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Risk factors contributing to early infection following transjugular intrahepatic portosystemic shunt in perioperative period

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ABSTRACT

Introducción and aim. To investigate and identify the risk factors associated with early infection following a transjugular intrahepatic portosystemic shunt (TIPS)procedure in perioperative period. **Material and methods.** The interventional radiology database at the West China Hospital in Sichuan, China was reviewed to identify all patients that underwent a TIPS procedure between January 30, 2013 and August 30, 2015. Four hundred and sixty-six TIPS patients with liver cirrhosis were enrolled in this study. Liver function was assessed using the Child-Pugh classification system and bacteremia was defined as patients that had a positive blood culture. Statistical analysis was performed using χ^2 tests (include Fisher's exact tests χ^2) and logistic regression analyses. A $P < 0.05$ was set as the threshold for statistical significance. **Results.** One hundred and forty-eight of the 466 (31.7%) patients developed a fever. Eighty-three of the 148 fever patients subsequently had blood drawn for cultures and 9/83 (10.8%) patients developed bacteremia as defined by a blood culture analysis. Cholangiolithiasis ($P = 0.006$), Child-Pugh class A designation ($P = 0.001$), Child-Pugh class C designation ($P = 0.005$) and hepatitis C virus infection ($P = 0.011$) were significantly correlated with fever in these patients. No statistically significant correlations were found between the other factors (age, gender, clinical manifestation, diabetes mellitus, cholangiolithiasis, etc.) and bacteremia, with the exception of periprocedure cholangiolithiasis, which was significantly correlated with blood culture-defined bacteremia ($P < 0.05$). **Conclusions.** Cholangiolithiasis is a risk factor for infection after a TIPS procedure in the periprocedure period.

Key words. Cholangiolithiasis. Infection. Risk factors. Transjugular intrahepatic portosystemic shunt.

INTRODUCTION AND AIM

Over the past 30 years, transjugular intrahepatic portosystemic shunt (TIPS) placement has become a vital procedure in the treatment of liver cirrhosis patients complicated with portal hypertension, refractory ascites and variceal bleeding.[1] Infectious complications of TIPS are uncommon but when they occur, they can be devastating.[2] The TIPS procedure is performed using stent-grafts in the liver parenchyma after a tract between the hepatic and portal veins is established with a puncture needle. Despite a dramatic decrease in the morbidity and mortality associated with TIPS procedures, complications still occur. Currently, there is little data available regarding the late infectious complications after a TIPS procedure (e.g., Stent infections associated with bacteremia).[3] Moreover, even less has been documented regarding the incidence of infection associated with TIPS procedures during the periprocedure period. To this end, we undertook the present study to investigate the factors associated with early infection following the TIPS procedures in the periprocedure period.

MATERIAL AND METHODS

Subject enrollment and data collection

The radiology database at the West China Hospital (Sichuan, China) was reviewed to identify all patients who

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underwent a TIPS procedure between January 30, 2013 and August 30, 2015. Stent-grafts 10 mm in diameter (Fluency Plus; Bard, Tempe, AZ, United States) were used for all procedures. Laboratory results and body temperature data were used to identify patients who developed a fever or bacteremia subsequent to the TIPS procedure. Axillary temperture > 37.3 °C was definited as fever. Bacteremia was diagnosed after two positive blood cultures were found in patients with a temperature > 38.5 °C. The following demographic and clinical data were collected from each patient: sex, age, underlying liver disease, clinical manifestation (refractory ascites or hemorrhage), and comorbid conditions such as diabetes mellitus, cholecystolithiasis, and cholangiolithiasis. cholecystolithiasis and cholangiolithiasis was diagnosed by the upper abdominal CT 3D imagin and (or) color Doppler ultrasound, which were done to every patient before their TIPS procedure. Liver function was assessed according to the Child-Pugh classification system. Antibiotics were not administered prophylactically, since all TIPS procedures were performed electively and none of the patients had a fever prior to the TIPS procedure.

TIPS procedure

The catheter was introduced through the internal jugular vein, and guided into the hepatic vein through the superior vena cava, right atrium, and the inferior vena cava. The needle was used to puncture through the liver parenchyma and connect the intrahepatic branch of the portal vein. The balloon catheter was used to dilate the tract between the portal vein and the hepatic vein in the liver parenchyma. Finally, stent-graft(s) was inserted in the parenchymal tract.

Statistical analysis

Statistical analysis was performed using a χ^2 test (include Fisher's exact tests χ^2) and logistic regression by SPSS 22.0 software (IBM Corp., Armonk, NY, United States). A P value of < 0.05 was set as the threshold for statistical significance.

RESULTS

A total of 466 cases were reviewed and the clinical data are summarized in table 1. The patients in the case series

Table 1. Clinical characteristics of the populations enrolled in the study.

