Management of Recurrent Transudative Effusions in Congestive Heart Failure and Hepatic Hydrothorax

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KEYWORDS

• Transudative effusion • Hepatic hydrothorax • Congestive heart failure

KEY POINTS

- Recurrent transudative pleural effusions are often caused by decompensated heart failure and hepatic hydrothorax, both of which have a poor prognosis and high 1 year mortality.
- The primary management for these recurrent transudative pleural effusions is to optimize medical treatment of the underlying disease.
- In patients with recurrent cardiac-related pleural effusion that is refractory to medical management, the next step should be personalized, considering the overall treatment goals and candidacy for cardiac transplant.
- For patients with hepatic hydrothorax that is refractory to medical management, the next step requires a personalized approach and multidisciplinary discussion to evaluate for transjugular intrahepatic portosystemic shunt) placement and/or liver transplant candidacy.

INTRODUCTION

Pleural effusion is estimated to affect 1.5 million people in the United States each year,[1-3] with up to 1.3 million caused by nonmalignant origins.[4] A nonmalignant pleural effusion (NMPE) is usually due to cardiac, hepatic, or renal dysfunction or failure, among other causes such as infection, inflammatory pleuritis, pulmonary embolism, and postoperative effusion. The leading cause of NMPE is congestive heart failure (CHF) with an incidence reported to be 500,000 annually, whereas the incidence of hepatic hydrothorax (HH) is approximately 50,000 annually.[3,5,6] The management of these effusions poses a challenge for both patients and health care providers, particularly when the effusion is symptomatic and refractory. The term "refractory" organ failure associated with pleural effusion is not well defined in the literature. However, a pleural effusion in the setting of decompensated heart or liver failure that does not respond, or only partially responds to aggressive medical management and requires repeated pleural fluid drainage procedures, is generally defined as a refractory organ failure-induced effusion.

Congestive Heart Failure

Background

Up to 87% of patients with decompensated heart failure who required diuresis have pleural effusion

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Abbreviations

ANC	absolute neutrophilic count
CHF	congestive heart failure
HH	hepatic hydrothorax
HVPG	hepatic venous pressure gradient
INR	international normalized ratio
IPS	indwelling pleural catheters
NMPE	nonmalignant pleural effusion
REPE	re-expansion pulmonary edema
TIPS	transjugular intrahepatic portosystemic shunt

on evaluation.[7] Pleural effusion due to CHF is primarily due to increasing hydrostatic pressure in the alveolar capillaries secondary to increased end diastolic left ventricular and left atrial pressure, leading to increased interstitial fluid. The fluid then moves from the interstitial space to the pleural space due to a pressure gradient. The most common presentation of pleural effusion in decompensated CHF is bilateral effusion (70%), although occasionally unilateral right-sided (21%) or left-sided (9%) effusions are detected.[8]

Diagnostic evaluation

In addition to clinical diagnosis, thoracentesis with fluid analysis can help identify other causes of effusion, such as infection or malignancy, especially when the effusion is unilateral. Pleural fluid NT-proBNP levels greater than 1500 pg/mL have shown good sensitivity (94%) and specificity (91%) and are comparable to serum NT-proBNP levels.[9–11] Therefore, in practice, a serum NT-proBNP level of greater than 1500 pg/mL, typically obtained in the primary workup in patients with CHF and the presence of bilateral pleural effusions, indicates a CHF-related effusion. In decompensated CHF, if the pleural fluid is drained, it is generally transudative, but may appear as a pseudoexudate by Light's criteria, in patients who undergo diuresis. In such cases, a serum-to-pleural fluid albumin gradient greater than 1.2 g/dL or a serum-to-pleural fluid protein gradient greater than 3.1 g/dL can reclassify the pseudoexudate as transudate.[12]

Prognosis

The mortality rate in patients with CHF ranges from 11% to 30%. The 1 year mortality rate in patients with CHF-induced effusion due to cardiac decompensation is reported to be as high as 46% to 50%.[1,13]

Management of pleural effusions in congestive heart failure

The primary approach to managing pleural effusion in CHF focuses on optimizing cardiac function. Up to 69% of patients may see resolution of pleural effusion with diuresis and improved medical management of decompensated CHF.[14] However, 30% to 50% of patients may remain refractory to treatment due to complications like renal failure and hypotension, necessitating additional procedures to relieve the effusion.[1] The details of the medical management of CHF, including optimization of dietary salt and fluid intake, choice of diuretics, and titration of guideline-directed medical therapy, are beyond the scope of this article.

