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Indwelling pleural catheters in hepatic hydrothorax: A single-center series of outcomes and complications

Christopher Kniese[1], Khalil Diab[1], Marwan Ghabril[2], Gabriel Bosslet[1]

[1]Department of Pulmonary, Critical Care, Sleep, and Occupational Medicine, Indiana University School of Medicine, Indianapolis, Indiana

[2]Department of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, Indiana

Address all correspondences to:

Christopher Kniese, MD, Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine, Indiana University School of Medicine, Gatch Hall CL260, 1120 W. Michigan St., Indianapolis, IN 46202. Email: cmkniese@iupui.edu

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Abbreviations:

BMI, body-mass index

BPE, benign pleural effusion

HH, hepatic hydrothorax

IPC, indwelling pleural catheter

MELD, model for end-stage liver disease

NASH, non-alcoholic steatohepatitis

SBE, spontaneous bacterial empyema

TIPS, transjugular intrahepatic portosystemic shunt

ABSTRACT

Background: Treatment of hepatic hydrothorax (HH) generally involves sodium restriction, diuretics, and serial thoracentesis. In more advanced cases, transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation may be required. In the past, indwelling tube drainage has been avoided due to concerns about high complication rates and overall poor outcomes. Recently, indwelling pleural catheters (IPCs) have been proposed as a novel treatment option for HH.

Methods: We retrospectively reviewed patients who had undergone IPC placement for HH over a 10-year period at a large liver transplant referral center. We tracked outcomes, including complication rates and liver transplantation, as well as biomarkers of nutritional status.

Results: Sixty-two patients underwent IPC placement between 2007 and 2017, with 33 (53%) of IPCs placed as a bridge to liver transplant. Complications were seen in 22 (36%) of patients, with empyema being the most common in 10 (16.1%). 10 patients evaluated for liver transplant were successfully transplanted after IPC placement. There were statistically significant decreases in both body mass index and serum albumin levels after IPC placement.

Conclusions: IPCs represent a potential treatment for refractory hepatic hydrothorax and should be used with caution in patients eligible for liver transplantation. Ideally, IPC use for these patients would be evaluated by a multidisciplinary team. IPC use may lead to small decreases in BMI and serum albumin levels in patients over time.

Introduction

Hepatic hydrothorax (HH) is a pleural effusion in a patient with portal hypertension without a primary cardiac, pulmonary, or pleural disease[1]. It is an uncommon complication of portal hypertension, occurring in approximately 5-10% of patients with cirrhosis[1,2,3,4]. Development of hydrothorax carries a poor prognosis, with a median survival of 8.6 months[5].

Management of HH centers on salt restriction, diuretics, and serial thoracentesis[2]. Transjugular intrahepatic portosystemic shunt (TIPS) can be an effective treatment for those who fail medical management, with success rates as high as 80% [6,7]. Unfortunately, many patients with HH have contraindications to TIPS (i.e. hepatic encephalopathy or hyperbilirubinemia). Transplant is the only other treatment shown to be effective for patients who fail medical management[8].

Historically, tube thoracostomy has been strongly discouraged in HH due to concerns about complications, including renal failure, infection, electrolyte depletion, and protein loss[9,10,11]. However, newer indwelling tunneled pleural catheters (IPCs) have been proposed as a novel treatment approach for the patient with refractory hydrothorax. The tunneled nature of these catheters theoretically ameliorates the risk of infection. These pleural catheters are widely accepted as an option for symptomatic management of malignant pleural effusions[12,13], with increasing attention to their potential therapeutic applications in non-malignant effusions[14,15]. Some centers have begun utilizing IPCs for treatment of HH[16,17]. Recently, a pilot study with 24 transplant-eligible patients demonstrated feasibility of this approach[18].

The purpose of this study was to assess outcomes and complication rates of patients who underwent IPC placement for HH at a large tertiary referral center for patients with advanced liver disease. Our study, which includes a significant portion of patients who were eligible for liver transplantation, represents the largest series of such patients described in the literature to date.

Materials and Methods

A single-center, retrospective analysis was performed on all patients from 2007 to 2017 with a diagnosis of cirrhosis who underwent placement of an IPC. Data was extracted from the electronic medical record system (Cerner Corporation, Kansas City, MO) using search terms 'cirrhosis' and 'IR Insert Tunneled Cath Pleural' in order to capture those IPCs placed by the interventional radiology service at our institution. A subsequent query using the terms 'cirrhosis' and 'pleural catheter' was performed under the endoscopy schedule in the same electronic records system to identify those patients who underwent IPC placement by the pulmonary service. At our institution, it is standard that interventional radiology places either the Aspira™ (C.R. Bard, Murray Hill, NJ) or Pleurx™ (BD, Sydney, Australia) catheters, while the pulmonary service exclusively places Pleurx™ (BD, Sydney, Australia) catheters.

