Pleural Fluid Analysis and Radiographic, Sonographic, and Echocardiographic Characteristics of Hepatic Hydrothorax

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Background: There are limited published data defining complete pleural fluid analysis, echocardiographic characteristics, or the presence or absence of ascites on sonographic or CT imaging in patients with hepatic hydrothorax.

Methods: We reviewed pleural fluid analysis and radiographic, sonographic, and echocardiographic findings in 41 consecutive patients with hepatic hydrothorax referred to the Pleural Procedure Service for thoracentesis.

Results: Ascites was detected on sonographic or CT imaging in 38 of 39 patients (97%). Diastolic dysfunction was found in 11 of 21 patients (52%). Contrast echocardiography with agitated saline demonstrated an intrapulmonary shunt in 18 of 23 cases (78%). Solitary hepatic hydrothorax had a median pleural fluid pH of 7.49 (fifth to 95th percentile, 7.40-7.57), total protein level of 1.5 g/dL (0.58-2.34), and lactate dehydrogenase (LDH) level of 65 IU/L (36-138). The median pleural fluid/serum protein ratio and pleural LDH/upper limit of normal serum LDH ratio were 0.25 (0.10-0.43) and 0.27 (0.14-0.57), respectively. The median absolute neutrophil count (ANC) was 26 cells/ μ L (1-230). Only a single patient had a protein discordant exudate despite 83% of patients receiving diuretics. When comparing solitary hepatic hydrothorax and spontaneous bacterial pleuritis, there was no statistically significant difference among pleural fluid total protein ($P = .99$), LDH ($P = .33$), and serum albumin ($P = .47$). ANC was higher in patients with spontaneous bacterial pleuritis ($P < .0001$).

Conclusions: Hepatic hydrothorax virtually always presents with ascites that is detectable on sonographic or CT imaging. The development of an "exudate" from diuretic therapy is a rare phenomenon in hepatic hydrothorax. In contrast, diastolic dysfunction and intrapulmonary shunting are common in patients with hepatic hydrothorax. There was no statistically significant change in pleural fluid parameters with spontaneous bacterial pleuritis, except an increased ANC.

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Abbreviations: ANC = absolute neutrophil count; BNP = brain natriuretic peptide; LDH = lactate dehydrogenase; TIPS = transjugular intrahepatic portosystemic shunt

Hepatic hydrothorax results from pathologic trans-diaphragmatic migration of ascitic fluid in patients with cirrhosis of the liver. It is diagnosed clinically after excluding primary pulmonary or cardiac causes of the pleural effusion in a cirrhotic patient with transudative pleural fluid. A definitive diagnosis can be established by demonstrating peritoneal-pleural communication at thoracoscopy, at nuclear medicine scan with radiolabeled albumin, or on contrast-enhanced ultrasonography.¹⁻³ The prevalence of hepatic hydrothorax ranges from 4% to 6% in patients with cirrhosis.^{4,5} Hepatic hydrothorax most commonly presents

as a right-sided pleural effusion but can result in a unilateral left effusion or bilateral pleural effusions.^{6,7} Although ascites is usually evident at presentation, hepatic hydrothorax can present without clinically detectable ascites.⁸ Patients may be asymptomatic or may present with dyspnea, cough, or hypoxemia. They are prone to recurrent bouts of spontaneous bacterial pleuritis with or without concurrent spontaneous bacterial peritonitis.⁹

The initial evaluation of this effusion should be pleural fluid analysis. Complete pleural fluid analysis will establish the transudative nature of the fluid and

identify the presence or absence of spontaneous bacterial pleuritis. It is also helpful in excluding malignant, infectious, or inflammatory causes of the pleural effusion. Although the transudative nature of hepatic hydrothorax is well established, there are limited data defining the complete pleural fluid characteristics, the effect of diuretics on pleural fluid analysis, the detection of ascites on sonographic or CT imaging, and the echocardiographic characteristics in patients with hepatic hydrothorax. We report complete pleural fluid analysis, prevalence of ascites on sonographic or CT imaging, and echocardiographic characteristics of patients with hepatic hydrothorax.

