

Pleural Interventions in the Management of Check for updates Hepatic Hydrothorax



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> Hepatic hydrothorax can be present in 5% to 15% of patients with underlying cirrhosis and portal hypertension, often reflecting advanced liver disease. Its impact can be variable, because patients may have small pleural effusions and minimal pulmonary symptoms or massive pleural effusions and respiratory failure. Management of hepatic hydrothorax can be difficult because these patients often have a number of comorbidities and potential for complications.

> Minimal high-quality data are available for guidance specifically related to hepatic hydrothorax, potentially resulting in pulmonary or critical care physician struggling for best management options. We therefore provide a Case-based presentation with management options based on currently available data and opinion. We discuss the role of pleural interventions, including thoracentesis, tube thoracostomy, indwelling tunneled pleural catheter, pleurodesis, and surgical interventions.

> In general, we recommend that management be conducted within a multidisciplinary team including pulmonology, hepatology, and transplant surgery. Patients with refractory hepatic hydrothorax that are not transplant candidates should be managed with palliative intent; we suggest indwelling tunneled pleural catheter placement unless otherwise contraindicated. For patients with unclear or incomplete hepatology treatment plans or those unable to undergo more definitive procedures, we recommend serial thoracentesis. In patients who are transplant candidates, we often consider serial thoracentesis as a standard treatment, while also evaluating the role indwelling tunneled pleural catheter placement may play within the course of disease and transplant evaluation. CHEST 2022; 161(1):276-283

KEY WORDS: hepatic hydrothorax; indwelling tunneled pleural catheter; pleurodesis; thoracentesis

Hepatic hydrothorax (HH) is defined by the presence of a pleural effusion in the setting of a patient with underlying liver disease,

without evidence of other cardiopulmonary disorders. Its presence is likely reflective of advanced disease and has been associated

ABBREVIATIONS: HH = hepatic hydrothorax; IPC = indwelling tunneled pleural catheter; TIPS = transjugular intrahepatic portosystemic shunt; VATS = video-assisted thoracoscopic surgery

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with significant morbidity and mortality. ¹⁻³ The true clinical impact of HH may be difficult to ascertain, because patients can have radiographic abnormalities that range from small effusions and minimal pulmonary symptoms to massive pleural effusions and respiratory embarrassment.

HH is not uncommon in the inpatient or outpatient setting, with a reported incidence of 5% to 15% in patients with cirrhosis and portal hypertension. ⁴⁻⁸ The management of these patients and the multiple medical problems that may manifest during the course of their disease can be complex and frustrating for both the patient and clinician. Once a decision is made to drain HH, multiple options for management exist, similar to other pleural effusions.

Case Example: A 47-year-old male is transferred from an outside facility for hepatology evaluation with a history of cirrhosis and pleural effusion. He was admitted with encephalopathy and dyspnea. Imaging reveals the presence of a large right pleural effusion.

Question: What are the best management options and available supporting data for the pulmonary or critical care physician in the management of HH?

Initial Evaluation and Confirmation of Hepatic Hydrothorax

The initial evaluation of a patient with this history would be to confirm HH, ruling out other pathologic conditions (eg, infection, malignancy) that would require different treatment. The diagnosis, initial evaluation, and pathophysiology of HH is beyond the scope of this article and is well covered in multiple reviews. 4,5,7,9,10 HH is diagnosed by a transudative pleural effusion after other cardiopulmonary pathologic conditions have been ruled out in the setting of liver disease. The pathophysiology of HH is related to liver failure and sodium/water imbalance. As with many problems in medicine, addressing the underlying problem is advised; therefore, optimization of these issues with sodium restriction and diuretics is recommended as first-line therapy. 4,5,8 Depending on local resources, referral to hepatology or liver transplant team(s) is also advised.4

Initial workup should be directed toward the cause of this patient's current clinical problems, including evaluation of encephalopathy and dyspnea. In light of worsening dyspnea and effusion, we would perform thoracentesis. Pleural drainage via thoracentesis would be reasonable because it may offer both diagnostic and therapeutic benefits. Ruling out bleeding (hemothorax), infection (empyema, spontaneous bacterial empyema), and malignancy in the pleural space are helpful in narrowing the differential diagnosis for his decompensation and allow confirmation of HH. It would also be prudent to evaluate for significant ascites, because if it is present it also serves as a likely and often primary target for drainage to improve symptoms.