Inclusion criteria included age greater than or equal to 18 years, diagnosis of cirrhosis and hepatic hydrothorax, and IPC placement for management of recurrent effusion. Exclusion criteria included patients with a pleural effusion due to a condition other than hepatic hydrothorax or those who had a diagnosis of empyema prior to IPC

placement. A diagnosis of hepatic hydrothorax was confirmed by the presence of a recurrent effusion in the setting of cirrhosis for which alternate etiologies had been excluded. Prior pleural fluid studies were examined when possible. The Institutional Review Board (IRB) of Indiana University School of Medicine approved the study protocol (protocol number 1701955275).

Procedure

Patients underwent IPC placement per standard practice of the interventional radiology service or the pulmonary service. Both the Pleurx™ (BD, Sydney, Australia) and Aspira™ (C.R. Bard, Murray Hill, NJ) catheters are 15.5 Fr silicone tubes designed for placement using local anesthetic and light to moderate sedation[19]. Procedures were performed during either inpatient or outpatient encounters. All procedures were performed in operating rooms (ORs), using standard sterile procedure. Peri-procedural antibiotics were administered in some cases. Patients were provided the appropriate drainage equipment per standard practice and follow-up was dictated by their clinical course.

Data Collection

Data collected at the time of IPC placement included age, gender, body mass index (BMI), etiology of cirrhosis, serum bilirubin, creatinine, international normalized ratio (INR), sodium, and albumin levels. In cases where laboratory and BMI data were not available on the day of IPC placement, values within 14 days prior to the procedure were accepted. Additional baseline data points included prior therapeutic interventions

for hydrothorax (including salt restriction, diuretics, prior thoracentesis, prior TIPS, pleurodesis, or octreotide). Date, laterality, type of IPC, reason for IPC placement, and liver transplant status were also collected at baseline. Patients who were listed for transplant, or actively under evaluation for listing were classified as 'bridge to transplant,' while those who were definitively not transplant candidates, including those enrolling in comfort-based care, were classified as 'palliative.' There were some patients for whom it was not clear from available documentation whether the IPC was placed with palliative intent or as a bridge to transplant; these patients were classified as 'unclear.'

Follow-up data included presence of complications, categorized as empyema, catheter site infection, catheter dislodgement, pneumothorax, catheter malfunction, hemothorax, or other. Catheter malfunction referred to issues connecting the IPC with the associated drainage system and issues with drainage due to catheter occlusion. Empyema was defined as an infection of the pleural space confirmed by positive pleural fluid cultures or an exudative effusion with clinical signs of infection. Pleural fluid studies in patients with infectious complications were collected when able. Pleurodesis after IPC placement was included, defined as resolution of the effusion after IPC placement allowing for catheter removal based on clinician discretion without additional intervention. Presence of unexpandable lung was recorded and defined as inability of the lung to completely expand after IPC placement despite drainage[20]. Data regarding transplant status post-IPC, receipt of liver transplant, IPC removal, hospitalizations within 6 months post-IPC placement at our institution, follow-up serum albumin and BMI data, and death were also collected. Follow-up albumin and BMI data were first collected during the initial hospitalization post-IPC placement to minimize confounding

from albumin infusions and additional interventions during the hospital stay. In those patients who were not hospitalized within six months, the data points closest to IPC removal were recorded. Death was recorded as a composite outcome that included actual date of death or discharge to hospice care. No additional follow-up data was recorded after discharge to hospice in applicable patients.

Statistical Analysis

Data were collected from medical records and managed using REDCap electronic data capture tools hosted at the Indiana Clinical and Translational Sciences Institute[21]. Descriptive statistics were used to analyze demographic data. Model for End-Stage Liver Disease (MELD-Na) scores were calculated from baseline laboratory values[22]. Means and standard deviations (SD) were reported for all continuous data. Paired t-tests were used to compare baseline and follow-up albumin and BMI values. The data was analyzed using SAS™® version 9.4 (SAS Institute, Cary, NC). Statistical analysis support was provided by the Indiana University Department of Biostatistics.