MATERIALS AND METHODS

Pleural fluid analysis with clinical, laboratory, radiographic, sonographic, and echocardiographic data of 975 consecutive, ultrasound-guided thoracenteses performed between January 2001 and December 2008 by the Pleural Procedure Service at the Medical University of South Carolina were reviewed. Forty-one cases of hepatic hydrothorax were identified from our database after a review of all available clinical, radiographic, sonographic, and laboratory data. All cases were referred to the Pleural Procedure Service after the primary physician responsible for the care of these patients had determined that thoracentesis was warranted based on worsening respiratory symptoms or suspected infection. Patients with cirrhosis and pleural effusion who had a concurrent cause of the pleural effusion as determined by the clinical evaluation and subsequent laboratory and radiographic tests were excluded. For each of these cases, the clinical diagnosis was based on the consensus of three experts in pleural disease (S. A. S., P. D., and J. T. H.).

The medical records were reviewed for demographic data, medical history, current medications, and clinical outcomes of each case. The procedure records were reviewed for laterality, sonographic appearance of the effusion, and volume removed during thoracentesis. Pleural fluid analysis included pH, total nucleated cell count with differential, total protein level, lactate dehydrogenase (LDH) level, glucose level, triglycerides level, amylase level, bacterial cultures, and cytology. Radiographic data were reviewed for laterality of the effusion and presence of ascites on CT imaging and to assess pulmonary or cardiac causes of the pleural effusion. Sonographic data (ie, abdominal ultrasonography) were reviewed for presence of ascites. Echocardiographic data, including left ventricular ejection fraction, presence of diastolic dysfunction, left atrial diameter, right ventricular systolic pressure,

and intrapulmonary shunting, were also reviewed. Laboratory data, including brain natriuretic peptide (BNP) level, renal function, liver panel, coagulation profile, and CBC count, were reviewed, in addition to ascitic fluid analysis and cultures.

The pleural fluid cell count differential was prepared on slides, and 100 cells were counted for the differential count following Wright staining. Pleural fluid albumin was measured on a spectrophotometer at the ARUP reference laboratory (Dade Behring Fusion 5.1 spectrophotometer; Dade Behring Holdings Inc; Deerfield, Illinois). Pleural fluid pH was measured using a radiometer. All other components of the pleural fluid analysis were measured using an analyzer (DXC analyzer; Beckman Coulter; Brea, California). All BNP measurements after 2003 were performed using the Bayer ADVIA automated BNP assay (Bayer Diagnostics Corp; Tarrytown, New York) with normal values assumed to be <100 pg/mL. The study was approved (Human Research No. 20395) by the Office of Research Integrity of Medical University of South Carolina, which exempted the need for patient consent.

Definition of Terms

The following terms are used:

- **Transudates:** These effusions have a pleural fluid/serum protein ratio of ≤ 0.50 and an LDH of ≤ 160 IU/L (two-thirds of the upper limit of normal serum LDH concentration [240] at our institution).
- **Exudates:** Concordant exudates were effusions with a pleural fluid/serum protein ratio of >0.50 and an LDH concentration of >160 IU/L. Effusions classified as "exudates" by either LDH or protein criteria were classified as discordant exudates. Protein-discordant exudates have a pleural fluid/serum protein ratio of >0.50 and an LDH concentration of ≤ 160 IU/L; LDH-discordant exudates have a pleural fluid/serum protein ratio of ≤ 0.50 and an LDH concentration of >160 IU/L.
- **Spontaneous bacterial pleuritis** was diagnosed by positive pleural fluid culture or, if negative, a pleural fluid absolute neutrophil count (ANC) >500 cells/ μ L in patients with a clinical diagnosis of spontaneous bacterial pleuritis without radiographic evidence of pneumonia.

