

## Bacteremia and "Endotipsitis" following transjugular intrahepatic portosystemic shunting

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### Abstract

**AIM:** To identify all cases of bacteremia and suspected endotipsitis after Transjugular intrahepatic portosystemic shunting (TIPS) at our institution and to determine risk factors for their occurrence.

**METHODS:** We retrospectively reviewed records of all patients who underwent TIPS in our institution between 1996 and 2009. Data included: indications for TIPS, underlying liver disease, demographics, positive blood cultures after TIPS, microbiological characteristics, treatment and outcome.

**RESULTS:** 49 men and 47 women were included with a mean age of 55.8 years (range 15-84). Indications for TIPS included variceal bleeding, refractory ascites,

hydrothorax and hepatorenal syndrome. Positive blood cultures after TIPS were found in 39/96 (40%) patients at various time intervals following the procedure. Seven patients had persistent bacteremia fitting the definition of endotipsitis. Staphylococcus species grew in 66% of the positive cultures, Candida and enterococci species in 15% each of the isolates, and 3% cultures grew other species. Multi-variate regression analysis identified 4 variables: hypothyroidism, HCV, prophylactic use of antibiotics and the procedure duration as independent risk factors for positive blood cultures following TIPS ( $P < 0.0006, 0.005, 0.001, 0.0003$ , respectively). Prophylactic use of antibiotics before the procedure was associated with a decreased risk for bacteremia, preventing mainly early infections, occurring within 120 d of the procedure.

**CONCLUSION:** Bacteremia is common following TIPS. Risk factors associated with bacteremia include failure to use prophylactic antibiotics, hypothyroidism, HCV and a long procedure. Our results strongly support the use of prophylaxis as a means to decrease early post TIPS infections.

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**Key words:** Tips; Bacteremia; Ascites; Bleeding; Liver Insufficiency

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## INTRODUCTION

Transjugular intrahepatic portosystemic shunting (TIPS) is a procedure that uses minimally invasive image guided techniques to decompress the portal system and reduce portal hypertension. TIPS was first described as a research technique in 1969 and gained clinical acceptance in the early 1990s<sup>[1,2]</sup>. The most common indications for TIPS are for the treatment of variceal bleeding<sup>[3-5]</sup>, and refractory ascites<sup>[6-8]</sup>. Other less common indications include: Budd-Chiari syndrome<sup>[9,10]</sup>, hepatorenal syndrome<sup>[11,12]</sup>, veno-occlusive disease<sup>[13]</sup> hepatic hydrothorax<sup>[14]</sup>, non-variceal bleeding and pre-operative portal decompression<sup>[15]</sup>.

The widespread use of the TIPS procedure has led to the recognition of multiple complications, both systemic and local. Systemic complications include hepatic failure, encephalopathy, sepsis and death. Local complications are less frequent but include laceration of vessels, massive hemorrhage and pneumothorax, as well as prosthesis-associated complications such as occlusion, migration and misplacement<sup>[16-18]</sup>.

Bacteremia associated with endovascular infection of TIPS stents is an infrequently reported serious complication<sup>[19]</sup>. The term “endotipsitis” was proposed by Sanyal and Reddy<sup>[20]</sup>, who defined it as: (1) the presence of continuous bacteremia indicating an infectious focus in continuity with the venous circulation and (2) failure to find an alternate source of infection despite an extensive search. While fever and transient bacteremia have been described in 2% to 25% of the patients after TIPS<sup>[21,22]</sup>, the overall incidence of “endotipsitis” is unknown because of its rarity, lack of uniform definition and the unknown number of total TIPS procedures. The purpose of this study was to identify all cases of bacteremia and suspected endotipsitis after TIPS at our institution and to determine risk factors for their occurrence. We analyzed data from all the patients who underwent TIPS in our institution over a 13 year period (1996-2009).

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed the records of all patients who underwent TIPS between January 1996 and January 2009 at a single tertiary referral center the Hadassah-Hebrew University Medical Center in Jerusalem, Israel.

### Clinical information

Data recorded included age, sex, underlying liver disease, other co-existing diseases, indications for TIPS, positive blood cultures after TIPS, time between TIPS and occurrence of bacteremia, type of microorganism isolated, extent of diagnostic work-up, type of treatment and outcome. Also recorded was the duration of the TIPS procedure, direct portal venous pressure before and after procedure, use of prophylactic antibiotics and length of hospitalization after procedure. The severity of chronic liver disease was assessed by the MELD score<sup>[23]</sup>, and Child-Pugh-Turcotte (CPT) score<sup>[24]</sup>,

### Definitions

We used the definition used by Sanyal *et al.*<sup>[20]</sup> for persistent bacteremia as fever with at least two positive blood cultures in which the same organism grew. Non-persistent bacteremia was defined as fever with multiple/single positive cultures of any organism over the study time period.