Pleural Interventions in Refractory Symptomatic Congestive Heart Failure-induced Effusion

Thoracentesis

Various procedures exist for managing pleural effusion in patients with symptomatic CHF-induced pleural effusion. Thoracentesis is the most common procedure to drain pleural effusion and alleviate symptoms; however, it may involve complexities in patients with a history of cardiac disease who are on anticoagulation and/or antiplatelet therapy. The overall thoracentesis hemothorax risk associated with these medications in patients with CHF on dual antiplatelet/anticoagulation therapy remains unclear. Mahmood and colleagues[15] noted relatively low rates of clinically consequential post-procedure hemothorax among 25 patients on clopidogrel. A larger (n = 312) prospective observational cohort by Puchalski and colleagues[16] with 12% of patients with high bleeding risk on clopidogrel, and 34% with an elevated international normalized ratio (INR) due to liver disease or warfarin (anticoagulation), concluded that thoracentesis may be safely performed without prior correction of coagulopathy or medication-induced bleeding risk. Conversely, Dangers and colleagues,[17] in a French multicenter cohort study (n = 1124), reported a significant association between hemothorax and antiplatelet therapy (odds ratio = 4.13; 95% CI, 1.01%–17.03%; P=.044). Other considerations in patients requiring repeated thoracentesis include the burden of outpatient visits or hospital admissions to patients and their families and long periods of progressive breathlessness between procedures. Furthermore, there remains uncertainty regarding the safe volume of fluid that can be removed due to concerns about re-expansion pulmonary edema (REPE). Although some evidence suggests that REPE may not be directly correlated with the volume of fluid removed, establishing definitive guidelines for safe drainage volumes remains challenging.[18] Although pleural manometry has been employed to guide large-volume thoracentesis

procedures, routine pleural pressure monitoring has not demonstrated consistent effectiveness in alleviating symptoms of chest discomfort during and after drainage.[19]

Tunneled pleural catheters

An alternative procedure in symptomatic refractory CHF-induced effusion is the placement of indwelling pleural catheters (IPC) with or without pleurodesis. Studies on IPC use in CHF-induced refractory pleural effusions are predominantly single-center retrospective analyses.[20,21] Srour and colleagues performed the largest prospective cohort study (n = 38) of IPC use in patients with CHF and noted approximately one-third of patients obtained spontaneous pleurodesis, with nearly half of patients ultimately removed their catheter with a minimal (7%) effusion recurrence rate and significant improvement in dyspnea index scores.[21] In comparison to multiple single-center retrospective studies,[6,22–25] there were no reports of infectious complications, with pneumothorax and subcutaneous emphysema accounting for the largest percentage of the 34% complication rate. Most studies showed improved symptom palliation with spontaneous pleurodesis achieved in 42.1% of this population and median time to pleurodesis ranged from 66 to 150 days. A meta-analysis of 13 studies with 325 patients reported the pooled rate of all complications at 17.2% (95% CI, 9.8%–24.5%) and specifically, an empyema rate of 2.3% (95% CI, 0.0%–4.7%).[26]

IPCs are generally well tolerated and represent a viable option for managing refractory pleural effusions in patients with CHF, contingent upon multidisciplinary discussions regarding potential transplant candidacy and overall treatment goals (**Fig. 1**). The role of IPC versus serial thoracentesis in symptom control in NMPEs has been evaluated in a single open-label randomized controlled trial in 13 centers. Within the CHF cohort, no significant difference in breathlessness score was noted between the two groups. The number of required invasive procedures was lower in the IPC group; however, a higher overall adverse event rate was reported in the IPC versus serial thoracentesis groups (59% vs 37%).[27] Pleurodesis is appropriate for patients with expandable lungs, but it can pose challenges for subsequent thoracic surgeries. The evidence on the use of chemical pleurodesis in refractory pleural effusion due to CHF remains limited. In a propensity-matched study, Freeman and colleagues[20] reported no significant difference in palliation of symptoms, but the group managed with IPC had a shorter hospital stay with a lower rate of complications than patients who had talc pleurodesis. Majid and colleagues compared IPC-only management (n = 28) to IPC combined with thoracoscopic talc poudrage (n = 15) noting a higher pleurodesis rate in the talc poudrage group (80% pleurodesis compared to 25% in the IPC-only group).[24] The median time to IPC removal was shorter in selected patients with the addition of talc poudrage. This study was limited by selection bias, as patients within the thoracoscopy cohort were those who met safety criteria for thoracoscopic talc poudrage. Further research is needed to delineate the efficacy and safety of chemical pleurodesis in refractory CHF-related pleural effusions.