Characteristic	Fever		*n*	*P*-value*	*P*-value**	OR
	Yes	No				
Sex						
Male	106	217	323	0.461		
Female	42	101	143			
Age, yr						
≥ 65	17	58	75	0.065		
< 65	131	260	391			
Clinical manifestation						
Refractory ascites	23	55	78	0.701		
Hemorrhage	123	265	388	0.701		
Concomitant disease						
Diabetes mellitus	19	42	61	0.912		
Cholecystolithiasis	14	35	49	0.612		
Cholangiolithiasis	7	2	9	0.006	< 0.05	7.844
Child-Pugh class						
A	42	141	183	0.001	< 0.05	0.497
B	81	151	232	0.145		
C	25	26	51	0.005	< 0.05	2.283
Underlying liver disease						
PBC	11	17	28	0.378		
HBV	86	191	277	0.689		
HCV	12	9	21	0.011	< 0.05	3.029
AIH	1	7	8	0.238		
ALC	23	63	86	0.269		
BCS	8	10	18	0.238		
Schistosome	4	4	8	0.271		
Unknown	6	28	34	0.065		

** The χ^2 test. ** Logistic regression. AIH: autoimmune hepatitis. OR: Odds ratio. ALC: alcoholic liver cirrhosis. BCS: Budd-Chiari syndrome. HBV: hepatitis B virus. HCV: hepatitis C virus. PBC: primary biliary cirrhosis.*

had a mean age of 45 ± 15.3 years and included 323 males and 143 females. Two hundred and seventy-seven patients had hepatitis B virus-related cirrhosis, 21 ones had hepatitis C virus-related cirrhosis, 86 ones had alcoholic liver cirrhosis, and 96 ones had other diseases. Sixty-one patients in the cohort had diabetes mellitus, 49 ones had cholecystolithiasis and 9 of them had cholangiolithiasis. Of all the 466 patients, 148 ones developed a fever after undergoing the TIPS procedure. The stratification of patients by whether or not they had a fever in relation to the clinical characteristics is presented in table 1.

Out of the 148 patients that had a fever, 65 had a fever < 38.5°C and were thus not tested for bacteremia. In 58 of these patients, the fever was attributed to aseptic necrosis of material absorption and these patients recovered without antibiotics. The remaining 7/65 patients received antibiotics, as their fever was due to unknown origin. All the eighty-three patients who had a fever > 38.5°C had blood drawn twice for cultures, and 9/83 patients (seven male, two female; median age: 46.5 years; range: 39-60 years) had bacteremia as defined by a positive blood culture. Bacteremia onset occurred a median of 2.5 d (range: 1-5 d) after the TIPS procedure was performed. The bacteremia resolved in 7/9 patients within a median of 7 d after antibiotics were initiated. The remaining two patients died due to an infection of the bile duct. From the blood culture analysis, three bacteremia patients tested positive for *Escherichia coli*, while the remaining four patients tested positive for *Aeromonashydrophila, Gemellamorbillorum, Burkholderiacepacia, Citrobacter freundii, Klebsiella pneumoniae* subsp *Pneumoniae* and *Streptococcus cristatus (S. cristatus)* (Table 2). It was also suspected that one of the cholangiolithiasis patients had bacteremia due to a high body temperature and elevated procalcitonin levels. This patient was not included in our bacteremia numbers, as the blood culture did not come back positive. Cholangiolithiasis, Child-Pugh class A designation, Child-Pugh class C designation and hepatitis C virus infection were significantly correlated with fever. Only the Child-Pugh class A designation was negatively correlated with infection after χ^2 test (OR: 0.497). With the exception of cholangiolithiasis, which was significantly associated with blood culture-defined bacteremia (P = 0.025), no statistical correlation between the other characteristics and bacteremia was observed (Table 3).

Table 2. Blood culture results in patients with a fever > 38.5°C.

Patient	Liver disease	CP class	Antibiotic Px	Days after TIPS	Organism	Concomitant disease
1	HBV related	B	No	2	*Streptococcus cristatus*	Cholangiolithiasis
2	Alcohol related	C	No	3	*Escherichia coli*	Cholangiolithiasis
3	HBV related	C	No	2	*Escherichia coli*	Cholangiolithiasis
4	HBV related	B	No	5	*Escherichia coli*	None
5	HCV related	B	No	1	*Burkholderiacepacia*	None
6	HBV related	C	No	3	*Gemellamorbillorum*	None
7	HBV related	A	No	2	*Aeromonashydrophila*	None
8	HBV related	B	No	3	*Citrobacter freundii*	None
9	PBC related	C	No	2	*Klebsiella pneumoniae* subsp *pneumoniae*	Diabetes mellitus

CP: Child-Pugh. HBV: hepatitis B virus. HCV: hepatitis C virus. Px: prophylaxis. TIPS: transjugular intrahepatic portosystemic shunt. PBC: primary biliary cirrhosis.