Results

A total of 62 patients were included in the analysis. The mean age at time of IPC placement was 61 years (range 35-89) (see **Table 1**), and 34 (55%) were male. The most common etiology of cirrhosis was non-alcoholic steatohepatitis (NASH) (42%), followed by alcohol (32%). The mean MELD-Na score at time of IPC placement was 24 (range 11-38). The majority of effusions were right-sided, and the most common type of catheter placed was the Aspira drain used in 36 (58%) patients. The majority of patients

had received prior therapy with salt restriction, diuretics, and serial thoracentesis. Five patients underwent TIPS prior to IPC placement. Twenty-one patients (34%) received peri-procedural antibiotics.

Thirty-three of the 62 patients (53%) had IPCs placed as a bridge to transplant, while 24 patients (39%) had the catheters placed with palliative intent. In the remaining 5 patients, the context of IPC placement could not be discerned. Twenty-two (35%) of the IPCs were ultimately removed: 9 due to pleurodesis (5 in transplant group, 4 in unclear group), 6 after transplant, and 7 due to complications which included empyema (2), dislodgement (1), and others (4). The mean time to pleurodesis was 118 days (range 15-373). Forty-eight of the patients died during the study period, with a mean time to death after IPC placement of 180 days (range 0-1258). This included 19 (58%) patients where IPC was used as a bridge to transplant. Five patients (8%) were lost to follow-up.

Complications

Catheter-related complications occurred in 22 patients (see **Table 2**). The most serious complication was empyema, seen in 10 patients (16.1%). In 3 of these, death was directly related to the empyema. Specific details regarding patients with empyema can be seen **Table 3**. Other notable complications include catheter dislodgement (6), pneumothorax (2), and cellulitis (1). Unexpandable lung was diagnosed in 3 patients after IPC placement, 2 of which were successfully listed and received a liver transplant, with IPC removal at the time of transplant or shortly thereafter. The third patient was listed after IPC placement, but suffered additional complications including infection of

the pleural space and died in the intensive care unit of multi-organ dysfunction syndrome prior to transplant.

Transplant Outcomes

Thirty-three patients were under consideration for liver transplantation at the time of IPC placement (see **Figure 1**). Of those, 7 patients were actively listed for transplant when the catheter was placed. Twelve additional patients were listed after IPC placement, for a total of 19 patients listed for liver transplant. Of these, 10 went on to receive successful transplantation, with a mean time to transplant after IPC placement of 87 days (range 20-175). In 6 patients, the IPC was removed after transplant, and in 3 it was removed prior to transplant. One of these 3 patients developed an empyema, recovered, and was successfully transplanted. One patient died of refractory shock, with the IPC still in place in the days following transplant. Of the remaining 9 patients who were listed, 1 was lost to follow-up, and 8 died while awaiting transplant. Of these 8, 2 died due to septic shock related to empyema, whereas the others died of various complications of end-stage liver disease that appeared unrelated to the IPC. Of the original 33 patients under consideration for transplant at the time of IPC placement, 14 were never listed for transplant.

Effect on Albumin and BMI

The mean baseline BMI was 27.8 kg/m^2 (n=56; range 15.7-57.1) (see **Figure 2**). The mean follow-up BMI was 26.7 kg/m^2 (n=53; range 16.0-57.1), with a mean time to follow-up of 32.6 days (range 1-141). The mean difference between pre and post-IPC

BMI values was a decrease of 1.13 kg/m^2 (n=50), which reached statistical significance (p=0.008). The mean baseline serum albumin level was 3.0 g/dL (n=59; range 1.7-5.3), with mean follow-up level of 2.7 g/dL (n=55; range 1.2-4.2) (see **Figure 3**). The mean time to follow-up for albumin was 29.6 days (range 1-122). The mean difference between pre and post-IPC values was a decrease of 0.3 g/dL (n=53), which also reached statistical significance (p=0.005).

Discussion

IPCs are now accepted for the management of symptomatic malignant pleural effusions[12,13], and their use has recently been expanded to many forms of benign pleural effusion (BPE)[14,15]. We report the largest study to date assessing outcomes of IPCs in patients with medically refractory HH at a large tertiary liver transplantation center. The majority of the patients included in this study had either failed prior TIPS or were not considered candidates for TIPS, necessitating alternate means of controlling their HH. Common contraindications to TIPS include prior history of hepatic encephalopathy, hyperbilirubinemia, pulmonary hypertension, severe congestive heart failure, and structural lesions of the liver that may preclude placement of the shunt[22].