Statistical Analysis

Continuous variables were summarized by their means, SDs, medians, and fifth to 95th-percentile ranges. Categorical variables were expressed using percentages. Differences between two groups were evaluated using two-sided Wilcoxon rank sum tests, with P values $<.05$ considered statistically significant. Statistical analysis was performed with SAS, version 9.2 (SAS Institute; Cary, North Carolina).

RESULTS

Forty-one cases of hepatic hydrothorax were identified after reviewing the clinical, radiographic, sonographic, and laboratory data of 975 consecutive thoracenteses. Demographic and clinical data for these cases are listed in Table 1. Hepatitis C was the most frequent cause of cirrhosis (11), followed by alcoholic cirrhosis (10) and nonalcoholic steatohepatitis cirrhosis (8). There were four cases of alcoholic/hepatitis C cirrhosis, two cases of primary

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Table 1—Demographic and Clinical Data for Hepatic Hydrothorax (N = 41)

Characteristics	No.
Median age, y (range)	52 (22-78)
Gender, M (%), F (%)	22 (54), 19 (46)
Liver cirrhosis diagnosis, No. (%)	
Biopsy proven	27 (66)
Clinical diagnosis	14 (34)
Median MELD score (range)	19 (8-38)
Renal disease, No. (%)	
AKI	9 (22)
CKD	4 (10)
ESRD on HD	1 (2)
Median furosemide dose (range), mg/d	40 (20-160)
Median spironolactone dose (range), mg/d	100 (25-400)

AKI = acute kidney injury; CKD = chronic kidney disease; ESRD = end-stage renal disease; F = female; HD = hemodialysis; M = male; MELD = model for end-stage liver disease.

biliary cirrhosis, two cases of α_1 -antitrypsin deficiency, and one case each of primary sclerosing cholangitis, granulomatous hepatitis, hemochromatosis, and hepatitis B/hepatitis C cirrhosis. The radiographic and sonographic findings in hepatic hydrothorax are listed in Table 2. The volume of pleural fluid removed and thoracic sonography findings were not documented in two cases. Ascites was detected on abdominal ultrasonography in 22 (56%), on abdominal CT scan in five (13%), and on chest CT scan in 11 of 39 patients (28%) who had undergone sonographic or CT imaging of the abdomen near the time of thoracentesis. Only 22 of these 38 patients (58%) with ascites detected by sonographic or CT imaging had ascites on clinical examination. The echocardiographic findings in hepatic hydrothorax are listed in Table 3. Of 37 patients who underwent echocardiography, the ejection fraction was reported for all patients, whereas evaluation for diastolic dysfunction was reported in 21 and left atrial diameter was measured

Table 2—Radiographic and Sonographic Findings in Hepatic Hydrothorax

Radiographic and Sonographic Findings	No.
Laterality of pleural effusion (n = 41)	
Right unilateral	24 (59)
Bilateral ^a	10 (24)
Left unilateral	7 (17)
Thoracic sonography (n = 39)	
Anechoic	39 (100)
Thoracentesis (n = 39)	
Diagnostic	9 (23)
Therapeutic	30 (77)
Median volume, ^b (range), mL	1,800 (504-6,500)
Ascites on clinical exam (n = 41)	22 (54)
Ascites on sonographic or CT imaging (n = 39)	38 (97)

Data are presented as No. (%) unless indicated otherwise.

^aEight of 10 bilateral effusions had a larger effusion on the right side.

^bMedian volume removed during 30 therapeutic thoracenteses.

in 35. Fifteen had measurements for estimating right ventricular systolic pressure, and 23 underwent contrast echocardiography for evaluation of intrapulmonary shunt.