Highly suspected “endotipsitis” was defined as persistent bacteremia with vegetations or occlusive thrombus within the TIPS, or a patent TIPS, with no other obvious source of infection. Because there is no definition in the literature of the time span between the TIPS procedure and the bacteremia, we did not limit the time until the first bacteremia.

Underlying liver disease, concomitant medical conditions, treatments, extent of diagnostic work-up and complications were individually collected from patient’s files. Laboratory data was collected from the hospital’s computerized laboratory results. Outcome data was collected from the Israeli national registry and individually from other medical centers in Israel.

### Statistical analysis

The Pearson Chi-square test, as well as the Fisher’s exact test, were used to test the association between any two categorical variables. Comparison of continuous variables between two independent groups was performed by application of the two-sample *t*-test. The multiple stepwise logistic regression model was applied in order to test which variables simultaneously influence the development of bacteremia and endotipsitis post TIPS procedure. Continuous variables are presented as mean  $\pm$  SD. All statistical tests were two-tailed, and a *p*-value of 5% or less was considered statistically significant.

## RESULTS

We identified 96 patients who underwent TIPS between 1996-2009. There were 49 males and 47 females, with a mean age of 55.8 years (range 15-84). Patient characteristics are summarized in (Table 1). Indications for TIPS were: variceal bleeding in 51 patients (53%), refractory ascites in 41 patients (42%), hepatic hydrothorax in 4 patients (4%) and hepatorenal syndrome in one patient (1%). One patient had both bleeding and refractory ascites. The underlying liver disease was HCV in 31 patients (32.3%), HBV in 17 patients (17.7%), cryptogenic cirrhosis in 18 patients (18%), Budd-Chiari syndrome in 10 patients (10%), non-alcoholic steatohepatitis in 5 patients (5%), and miscellaneous causes in 15 patients (18%). One patient was a chronic carrier of both HBV and HCV. The mean MELD and CPT scores at the time of TIPS were 14.04 (range 6-32), and 9 (range 5-13) respectively. The mean procedure duration was 85.2 min (range 26-300 min).

We identified 39/96 (40%) patients with positive blood cultures. Twenty four of the positive blood cultures (62%) occurred within 60 days of the procedure. Thirty-two were non-persistent (13 single, 19 multiple) and 7 Persistent.

**Table 1 Patients characteristics**

Group characteristics	No bacteremia	Positive culture	Persistent bacteremia	P value	
Number of patients	57	32	7	<i>P</i> = NS	
Gender (M/F)	30/27	19/20	3/4	<i>P</i> = NS	
Mean age at time of procedure (years) (range)	55.76 ± 13.44	55.89 ± 13.62	55.85 ± 13.38	<i>P</i> = NS	
Underling liver disease	HCV	13 (21.05%)	6 (85.7%)	<i>P</i> < 0.004	
	HBV	12 (21.05%)	4 (12.5%)	<i>P</i> = NS	
	Cryptogenic	13 (22.8%)	5 (15.6%)	<i>P</i> = 0.08	
	Budd-Chiari	7 (12.28%)	3 (9.3%)	<i>P</i> = 0.08	
	NASH	3 (5.26%)	2 (6.25%)	<i>P</i> = NS	
	Miscellaneous	10 (17.54%)	6 (18.75%)	<i>P</i> = NS	
	Variceal bleeding	30 (31.2%)	9 (28.1%)	4 (57.1%)	<i>P</i> = 0.056
Indication for TIPS	Refractory ascites	27 (28.12%)	21 (23.95%)	2 (28.57%)	<i>P</i> = NS
	Hepatic hydrothorax	1 (1.04%)	None	1 (14.2%)	<i>P</i> = NS
	Hepatorenal syndrome	2 (2.08%)	1 (1.04%)	None	<i>P</i> = NS
Time of procedure (min), mean (range)	70 ± 37	85 ± 51	109 ± 58	<i>P</i> < 0.039	
MELD, mean (range)	13.96 (6-32)	14.11 (6-32)	16.5 (9-22)	<i>P</i> = NS	
CPT, mean (range)	8.19 (5-13)	9.23 (5-13)	12 (9-13)	<i>P</i> < 0.001	
Hypothyroidism	7 (12.28%)	17 (53.1%)	6 (85%)	<i>P</i> < 0.001	
Failure to use prophylactic antibiotics	7 (12.28%)	18 (56.25%)	6 (85%)	<i>P</i> < 0.001	

M/F: Male/Female; CPT: Child-Pugh-Turcotte; MELD: Model for End-stage Liver Disease; TIPS: Transjugular intrahepatic portosystemic shunting; NASH: Nonalcoholic steatohepatitis.