Our study revealed complications in 36% of patients. A recent review of 325 patients with BPE who underwent IPC placement demonstrated a complication rate of 17% in the study population[15]. Notably, this review included a majority of patients with cardiac and renal-related pleural effusions, with only a minority of cases (12%) with liver disease. Our complication rate was considerably higher. One possible explanation for this finding is the natural course of patients with end-stage liver disease, including high

rates of infection and death[5]. This theory is supported by our finding that the mean MELD-Na score at the time of IPC placement in our study population was 24, which suggests a 3-month mortality rate of approximately 20% [23].

The most important complication of IPCs was empyema, diagnosed in 10 patients (16.1%). This rate is higher than that seen thus far in patients with IPCs placed after solid organ transplantation (11%) and in those with hematologic malignancies undergoing chemotherapy (5.2%-7.7%)[24,25,26]. However, this rate is almost identical to that seen in a recent prospective feasibility study (16.7%) assessing IPCs as a bridge-to-transplant strategy in patients with HH at a separate liver transplant referral institution[18]. This number is also comparable to a retrospective analysis of 508 cirrhotic patients with HH treated with thoracentesis in which the incidence of spontaneous bacterial empyema (SBE) was 15.9%[27]. In our study, 3 (4.8%) cases of empyema necessitated IPC removal and in 3 (4.8%) cases the empyema precipitated septic shock and death; thus, it represents a serious concern in patients being considered for IPC placement.

It should be noted that many of the pleural infections identified in this study likely represent spontaneous bacterial empyema, whereby bacterial infection of the pleural space occurs via translocation of enteric bacteria into the pleural space[28]. Thus, the infections may not have been directly caused by the catheters themselves. This is supported by the predominance of gram-negative and enteric pathogens isolated from pleural cultures. Patients with hepatic hydrothorax have demonstrably lower complement levels and decreased opsonic activity in pleural fluid compared to patients with effusions of other causes, which may predispose this population to pleural space infections[29]. Prior data in patients with IPCs for malignant pleural effusions showed

Staphylococcus aureus was the most common bacteria isolated from pleural cultures, and patients with gram-negative pathogens had worse outcomes, including death; in this cohort, the majority of patients were successfully treated without IPC removal[30]. In addition, 4 of the 10 patients with pleural space infections in our study had transudative effusions. Prior data has also shown traditional markers such as fluid LDH may be a less reliable marker of infection in patients with HH who develop SBE[31]. Thus, the significance of transudative effusions with positive cultures in the setting of an IPC is less clear. Lastly, some of the pleural fluid isolates in our study represented common skin flora, and we cannot rule out that in these cases that there was simply contamination rather than true infection. This would lower our true infection rate to more closely align with other recent studies. However, these patients were treated with antibiotics, so infection was assumed.

In our study, 10 of the 33 patients (30%) who were considered eligible for transplant went on to successfully receive a liver transplant, which is similar to the 25% of patients who were ultimately transplanted in a smaller pilot study of IPC feasibility for medically refractory HH[18]. In our study, IPCs were successfully removed in all transplanted patients with the exception of one patient who developed significant post-operative complications unrelated to the IPC and ultimately died. We did identify 2 patients who developed empyema while they were actively listed, and both died of septic shock, demonstrating the risk that IPC-related complications may preclude liver transplantation.

Prior studies have cited protein loss and electrolyte abnormalities as complications of traditional tube thoracostomy in HH[10,11]. We did see statistically

significant decreases in both measures, although the absolute decreases were small and of questionable clinical significance. Furthermore, the lack of a control group prevented us from assessing whether these effects truly related to the IPC or were simply manifestations of progressive end-stage liver disease.

Our study has several limitations. First, the retrospective and observational nature of this study means the data is subject to bias and limits the strength of our conclusions. All records were reviewed in detail, however only follow-up data that was available in our institution's records could be obtained, thus it is possible that additional complications could have occurred outside of our network. A small portion (8%) of the patients were ultimately lost to follow-up, including one patient who was actively listed for liver transplant, thus their final outcomes are unknown. The albumin and BMI data may also be subject to bias, and it is possible that data may have been influenced by factors that were not specifically captured in the electronic medical record. Our results may be subject to selection bias, and it is possible we may not have identified all patients who may have benefitted from an IPC. Lastly, patients in this study were not given a standardized drainage protocol, which has shown benefit in patients with malignant pleural effusion[32].