Thirty-three patients had solitary hepatic hydrothorax, and eight had concurrent spontaneous bacterial pleuritis. The pleural fluid characteristics of solitary hepatic hydrothorax are listed in Table 4. Sixteen (48%) had a pleural fluid total protein level < 1.5 g/dL. None of the patients had a serum albumin value of < 1.5 g/dL. Microbiologic cultures were negative in 31 patients; the cytologic evaluation did not show any malignant cells in 30 patients. Thirty-one (94%) were transudates. There was one protein-discordant and one LDH-discordant exudate; both patients were treated with diuretics. The serum-to-pleural fluid albumin gradient was 0.83 in the protein-discordant exudate and 1.5 in the LDH-discordant exudate. Of 33 patients with solitary hepatic hydrothorax, six underwent a transjugular intrahepatic portosystemic shunt (TIPS) for refractory hepatic hydrothorax, and one underwent TIPS revision. Liver transplant was performed in six patients.

The pleural fluid characteristics and outcomes in eight patients with spontaneous bacterial pleuritis are listed in Table 5. There were a single protein discordant exudate and two LDH discordant exudates. All eight patients with spontaneous bacterial pleuritis were receiving diuretics. Three had a pleural protein level < 1.5 g/dL. Of the four who had paracentesis within 1 week of thoracentesis, three had concurrent spontaneous bacterial peritonitis. Five were on antibiotics prior to thoracentesis. When comparing solitary hepatic hydrothorax and spontaneous bacterial pleuritis, there was no statistically significant difference among pleural fluid protein ($P = .99$), pleural fluid LDH ($P = .33$), and serum albumin ($P = .47$) (Table 6). However, ANC was significantly higher ($P < .0001$) in patients with spontaneous bacterial pleuritis (median, 1,371; fifth to 95th percentile range, 617-15,919) compared with patients with solitary hepatic hydrothorax (median, 26; fifth to 95th range, 0-230).

DISCUSSION

The aim of our study was to define complete pleural fluid analysis, evaluate the prevalence of ascites on sonographic and CT imaging, and characterize the echocardiographic findings in patients with hepatic hydrothorax. We also reviewed the incidence of spontaneous bacterial pleuritis and clinical outcomes of these cases.

As in previous reports, our data confirm that hepatic hydrothorax is typically a right-sided pleural effusion.^{6,10} Our study, however, showed a slightly higher

Table 3—Echocardiographic Findings in Hepatic Hydrothorax

Echocardiographic Findings	No.
Median LVEF (n = 37), %	60 (50-79)
Diastolic dysfunction (n = 21)	11 (52)
Left atrial enlargement (n = 35) ^a	23 (66)
Median RVSP (n = 15), mm Hg	37 (26-72)
RVSP ≥ 45 mm Hg	5 (33)
Intrapulmonary shunt (n = 23)	18 (78)
Median BNP (n = 11), ^b pg/mL	114 (24-388)

Data are presented as No. (range) or No. (%). BNP = brain natriuretic peptide; LVEF = left ventricle ejection fraction; RVSP = right ventricular systolic pressure.

^aLeft atrial diameter ≥ 4.0 cm.

^bNormal value < 100 pg/mL.

prevalence of unilateral left (17%) and bilateral (24%) pleural effusions in hepatic hydrothorax. This is likely secondary to use of chest and abdominal CT scans, which are more sensitive than the routine chest radiograph in detecting pleural effusion. In patients with bilateral pleural effusions, the right-sided effusion tended to be larger than the left. The effusion was anechoic on thoracic sonography. Hepatic hydrothorax in the absence of ascites (as detected by clinical examination and attempted paracentesis) has been reported previously.⁸ Our results show that hepatic hydrothorax almost always presents with ascites detectable on sonographic or CT imaging. Of 39 patients who had concurrent abdominal sonographic or CT imaging, only one case did not have ascites on a limited upper abdominal ultrasound. Our study also confirms the limited accuracy of clinical examination in detecting ascites.¹¹ The clinical examination detected ascites accurately in only 56% of the patients with ascites.

