomas Leukemia

		Solid organ malignancies
Congenital	Disrupted or dilated lymphatic vessels	Lymphangiectasia Waldmann's disease Yellow-nail syndrome Klippel-Trenaunay syndrome Lymphangioma
TB: Tuberculosis, SLE: systemic lupus erythematous		

Table 2. Approach to therapy in chylous ascites

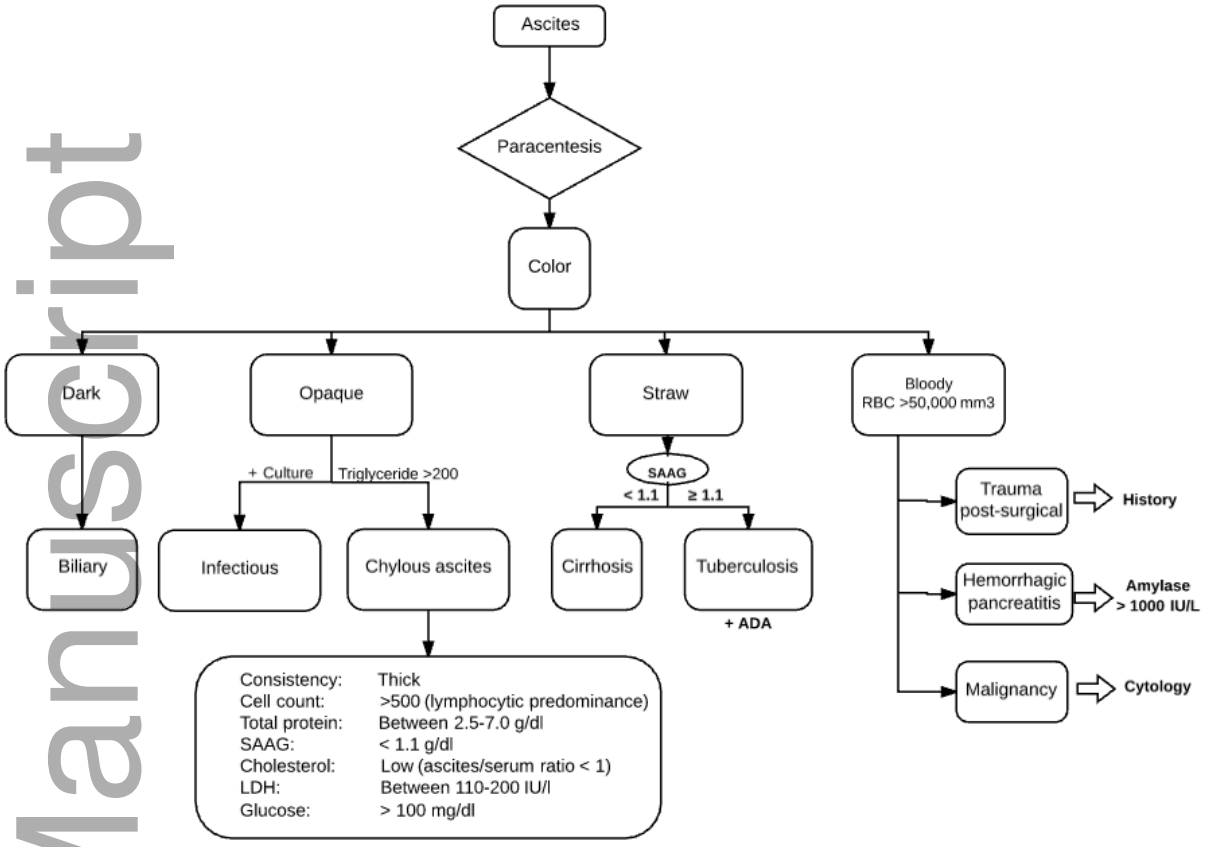
Treatment	Indication	Mechanism	References
First treat underlying cause			
Dietary Adjustments: 1) Low-fat, high protein diet 2) Medium-chain triglycerides 3) Low-salt (particularly in cirrhosis)	All causes of chylous ascites	Reduces production and flow of chyle	[64, 65]
Therapeutic paracentesis		Temporary symptomatic relief	[73]
Orlistat*		Reversibly inhibits gastric and pancreatic lipase, reducing absorption of fats	[66]
Somatostatin/Ocreotide*		Exact mechanism unknown. Believed to decrease portal pressure and reduce intestinal fat absorption	[67-70]
Diuretics	Cirrhosis and	Facilitate excretion of volume	[64]

	cardiac related chylous ascites	reducing ascites formation	
Transjugular intrahepatic portosystemic shunt *	Refractory cirrhosis related chylous ascites	Reduce portal pressure	[13, 14, 74]

*There is not sufficient data for these interventions.