Hepatic Hydrothorax

Background

HH occurs in 5% to 16% of patients with cirrhosis and portal hypertension. Pleural effusion in these patients is often linked to fluid collection in the peritoneal cavity, although up to 42% may lack clinically apparent ascites.[28] One suggested mechanism involves the direct passage of ascitic fluid through small defects in the diaphragmatic tendinous structure, establishing a pleuroperitoneal communication and allowing ascitic fluid to enter the pleural cavity.[29] Other contributing factors may include hypoalbuminemia and azygos vein hypertension.[30]

Diagnostic evaluation

In patients suspected of having HH, a comprehensive evaluation is essential, incorporating detailed clinical history, physical examination, ultrasound assessment, and pleural fluid analysis to explore potential cardiac, renal, and malignant etiologies of pleural effusion. Typically, HH presents as a transudative effusion by Light's criteria, although some cases may meet the criteria for exudative effusion. Therefore, assessing the pleural fluid-to-serum bilirubin ratio, typically less than 0.6, and serum-to-pleural fluid albumin gradient exceeding 1.1 g/dL can support the transudative nature of the fluid.[31] Additionally, chylous effusion, characterized by elevated triglyceride levels, may occur, particularly in patients with increased liver capillary pressure and lymphatic flow in the liver and thoracic duct.[32] In atypical presentations of pleural effusion in cirrhotic patients, nuclear scans utilizing intraperitoneal instillation of radiotracers (99mTc-human serum albumin 99mTc-sulfur-colloid) and/or scintigraphy can aid in evaluating pleuroperitoneal communication, even in the absence of ascites.[33–35] The nuclear imaging is best performed shortly after a therapeutic thoracentesis when the fluid is reaccumulating in the pleural cavity to allow transfer of the isotope across the diaphragm.