Concurrent kidney disease in the form of acute kidney injury or chronic kidney disease was found in one-third of cases with hepatic hydrothorax. Such patients would have had an impaired ability to maintain a negative sodium balance given their low glomerular filtration rate and, therefore, were likely to have hepatic hydrothorax refractory to diuretic therapy. This group was more likely to require TIPS for management of refractory hepatic hydrothorax. The literature reports a high incidence of intrapulmonary shunts in patients with advanced cirrhosis.^{12,13} We found a high prevalence of diastolic dysfunction and left atrial enlargement in this group of patients with hepatic hydrothorax. The increased frequency of diastolic dysfunction in these patients is intriguing. It has been speculated that increased neurohumoral activity promoting cardiac hypertrophy and fibrosis, along with impaired relaxation, cause diastolic dysfunction in patients with cirrhosis.^{14,15} There has been a report of improvement in diastolic dysfunction after paracentesis.¹⁴ Given the high prevalence of diastolic dysfunction and left atrial enlargement in hepatic hydrothorax, clinicians should not be dissuaded from making an accurate clinical diagnosis of hepatic hydrothorax in similar patients.

The pleural fluid analysis of solitary hepatic hydrothorax shows a paucicellular transudate with an alkaline pH and normal glucose value. Although most patients were receiving diuretics, conversion of the pleural fluid to a protein-discordant exudate was seen in only a single patient. About one-half (48%) of the patients with solitary hepatic hydrothorax had a pleural total protein < 1.5 g/dL, whereas three (38%) of eight patients with spontaneous bacterial pleuritis had a pleural total protein level < 1.5 g/dL. Previous studies have reported a higher incidence of

Table 4—Pleural Fluid Analysis in Solitary Hepatic Hydrothorax

PFA Characteristic	No. ^a	Mean (SD)	Median	Fifth to 95th Percentile
pH	29	7.49 (0.06)	7.49	7.40-7.57
Total protein, g/dL	33	1.49 (0.65)	1.50	0.58-2.34
Pleural fluid/serum protein ratio	32	0.25 (0.11)	0.25	0.10-0.43
LDH, IU/L	33	78 (56)	65	36-138
LDH ratio ^b	33	0.33 (0.23)	0.27	0.14-0.57
Pleural albumin, g/dL	15	0.79 (0.49)	0.53	0.22-1.57
Serum to pleural fluid albumin gradient, g/dL	15	1.5 (0.41)	1.5	0.94-2.02
Glucose, mg/dL	32	134 (50)	118	86-251
RBC, /μL	32	12,159 (20,740)	3,916	74-60,800
TNC, /μL	32	411 (367)	284	60-1143
ANC, /μL	32	68 (81)	26	1-230
Lymphocytes, %	32	35 (24)	30	9-79
Macrophage, %	32	43 (20)	46	13-69
Triglyceride, mg/dL	20	25 (15)	22	10-58
Amylase, IU/L	18	17 (11)	15	5-38

ANC = acute kidney injury; LDH = lactate dehydrogenase; PFA = pleural fluid analysis; TNC = total nucleated cell.

^aComplete pleural fluid analyses were not reported in all 41 patients, leading to a different total for each pleural fluid parameter.

^bPleural fluid LDH/upper limit of normal serum LDH (240 IU/L in our institution).

Table 5—Pleural Fluid Characteristics and Outcomes in Patients With Spontaneous Bacterial Pleuritis

Age, y/Sex	MELD Score	pH	Protein, g/dL (Protein Ratio ^a)	LDH IU/L (LDH Ratio ^b)	Glucose, mg/dL	TNC, /μL	ANC, /μL	Microbiology	Concurrent SBP Within 1 wk	Outcome
44/M	26	N/A	1.00 (0.20)	49 (0.20)	N/A	952	617	Negative	Yes	Liver Tx after 2 mo, A&W at 6 y
44/M	16	7.48	2.30 (0.38)	120 (0.50)	276	2,802	1,457	N/A	No paracentesis	Discharged to home hospice after 1 mo
22/M	15	7.43	2.70 (0.50)	67 (0.28)	177	2,959	1,673	Propionibacterium acnes	No paracentesis	No F/U data
53/F	24	7.35	0.37 (0.08)	63 (0.26)	103	1,761	1,074	GPC in pairs on Gram stain	Yes	Discharged to home hospice after 2 mo
44/M	17	7.52	1.10 (0.19)	94 (0.39)	106	1,669	1,285	Negative	No	Liver Tx after 7 mo, A&W at 4 y
54/F	33	N/A	1.70 (0.34)	190 (0.79)	137	2,923	2,075	Negative	Yes	Hypotension during liver Tx; expired
49/M	12	7.34	1.70 (0.33)	840 (3.50)	83	22,421	15,919	GNR on Gram stain	No paracentesis	A&W after 2 y
54/F	19	7.39	1.00 (0.16)	32 (0.13)	104	1,118	883	Negative	No paracentesis	Liver Tx after 2 mo, A&W after 3 y