Table 3. Risk factors for bacteremia after TIPS on multivariate analysis.

	Culture		*n*	*P*-value*	OR
	Positive	Negative			
Hepatitis C virus				0.509	
Yes	1	5	6		
No	8	69	77		
Cholangiolithiasis				0.025	8.750
Yes	3	4	7		
No	6	70	76		
Child-Pugh class C				0.065	
Yes	4	12	16		
No	5	62	67		

** The χ^2 test (Fisher's exact tests).*

CONCLUSIONS

Over the past few years, TIPS placement has become a universally accepted method in the management of complications associated with portal hypertension, and variceal bleeding in particular. TIPS placement is a minimally invasive technique that reduces portal venous pressure without the requirement of a surgical laparotomy and its associated complications. Patients with impaired liver function or cirrhosis frequently develop bacterial infections, which causes death in 30%-50% of cases.[4,5] Infectious complications resulting from TIPS placement, however, have been reported infrequently. One case series documented fever following the TIPS procedure in 10%-35% of patients; sustained bacteremia was rare, however, with an estimated annual incidence of 7/1000 cases post-TIPS.[6,7] In our study, 148/466 (31.7%) patients developed a fever, 83/148 (56.0%) patients had blood drawn for cultures, and 9/83 (10.8%) developed blood culture-confirmed bacteremia.

Of all the factors investigated in our study, only cholangiolithiasis, Child-Pugh class A designation, Child-Pugh class C designation and hepatitis C virus infection were significantly correlated with fever. The Child-Pugh A classification was the only factor negatively correlated with infection. Because decompensated liver cirrhosis is a contraindication of interferon therapy, patients with hepatitis C viral infections and liver cirrhosis were difficult to treat and were more susceptible to infection.

In our analysis, only cholangiolithiasis was significantly associated with bacteremia. Although intrahepatic stenting may cause liver inflammation, an inflammatory response initiated by translocation of intestinal bacteria more likely accounts for the bacteremia.[6,7] The pathophysiologic role of bacteria in the formation of gallstones was proposed many years ago. In Western countries, gallstones are predominantly composed of cholesterol, and bacteria do not play a significant role in the pathogenesis.[8] Bacterial infections of the bile duct, however, may play a critical role in the development of "brown-pigment" gallstones, which are composed primarily of bilirubin. Bacteria are often found in high concentrations in brown-pigment gallstones and less frequently in cholesterol gallstones.[9] The brown-pigment stones may provide an environment conducive to bacterial infection in some cases.[10-14] Other studies have instead suggested that the bacteria play a role in the formation of gallstones, which often co-present in patients with juxtapapillary duodenal diverticula.[15] Thus, there may be an increase in bacteria in the bile duct in cholangiolithiasis patients, who may be more susceptible to infection. Similar to what has been published previously, our study found that the majority of infection cases were due to enteric bacteria.[7,16] In our study, blood culture results for 3/9 patients with cholangiolithiasis were positive, with two patients positive for *E. coli* and one patient positive for *S. cristatus.* During the TIPS procedure, the needle is punctured through the parenchyma between the portal vein and hepatic veins, which we hypothesize may injure the enlarged bile duct and cause the release of bacteria into the blood stream. Bacteremia may also be caused by translocation of the bile stone itself, which leads to bile duct obstruction and subsequent infection. Despite the widespread use of antimicrobial prophylaxis, it was not administered in our study. Although studies evaluating antibiotic prophylaxis for TIPS procedures have yielded conflicting results and a one-time dose of ceftriaxone (1 or 2 g) has been shown to reduce the rate of post-TIPS infection.[17] The most common agents used are third generation cephalosporins, though it has been noted that they provide inadequate coverage against *Enterococcus faecalis*, one of the most commonly implicated organisms.[18] In our study, cholangiolithiasis may determine whether antibiotics should be administered prophylactically during the periprocedure period following a TIPS procedure.

In the present study, bile cultures were not performed. Grill, *et al.*[19] suggested that the detection of bacteria in bile cultures is influenced by the toxicity of bile salts. Therefore, traditional bile culture methods may overlook a significant number of underlying bacterial infections.[19-22]

There are a few limitations to the present study. One limitation is that blood culture was only done to those patients with a fever > 38.5°C, though some patients with a fever < 38.5°C may have also had bacteremia. A second limitation was that this case series did not include a control group of cirrhotic patients that did not undergo a TIPS procedure. In the present study, we identified periprocedure cholangiolithiasis as a potential risk factor for infection following TIPS procedures. Further research is warranted to better define infectious risk factors before and after TIPS procedures.

ABBREVIATIONS

- **TIPS:** transjugular intrahepatic portosystemic shunt.

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