Conclusions

In conclusion, we present our single-center experience with IPC use in patients with medically refractory hepatic hydrothorax. We believe that IPCs can serve as an effective means of palliation in patients with end-stage liver disease that are not transplant candidates and suffer from refractory hydrothorax. All such patients should be

counseled on the potential risks of this approach, including infection. We believe IPCs should be used with caution in patients who are eligible for liver transplantation. While we demonstrated success with IPCs as a bridge to transplant, we also observed cases in which complications of the IPC actually prevented patients' ability to undergo transplantation. Patients who are eligible for transplant and suffering from HH that have failed traditional treatment strategies would likely benefit from a multidisciplinary approach to care, including input from experts in the fields of Hepatology, Pulmonology, and Transplant Surgery. Prospective studies would help to identify the ideal patient population. Future controlled studies are also needed to better assess the effects of this approach with regard to infection risk, nutritional status, and use in transplant patients.

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of the data, and drafting and revision of the manuscript. GB contributed to the

conception and design of the study protocol, collection, analysis, and interpretation of the

data, drafting and revision of the manuscript, and generation of the tables and figures.

All authors approved the final manuscript.

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Table 1. Demographic Data

Characteristic	No. (%)
	n = 62
Age mean (range, SD), years	60.7 (35-89, 10.8)
Sex, male	34 (54.8%)
Affected side, right	56 (90.3%)
MELD-NA mean (SD)	24 (6.5)
Etiology of cirrhosis	
Alcohol	20 (32.3%)
Hepatitis C	18 (29.0%)
NASH	26 (41.9%)
Autoimmune	2 (3.2%)
Alpha-1 Antitrypsin Deficiency	2 (3.2%)
Other	10 (16.1%)
Transplant Status, listed*	7 (11.3%)
Indication for IPC	
Bridge to Transplant	33 (53.2 %)
Palliative	24 (38.7%)
Unclear	5 (8.1%)

* At time of IPC insertion

Table 2. Outcomes of IPC Placement

Outcome	No. (%)
Complications	22 (35.5%)
Type of complication	
Empyema	10 (16.1%)
Skin infection	1 (1.6%)
Catheter clogged	2 (3.2%)
Catheter dislodged	6 (9.7%)
Pneumothorax	2 (3.2%)
Catheter malfunction	5 (8.1%)
Other	3 (4.8%)
Unexpandable lung	3 (4.8%)
Pleurodesis	9 (14.5%)
Time to pleurodesis mean (range, SD), days	118 (15-373, 139.6)
Transplant status after IPC*†	
Listed	19 (57.6%)
Not listed	14 (42.4%)
Transplant after IPC†	10 (30.3%)
Time to transplant mean (range, SD), days	87 (20-175, 49.6)
Death after placement	48 (77.4%)
Time to death mean (range, SD), days	180 (0-1258, 284.0)
Death at 6 months	36 (58%)
Lost to follow-up	5 (8.1%)

* Excludes palliative patients

† Percentages calculated as fraction of transplant-eligible patients

Table 3. Patients with Pleural Infection

Indication	PA*	Removed	Transplant	Death†	LDH, Fluid‡ (U/L)	Organism
Bridge	Yes	No	No	Yes	37	*Coagulase-negative Staphylococcus*
Palliative	No	No	--	No	162‡	*Acinetobacter baumannii, Methicillin-resistant Staphylococcus aureus*
Bridge	No	Yes	Yes	No	152‡	No organism identified.
Bridge	No	Yes	No	No	206‡	*Coagulase-negative Staphylococcus*
Palliative	No	No	--	Yes	N/A	*Escherichia coli*
Unclear	No	No	--	No	106	*Klebsiella pneumoniae, Corynebacterium sp.*
Bridge	No	Yes	Yes	No	80‡	*Corynebacterium sp., Streptococcus agalactiae*
Bridge	No	No	No	Yes	54	*Klebsiella pneumonia*
Bridge	No	No	No	No	133‡	*Coagulase-negative Staphylococcus, Corynebacterium sp., Acinetobacter bauma*
Bridge	No	No	No	No	57	*Klebsiella oxytoca*

* PA = peri-procedural antibiotic

† Death due to infection

‡ Exudate per Light's criteria

62 Patients

Bridge = 33

Unclear = 5

Palliative = 24

Line represents time of IPC placement

7 Listed

26 Not Listed

Additional 12 Listed

14 Never Listed

5 Died (0)

1 Alive

1 Lost

22 Died (1)

19 Listed

3 Lost

11 Died (1)

10 OLT

8 Died (3)

1 Lost

() = Deaths related to IPC

Pre and Post-IPC BMI

Pre and Post-IPC Albumin Levels

*p=0.005