A&W = alive and well; F/U = follow-up; GNR = gram-negative rods; GPC = gram-positive cocci; N/A = not available; SBP = spontaneous bacterial peritonitis; Tx = transplant. See Tables 1 and 4 for expansion of other abbreviations.

^aPleural fluid/serum protein ratio.

^bPleural fluid LDH/upper limit of normal serum LDH (240 IU/L in our institution).

spontaneous bacterial peritonitis with a lower ascitic fluid protein concentration and improved outcome with norfloxacin prophylaxis in advanced liver failure from cirrhosis with an ascitic protein < 1.5 g/dL.^{16,17} To our knowledge, no studies have explored the benefits of antibiotic prophylaxis for those with a pleural fluid total protein < 1.5 g/dL in patients with hepatic hydrothorax.

A high ANC was documented in all cases of spontaneous bacterial pleuritis. Five of eight patients (63%) with spontaneous bacterial pleuritis were transudates; two were LDH-discordant exudates and one was a protein-discordant exudate. Gram stain was positive in two of seven (29%), and the culture was positive in an additional patient. This rate of positive cultures is lower than previously reported.¹⁸ We believe that our microbiological culture yield was lower secondary to delay in inoculation (conventional method) and use of prophylactic, as well as therapeutic dosage of antibiotics prior to thoracentesis. There was no statistically significant difference between pleural fluid protein and LDH in solitary hepatic hydrothorax and spontane-

ous bacterial pleuritis. Additionally, the pH in spontaneous bacterial pleuritis was not lowered as would be expected in an infection of the pleural space. This likely reflects the earlier and widespread use of prophylactic as well as therapeutic antibiotics in such cases, limiting the inflammatory process in the pleural space. Also, the constant transdiaphragmatic influx of a large volume of transudative fluid may dilute the inflammatory milieu in these cases. Our findings suggest that ANC is the earliest and most reliable marker for spontaneous bacterial pleuritis.

Limitations

Our findings may be affected by the retrospective nature of this investigation and the relatively small sample size from a single institution. All patients reported in this series were referred primarily for thoracentesis. Some patients in our series did not have a complete set of diagnostic tests reviewed for the study because the tests were ordered by the physician responsible for the care of the patient at that

Table 6—Comparison of Pleural Fluid Total Protein, LDH, ANC, and Serum Albumin in Solitary Hepatic Hydrothorax and Spontaneous Bacterial Pleuritis

Pleural Fluid Analysis and Serum Albumin	Solitary Hepatic Hydrothorax (Median Value)	Spontaneous Bacterial Pleuritis (Median Value)	P Value (Wilcoxon Rank-Sum Test)
Protein, g/dL	1.5	1.4	.99
LDH, IU/L	65	80.5	.33
ANC, /μL	26	1,371	< .0001
Serum albumin, g/dL	2.3	2.25	.47

See Table 4 for expansion of abbreviations.

time based on clinical presentation. These factors may have lead to some selection bias.

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Dr Huggins: contributed to the data review and final editing of the manuscript.

Dr Doelken: contributed to the data review and final editing of the manuscript.

Dr Nietert: contributed to the statistics and review of the manuscript.

Dr Sahn: contributed to the study concept and design, data review, and final editing of the manuscript.

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