Initial Management Options for Hepatic Hydrothorax

Thoracentesis has been the standard diagnostic and therapeutic treatment option for management of HH and is typically considered a low-risk procedure. 11,12 However, the benefits are often temporary, and many patients reaccumulate large amounts of fluid in very short amounts of time. Performing procedures on HH patients may provoke multiple concerns related to coexisting coagulopathy and removal of large volumes of fluid commonly found in patients with liver failure. Previous studies suggest that coagulopathy, in particular thrombocytopenia and elevated INR, seem to have minimal association with increasing bleeding risk during thoracentesis when performed by experienced operators. 13,14 In general, we do not advocate for preprocedural blood product administration (fresh frozen plasma, platelet infusions, and so forth) for thoracentesis. We also generally do not advocate for premature stopping of thoracentesis at prespecified volumes, such as 1 liter. Reexpansion pulmonary edema has been reported, but it is considered rare and without validated methods to predict risk. 15 As a result, we generally attempt to fully drain the space, stopping drainage if patients develop symptoms suggestive of lung entrapment or significant drop in pleural pressure occurs. The role of pleural manometry remains debatable, 15,16 but based on current evidence we do not recommend it routinely. Fluid and protein loss is a particular concern in advanced liver disease. The practice of administering albumin solution, as used during large volume paracentesis, is not supported by current evidence or guidelines during thoracentesis. It has been advocated by some, particularly in the context of draining larger volumes of fluid, but further research is needed to clarify the role of albumin.

Case Continuation

The patient underwent thoracentesis with improvement in dyspnea. Pleural fluid analysis was consistent with a

transudate, and cultures and cytology were negative. He was evaluated by hepatology, diuresed, and discharged 3 days later. He returned to clinic 2 weeks later, denying respiratory complaints. Imaging suggests no significant pleural effusion.

During the initial management of hepatic hydrothorax, general goals should be directed toward relief of symptoms as well as focus on the underlying problem. The initial treatment of HH should be toward sodium/water imbalance with the use of diuretics and dietary restrictions. ^{4-6,8,17} If these interventions are successful, no further pleural interventions are likely warranted.

Case Continuation

The patient did well initially, but 2 months later had multiple admissions for liver-related complications (GI bleeding, spontaneous bacterial peritonitis, volume overload). In clinic 3 weeks later, he reported worsening dyspnea and had recurrent effusion on imaging. He was compliant with medications and sodium intake. With the use of high-dose furosemide and spironolactone, he was developing intermittent orthostatic hypotension and mild renal insufficiency. What are the management options for his pleural disease?

Management Options for Recurrent Pleural Disease Including Review of Relevant Literature

We would again offer thoracentesis in light of worsening dyspnea, radiographic evidence of worsening HH, and likely optimized medical management. Given his recent spontaneous bacterial peritonitis, pleural infection (spontaneous bacterial pleuritis) should also be ruled out. Thoracentesis would be offered as a bridge to additional discussions for longer-term pleural management options, also attempting to keep him an outpatient. Additionally, this would help confirm that his current pulmonary symptoms (dyspnea) are related to his hydrothorax, and that drainage improves symptoms.

We consider serial thoracentesis a standard treatment modality for HH, but recent data have prompted reevaluation. Shojaee et al¹⁸ evaluated serial thoracentesis, noting increased cumulative risk of complications associated within a HH population compared with a non-HH population. They ultimately reported that cumulative complication risk in the HH group was 12.2%. Limitations of this study

include its retrospective nature, large number of trainees performing thoracentesis, as well as a fairly low overall complication rate (17/462 = 0.03%), all making generalizability potentially a concern. Although this study has caused some reexamination of what we consider standard management and calls for additional research, other small retrospective studies have suggested the use of chest tube drainage is associated with poor outcomes as well, including increased risk of death secondary to empyema and sepsis in HH¹⁹⁻²¹ (Table 1). Additionally, larger database series associate poor outcomes in HH patients undergoing tube thoracostomy. A Taiwanese national database identified 2,556 propensity-matched patients with cirrhosis (1,278 chest tube, 1,278 thoracentesis) with 30-day mortalities of 23.5% for tube thoracostomy and 18.6% for thoracentesis.² A similar American study (2009 national inpatient data sample) identified patients with cirrhosis undergoing thoracentesis (1,766) and chest tube (205), reporting a 2× greater inpatient mortality in the chest tube drainage group.²²