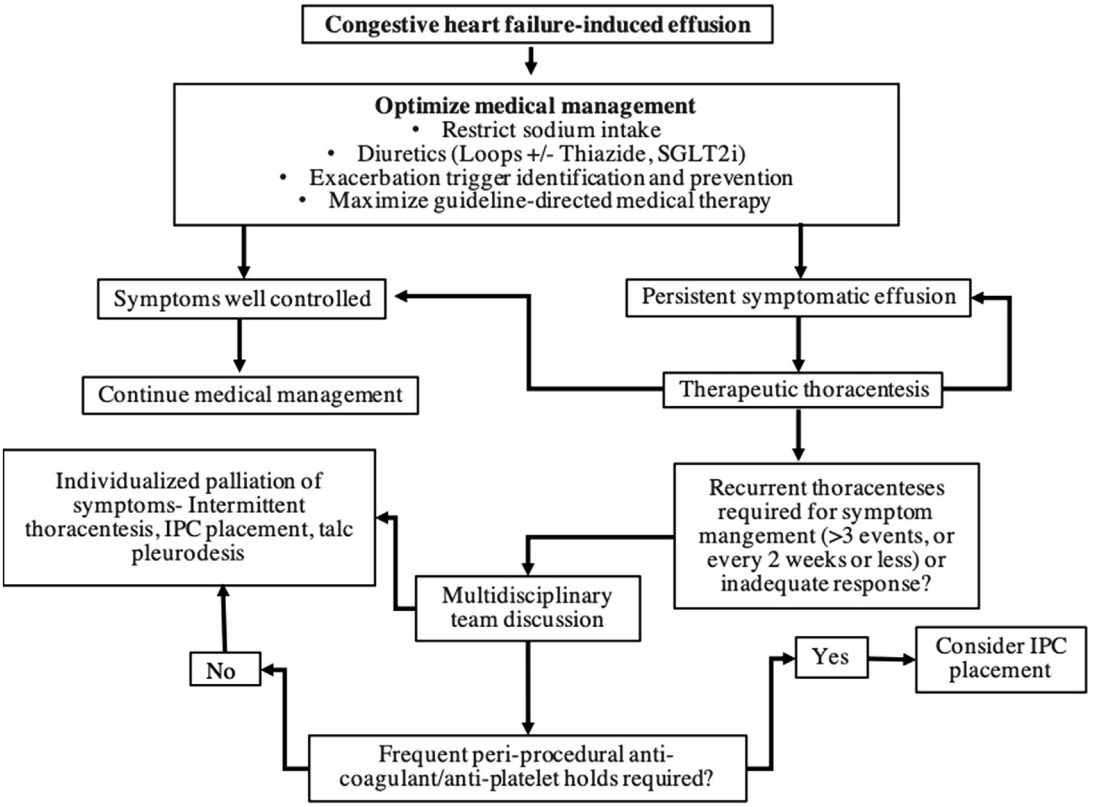

Fig. 1. Proposed algorithm in the management of CHF-induced effusion. Multidisciplinary discussion including pulmonary medicine, cardiology, transplant surgery

It is crucial to recognize that HH can lead to complications such as spontaneous bacterial empyema (SBE), reported in 10% to 16% of cases. Differentiating between HH and SBE relies on pleural fluid cell count, where an absolute neutrophilic count (ANC) less than 250 cells/mm^3 is indicative of HH, while ANC greater than 250 cells/mm^3 with positive fluid culture or ANC greater than 500 cells/mm^3 with negative culture suggests SBE.[36,37]

Prognosis

Patients with refractory HH face a significantly increased mortality risk. A study by Osman and colleagues reported a 1 year mortality rate of 51% in 47 patients with refractory HH, compared to 19% in patients with refractory ascites.[38] This finding is further supported by a retrospective study by Matei and colleagues,[39] which demonstrated a lower long-term survival rate in patients with HH (15.4%) compared to those without HH (30.9%) over 5 years. Additionally, in a prospective study by Walker and colleagues, the presence of HH was a significant predictor of mortality, with 25% of HH patients dying in 1 year.[1] In cases where HH is complicated by SBE, mortality rates can be as high as 20% to 38%, underscoring the critical need for timely recognition and treatment.[40]

Management of Refractory Hepatic Hydrothorax

Medical management

The primary goal in managing HH is to optimize the underlying disease process, which often includes dietary modifications and diuretic therapy, with additional considerations for transjugular intrahepatic portosystemic shunt (TIPS), diaphragmatic repair, and evaluation of liver transplantation. All patients with HH, with or without ascites, should adhere to dietary modifications centered on sodium restriction, limiting intake to no more than 5 g of salt per day.[41] This is in addition to diuretic use and addressing ongoing risk factors of decompensated liver disease. The first-line diuretic for patients with HH is spironolactone, an aldosterone receptor antagonist that prevents sodium reabsorption in the distal tubular cells. A loop diuretic, such as furosemide, can be added if patients do not respond to spironolactone monotherapy. Upon initiation of these

medications, patients require dose titration to achieve the intended effect and close monitoring of symptoms, hemodynamics (blood pressure and orthostatic vital signs), and renal function. Approximately 20% to 30% of patients with HH may not respond clinically despite being on high-dose diuretics.[42]

Splanchnic and peripheral vasoconstrictors such as terlipressin, octreotide, and midodrine may play a role in increasing renal sodium excretion by reducing the activation of the renin-angiotensin-aldosterone system.[43,44] More studies are needed to evaluate these therapies' role in managing HH.

Transjugular intrahepatic portosystemic shunt procedure

The presence of portal hypertension is typically measured to approximate the gradient in pressure between the portal vein and the inferior vena cava, known as the hepatic venous pressure gradient (HVPG). Portal hypertension is defined as an HVPG greater than or equal to 6 mm Hg and becomes clinically significant when the HVPG reaches or exceeds 10 mm Hg. Patients are at risk for developing varices and ascites when the HVPG is greater than or equal to 12 mm Hg. TIPS is a procedure performed to create a side-to-side shunt between the intrahepatic branch of the portal vein and the hepatic vein using a stent (bare metal or uncovered stent) to decrease portal hypertension. Patients who are not responsive to optimal medical management should be considered for TIPS after a multidisciplinary discussion, if there are no obvious contraindications. TIPS has been shown to relieve symptoms in 70% to 80% of patients.[45,46] However, a study by Young and colleagues demonstrated that TIPS did not provide a survival benefit, and the response rate and fluid accumulation were similar in both the TIPS and non-TIPS groups.[47] Common contraindications for the TIPS procedure include severe uncontrolled hepatic encephalopathy, significant pulmonary hypertension, heart failure or cardiac valvular dysfunction, uncontrolled systemic infection, and unrelieved biliary obstruction.[48] Among 332 patients in a meta-analysis by Singh and colleagues, TIPS was considered successful in 74% of cases. However, 25% of these patients had a partial resolution of their HH and required additional thoracenteses, and 27% of patients developed hepatic encephalopathy. The population 30 day and 1 year mortality were reported at 18% and 48%, respectively.[49]