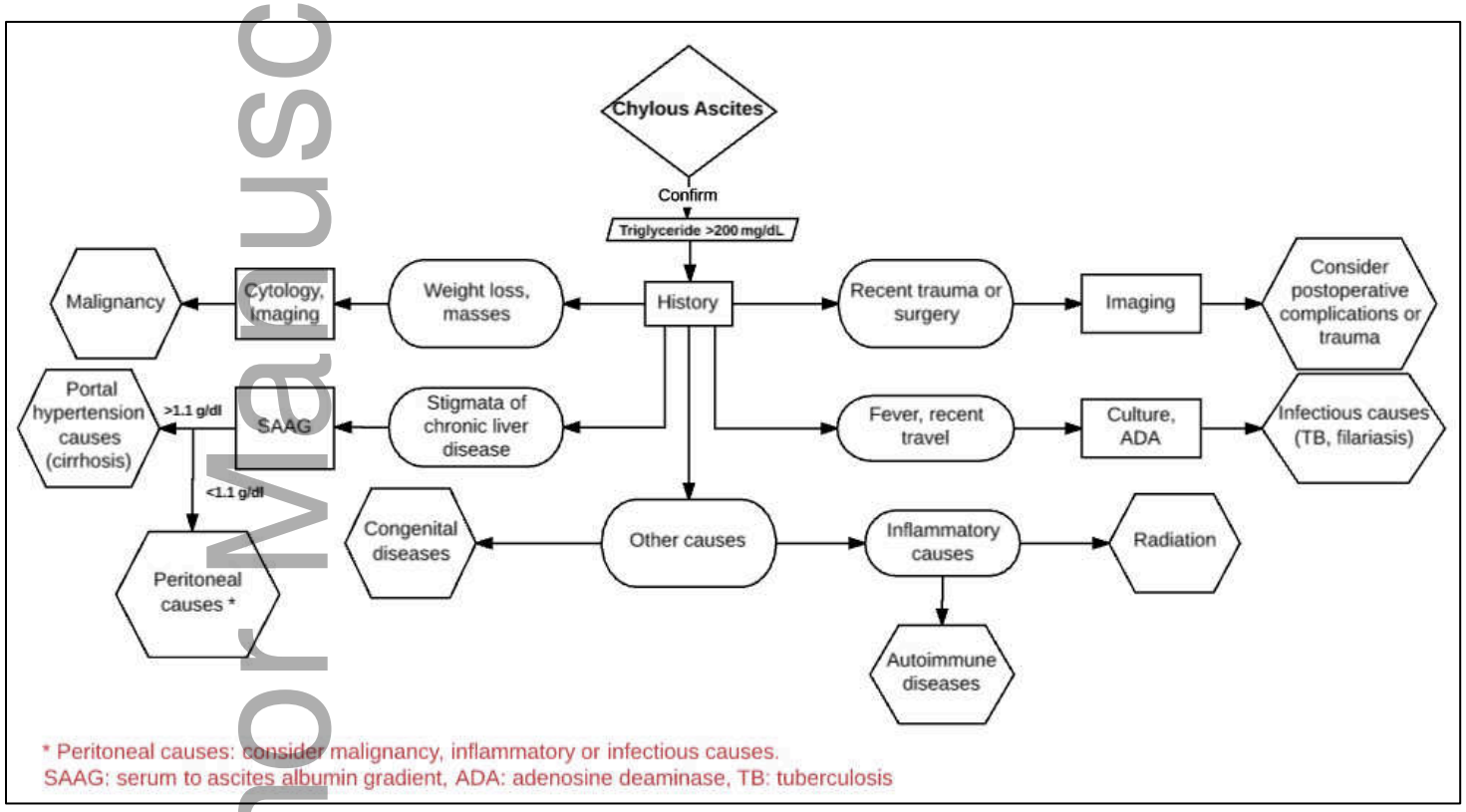
Other therapies such as glue embolization, spleno-renal shunt, surgical ligation and embolization of disrupted lymphatic channels are not recommended due to preliminary data. Peritoneovenous shunting is no longer used due to high morbidity from adverse effects.[75, 77, 78]

Figure 1. Ascites workup and chylous ascites fluid characteristics



RBC: red blood cells, SAAG: serum to ascites albumin gradient, LDH: lactate dehydrogenase, ADA: adenosine deaminase