As a general statement, we try to avoid tube thoracostomy in HH²³ based on the current data as well as recent guidelines from the American Association for the Study of Liver Diseases.⁴ Tube thoracostomy and pleurodesis remains in the algorithm of HH management options. However, the data do not appear to support improved outcomes with the use of tube thoracostomy, and the authors have anecdotally also had poor experiences/outcomes with such interventions. Additionally, moving forward with tube thoracostomy and chemical pleurodesis attempts commit patients to significant hospital stays while awaiting pleural symphysis. ^{22,24-26}

From the history provided, the patient appeared to be reaching the limits of medical optimization. We would contact hepatology to confirm or deny this, also confirming he was not a candidate for additional medication options (eg, splanchnic/peripheral vasoconstrictors) or nonmedical interventions (transjugular intrahepatic portosystemic shunt [TIPS]). We would also discuss the potential for liver transplantation and focus on multidisciplinary evaluation of management options for recurrent pleural disease, including the potential for more definitive pleural management (eg, indwelling tunneled pleural catheter [IPC], pleurodesis).

TABLE 1 Outcomes of Studies Evaluating Tube Thoracostomy in Patients With Cirrhosis and Hepatic Hydrothorax

Lead Author	Year	Study Population	Indications or Interventions	Morbidity	Mortality
Yoon et al ¹⁹	2019	Refractory hepatic hydrothorax and 12-month mortality	Serial thoracentesis (n = 11) Pigtail catheter without pleurodesis (n = 16) Surgery with diaphragm repair and pleurodesis (n = 10)	Not available	Thoracentesis— 18.2% Pigtail—87.5% Surgery—70.0%
Orman and Lok ²⁰	2009	Cirrhosis and chest tube placement	Chest tube placement ($n = 17$)	94%	35.3% at 3 mos
Liu et al ²¹	2004	Cirrhosis and chest tube placement	Hepatic hydrothorax $(n=24)$ Pneumothorax $(n=9)$ Empyema $(n=8)$ Thoracic surgery $(n=12)$ Hemothorax $(n=3)$	Renal failure—54% Electrolyte imbalance—57% Infection—48%	27%

Case Continuation

The patient underwent a TIPS procedure and continued transplant evaluation. He experienced no additional complications for another 2 months; however, during a hepatology clinic visit he complained of progressive dyspnea, was admitted to the hospital, and was found to have a large right pleural effusion. What were the management options for his pleural disease?

At this point, he appeared to have failed or had partial response to TIPS, as seen in up to 25% of TIPS recipients. In collaboration with hepatology, we would evaluate for interventions (eg, liver transplantation, Doppler investigation of TIPS, interventional radiology revision of TIPS, and so forth) related to potential TIPS failure. Additionally, we would collaboratively define a pleural management plan moving forward, because refractory HH can be difficult to manage and may require multiple resources. In the setting of end-stage liver disease that is non-transplantable, management of HH becomes a palliative endeavor. However, in transplantable candidates, attempting to balance potential downstream implications of pleural disease management strategies remains critical to overall success. As with many pleural disease processes, management options include pleural drainage with thoracentesis, indwelling tunneled pleural catheter, or pleurodesis. Additionally, in HH there has been some focus on diaphragmatic defects and leakage, with attempts at surgical correction.