In summary, while TIPS can be an effective intervention for reducing portal hypertension and alleviating symptoms in many patients with HH, it is not without risks and should be carefully considered on a case-by-case basis, weighing the potential benefits against the contraindications and individual patient circumstances.

Bridging to liver transplant or palliation

Repeat thoracentesis is a common and effective procedure to remove large volumes of pleural fluid and manage symptoms in patients with HH, particularly when draining ascites is insufficient.[50] However, patients with decompensated liver disease often have elevated INR, coagulopathy, and thrombocytopenia, which pose additional risks. Despite these concerns, when performed by an experienced operator, thoracentesis remains a low-risk procedure.[16] Nonetheless, the cumulative risk of complications, such as post-procedural hypotension, pneumothorax, and hemothorax, is significantly higher in patients with HH compared to those without HH.[51] Additionally, the presence of intercostal varicose veins in patients with end-stage liver disease can lead to spontaneous hemorrhage, hence, the use of a linear/vascular probe to evaluate the intercostal space before the procedure, especially in those with thrombocytopenia and coagulopathy is advised.[52]

Tube thoracostomy

The use of a conventional chest tube for continuous fluid drainage in patients with HH can result in significant volume loss, electrolyte imbalance, and protein loss, and is discouraged.[53,54] A large database study comparing thoracentesis to chest tube placement in patients with liver cirrhosis found that mortality was twice as high in the chest tube subgroup.[55] Consequently, the American Association for the Study of Liver Disease recommends against conventional chest tube placement in HH due to the poor outcomes observed.[50,56]

Tunneled pleural catheters

For carefully selected patients, IPC can be considered after multidisciplinary discussion due to the associated risks. IPCs may provide symptomatic relief but must be balanced against potential complications, particularly infections. The risk of pleural space infection ranges from 10% to 35%,[57] and is the most significant and common risk of IPC in HH management, leading to 0% to 3% mortality secondary to septic shock.[58] IPC are shown to lead to spontaneous pleurodesis rates from 15% to 33%; however, these studies are limited by their selection bias and retrospective nature and likely to represent an overestimation of pleurodesis rate. The two largest studies of IPC in HH reported that all patients achieved pleurodesis in one study,[50] and 50% of the patients from the second study[52] achieved pleurodesis after successful liver transplant completion. These patients