Figure 2. Chylous ascites differential diagnosis algorithm



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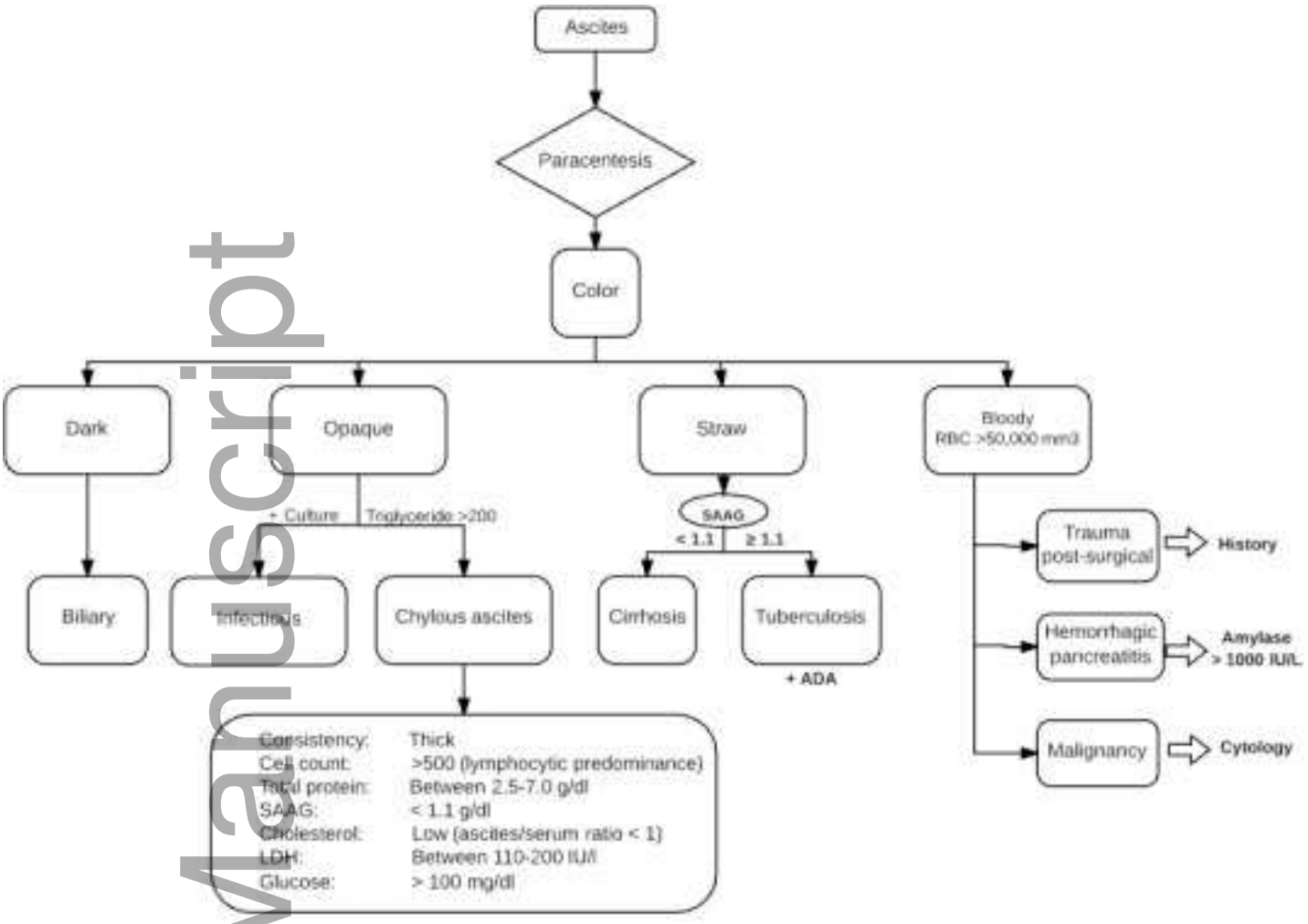

RBC: red blood cells, SAAG: serum to ascites albumin gradient, LDH: lactate dehydrogenase, ADA: adenosine deaminase

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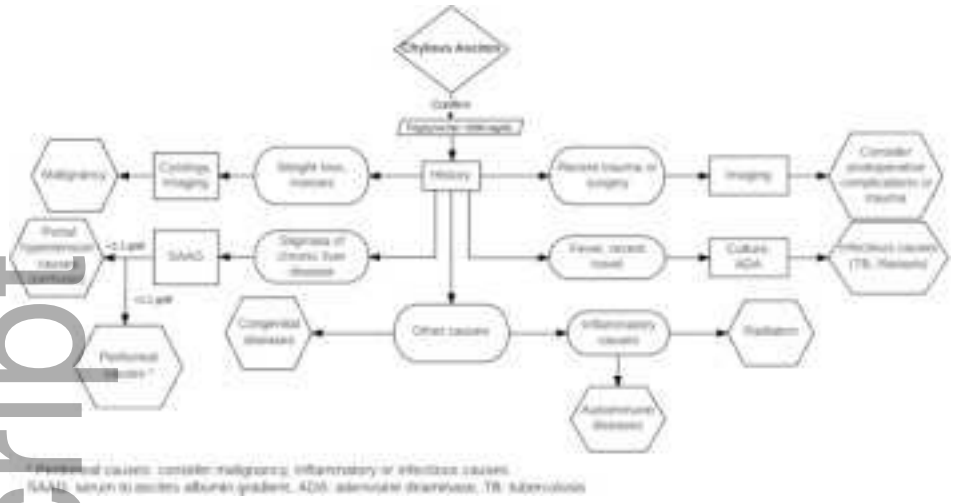

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