Refractory Hepatic Hydrothorax Management Including Review of Relevant Literature

In general, we support the use of serial thoracentesis as a "bridge" and sometimes "destination" management option, including its use within inpatient and outpatient

settings. When this option is used, patients may need frequent clinic visits. We attempt to schedule outpatient visits based on prior pleural drainage needs, but in some extreme cases may see patients for large-volume pleural drainage 2 to 3 times per week to palliate symptoms and avoid hospitalization. This treatment strategy should be carried out in a multidisciplinary fashion with the hepatology and transplant teams and may not be ideal from some practice or logistical constraints. Some may transition to more definitive pleural drainage strategies as the frequency and needs of patients increase; however, the literature to support or refute these strategies remain sparse. There remains an absence of literature in nonmalignant pleural disease as to the "correct" time to consider transitioning to a more definitive pleural drainage strategy. Which approach offers the best palliation, safety profile, and cost-effectiveness also remains unclear. We continue to explore the use of IPC for HH management, acknowledging the data look interesting, but infection rates and potential to exclude someone from transplant candidacy is clearly concerning.^{27,28} We also engage our thoracic surgery colleagues, inquiring about surgical interventions including pleurodesis and diaphragm repair. We review these additional strategies below, including a review of the literature to help support our comments.

IPC

The use of IPC in HH has become an increasingly debated topic. Because of frustrations and concerns related to pleural management options of HH, as well as previous experience in malignant pleural disease, many (including the authors) have begun to consider IPCs as an acceptable management option for select patients.

In general, the data (much like for thoracentesis and tube thoracostomy) come from small and retrospective

TABLE 2] Outcomes of Studies of Indwelling Tunneled Pleural Catheter Placement for Hepatic Hydrothorax Management

Lead Author	Year	Study Population	Pleurodesis Rate	Infection Rate	IPC-Related Mortality
Chen et al ²⁸	2016	Single-center, hepatic hydrothorax (n $=$ 24)	33%	16.7%	0.0%
Kniese et al ²⁹	2019	Single-center, hepatic hydrothorax (n $=$ 62)	15%	16.1%	3.2%
Shojaee et al ²⁷	2019	Multicenter, hepatic hydrothorax (n $=$ 79)	28%	10.0%	2.5%

series (Table 2). These studies have identified some evidence of pleurodesis, but also concern for infection, including some IPC-related mortality. 27-29 Two systematic reviews of IPC use in HH have also been performed, concluding that IPCs appear to be an acceptable therapeutic option.³⁰ Spontaneous pleurodesis rates are reported at 31% in some pure HH populations.³¹ Additionally, a review of nonmalignant pleural effusions reports spontaneous pleurodesis rates of greater than 50%, but closer analysis of the data is more disappointing. This report is hindered by a heterogeneous population (only 12% with HH) and that many reported pleurodesis events occurring after transplantation, perhaps confusing true pleurodesis rates vs simple resolution of HH.³⁰ Complications rates including empyema (2.3%-4.5%) and catheter blockage (1.1%-2.9%) are also reported. A significant limitation in all the above-mentioned IPC studies is the lack of patient-centric outcomes such as dyspnea and quality of life scores.

A potential difference between the use of conventional chest tubes and IPCs in HH patient outcomes may be their intended purpose. Conventional chest tubes are often placed as an inpatient for complete pleural space evacuation or pleurodesis. Conversely, IPCs are placed primarily for outpatient symptom management with a drainage regimen that is symptom-guided or on an every-other-day basis. Conventional drainage often is no more than 1 L at a time, ³² potentially reducing the chance of volume loss, electrolyte loss, and renal failure previously reported with conventional chest tubes.

As a result, we agree that IPC remains an option for carefully selected patients with HH. The decision to proceed forward with IPC placement (or other more definitive pleural interventions) can be difficult and should not be made unilaterally. We suggest these decisions are best made in concert with the transplant team and patient/family, also suggested by other authors. ^{27,29,33} In nontransplantable patients, we often advocate for IPC placement sooner in the course of their disease process, because most goals are palliative in