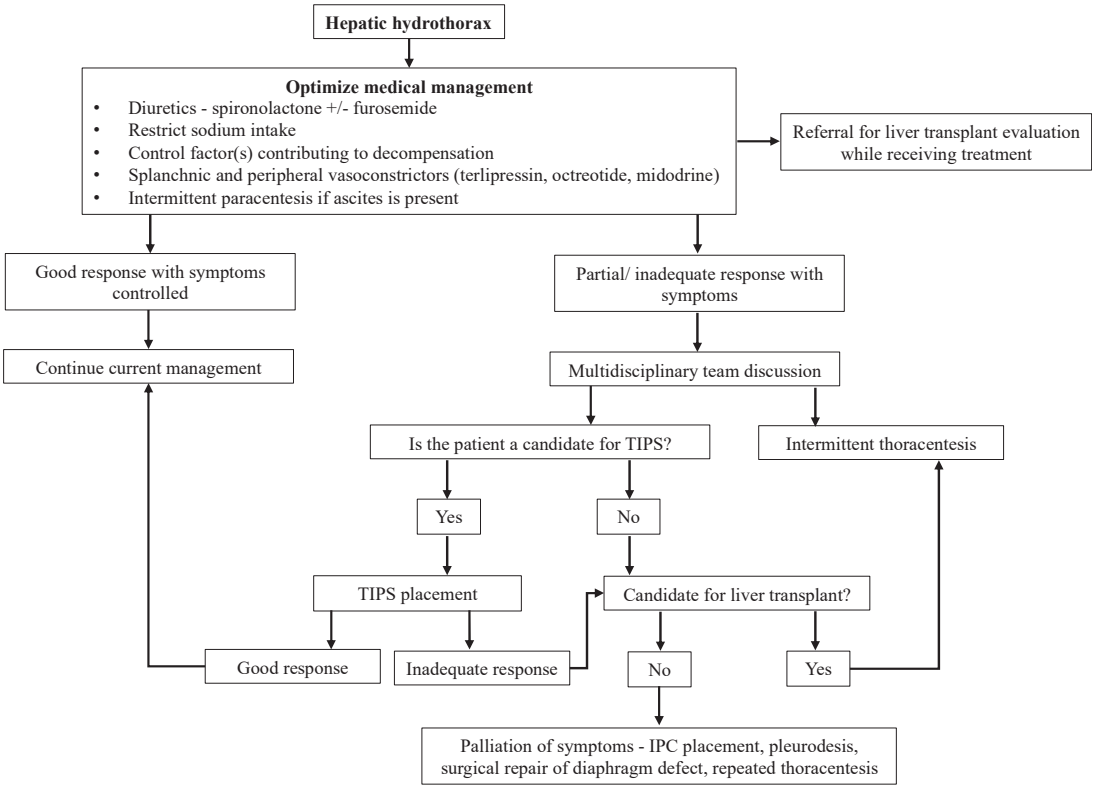

Fig. 2. Proposed algorithm in the management of HH.

were considered to have successful pleurodesis without ultrasound examination of the pleural space to confirm pleural space symphysis and were likely to have recovered from portal hypertension and HH as opposed to true pleurodesis.

A randomized controlled study by Walker and colleagues comparing IPC placement to serial thoracenteses found that patients in the IPC arm underwent fewer pleural procedures but experienced a higher rate of complications, with no significant difference in breathlessness over 12 weeks.[27] Therefore, IPC placement in HH remains debatable, requiring more studies to evaluate patient-centric outcomes and should only be considered after careful multidisciplinary review involving the transplant team, hepatology, and the patient and their family.

Other approaches include chemical or talc pleurodesis during video-assisted thoracoscopic surgery as part of HH management. A meta-analysis of case reports and case series showed a rate of pleurodesis of 72%, with a pooled complication rate of 82%.[59] Surgical closure of diaphragmatic defects has shown success in patients with Child-Turcotte-Pugh class A, with a relatively low recurrence rate of 6.3%, but it is associated with high mortality.[60] For these reasons, surgical management of HH should be considered, only in highly selective cases and after multidisciplinary discussion, including input from hepatology, pulmonology, interventional radiology, and transplant surgical teams.

Ultimately, liver transplantation is the definitive treatment of patients with decompensated liver failure. All patients with HH should be evaluated for liver transplant candidacy while providing symptomatic relief (**Fig. 2**). A retrospective study highlighted that the most crucial factor for 3 year survival was liver transplantation, with a mortality rate of 21.7% in the transplanted group compared to 77.5% in the non-transplant group over the first three years of having HH.[61]

SUMMARY

In conclusion, recurrent NMPE due to CHF and HH is prevalent and poses significant clinical challenges. Management strategies for pleural effusion in these conditions primarily focus on optimizing the underlying medical issues, such as enhancing cardiac function in CHF and effectively controlling ascites in HH. Thoracentesis and the placement of IPC provide significant relief for refractory pleural effusions. However, the

administration of anticoagulants and antiplatelet agents must be meticulously managed to minimize the risk of complications. While advancements in treatment options and procedural techniques have improved patient outcomes, continued research is vital to refine therapeutic strategies and enhance the quality of life for individuals afflicted by NMPE. It is imperative to adopt a multidisciplinary approach, involving specialists in cardiology, hepatology, transplant surgery, and pulmonology, to tailor individualized treatment plans that address the complex needs of these patients.

CLINICS CARE POINTS

- Addressing the underlying cause: Optimizing the underlying medical conditions contributing to recurrent pleural effusion is crucial for effective management of recurrent transudative pleural effusion.
- Personalized management: The approach to managing recurrent transudative pleural effusions should be tailored to each patient, taking into account factors such as symptom burden, prognosis, concurrent medications, and transplant candidacy.
- Alternative drainage options: For patients requiring frequent pleural drainage, especially those on chronic anticoagulation, antiplatelet therapy, or with social barriers to repeated procedures, a tunneled pleural catheter can be considered as a viable alternative.

DISCLOSURE

The authors have nothing to disclose.

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