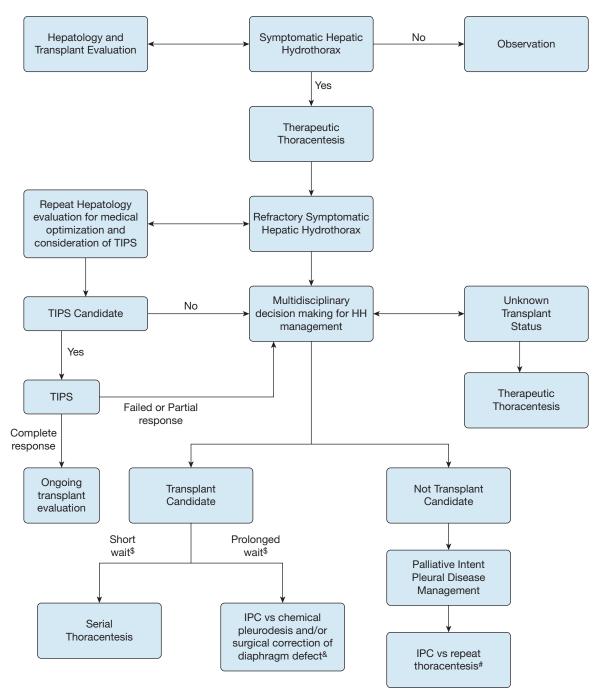
nature. However, in potentially transplantable patients, again it is often an ongoing discussion with the hepatology team about the current impact of HH, how an IPC may help, and the ultimate risks of IPC placement. Although some remain excited about potential IPC-related spontaneous pleurodesis, some authors have cautioned about the likely overestimation of reported pleurodesis rates, because in some studies half of the patients achieving IPC removal did so after liver transplantation.²⁷ Additionally, because the use of IPCs is not without consequence, the ultimate sin would be the development of an IPC-related complication (empyema) that precludes liver transplant—the only intervention with a mortality benefit in this disease.

Pleurodesis and Diaphragm Repair

Pleurodesis via video-assisted thoracoscopic surgery (VATS) remains an often-described but likely underused option based on the available literature. This is also likely related to reports suggesting an increased risk of morbidity and mortality of taking patients with advanced liver disease to the operating theater. The documented poor outcomes of nonhepatic surgical interventions may perpetuate decreased enthusiasm of thoracic surgeons; however, we do also suspect the role and involvement of thoracic surgery may be region and institution dependent.

The largest review of VATS or pleurodesis in HH identified 180 patients with a pooled pleurodesis rate of 72%, but also a pooled complication rate of 82%.³⁷ Of note, within this analysis, the three largest series included Cerfolio and Bryant³⁸ (45 patients over unclear timeframe), Assouad et al³⁹ (21 patients over 12 years), and Milanez de Campos et al⁴⁰ (18 patients over 14 years). One study not included within this review was a larger, single-center, retrospective series of 63 HH patients undergoing VATS with diaphragmatic defect repair, suggesting a very good success rate (93.7%), but a total complication rate of 31.7%, including a 3-month mortality of 25.4%.⁴¹ However, how generalizable the results of this series may be toward other surgeons or

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*Favor IPC if expect prolonged survival (> few weeks) or if attempting to discharge home on hospice

Figure 1 - Proposed treatment algorithm for patient evaluation and management of symptomatic hepatic hydrothorax.

centers is unclear, related to the fairly complicated perioperative care (pigtail drainage of effusion 1,000 mL $\rm qd \times 3$ and stabilization before operation, noninvasive ventilation for 5 days postoperatively, and so forth). The authors would therefore conclude that optimization of pleurodesis in HH has not been well studied, and large, multicenter, prospective data are needed.

Summary

Management of HH can be fairly complex and labor intensive. These patients often have multiple comorbidities and are at high risk of complications from their underlying disease as well as the interventions we offer. We therefore recommend that management be conducted within a multidisciplinary team including

SFavor thoracentesis if expected transplant waitlist time is short (AASLD suggest 2-3 months), whereas favor more definitive procedure is waitlist time is longer the authors currently favor IPC over pleurodesis efforts based on limited data and experience, however this experience may vary over institutions

pulmonology, hepatology, and transplant surgery, following some general principles (Fig 1). Identification of the "best" HH management option is likely highly patient and institutional dependent, but it should be directed at the best possible patient-centered outcomes.

Patients with refractory HH that are not transplant candidates should be managed with palliative intent, and we suggest IPC placement unless otherwise contraindicated. For patients with unclear or incomplete hepatology treatment plans or those refusing or unable to tolerate more definitive procedures, we recommend serial thoracentesis. In patients that are transplant candidates, we often consider serial thoracentesis as a standard treatment, but we will evaluate the role IPC placement, pleurodesis, or surgical interventions may play within the course of disease and transplant evaluation.

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