**Table 2 Microbiological characteristics**

Microorganism	Frequency (%)
Staphylococcus aureus	41
Staphylococcus coagulase negative	26
Enterococci species	15
Candida species	15
Others	3

Staphylococcus species were isolated from 26/39 patients (66% of all positive cultures). Sixteen of 39 patients had Staphylococcus aureus (41%) and 10 patients coagulase negative Staphylococcus (26%). Enterococcus and Candida species were each isolated from 6 patients (15% of the positive cultures). Streptococcus viridans grew from 1 patient (3 %) (Table 2). The median length of time to the first bacteremia following TIPS was 38 d (range 8-562 d, mean 151 d). Although 13 of the early bacteremias (within 120 d of the procedure), were due to Staphylococcus aureus this did not reach statistical significance because of the low incidence of other bacterial species in early cultures.

Organisms isolated from the 7 patients with persistent bacteremia that were highly suspected for endotipsitis, included 3/7 patients with enterococci (42%), 2/7 patients with Staphylococcus aureus (29%) and 2/7 patients with Candida albicans (29%). All the patients with highly suspected endotipsitis underwent a work up including: abdominal US, chest-abdomen-pelvic CT and transthoracic echocardiography. Further work-up in selected cases included transesophageal echocardiogram in 2/7 patients, bone scan in 4/7 and bone-marrow and liver biopsy in 2/7 patients. Six out of the 7 patients did not have indwelling central vein catheters at the time of bacteremia. One patient had an indwelling catheter prior to the diagnosis of bacteremia; however bacteremia persisted after removal

of the catheter. No underlying cause for bacteremia other than TIPS infection was identified. TIPS thrombosis was diagnosed in 4/7 (57%) patients with persistent bacteremia including the patient with the indwelling intra-venous catheter.

In the entire study group, the mean survival time after the TIPS procedure was 965 d (range 4-3072, median 609 d). Sixty-seven patients (70%) died during the study period and 15 patients underwent cadaveric liver transplantation. Of those 15 patients, 11 died during the study period with a mean survival for transplanted patients after TIPS of 1261 d (range 15-3585, median 542 d). In the persistent bacteremia group (*n* = 7), two patients underwent cadaveric liver transplantation while receiving antibiotics with negative cultures, 4 died of infectious complications associated with their suspected endotipsitis and one recovered following prolonged antibiotic treatment and is currently alive. There was no difference in survival rates between patients with persistent bacteremia and non-persistent bacteremia and between the group with bacteremia and without bacteremia.

### Assessment of risk factors

The following variables were not associated with increased risk of bacteremia in our study: age, sex, portal venous pressure after the procedure, type of microorganism and MELD score.

Univariate analysis identified the following variables as risk factors for bacteremia following TIPS: indication for TIPS procedure, duration of procedure, lack of prophylactic antibiotic treatment before the procedure, pre-procedure portal pressure, hypothyroidism, HCV and CPT score.

Four variables were identified as independent risk factors for bacteremia by multivariate analysis: failure to

use prophylactic antibiotics, the duration of the TIPS procedure and HCV or hypothyroidism as the underlying liver or concurrent disease.

Patients with highly suspected endotipsitis had a higher CPT score ( $12 \pm 1.51$  vs  $8.72 \pm 1.69$ ,  $P < 0.0001$ ), and a trend towards longer hospitalization post the TIPS procedure ( $16.8 \pm 11.82$  d vs  $10 \pm 6.31$  d,  $P < 0.08$ ), compared to patients with transient bacteremia and patients without bacteremia.

There were 31/96 (31%) patients who did not receive prophylactic antibiotics before the procedure. It is important to mention that until the year 2000 prophylactic antibiotic treatment was not a required part of our TIPS protocol. Bacteremia was significantly more common in the group that did not receive prophylaxis as compared to those that received it; 24/31 (77%) vs 15/65 (23%) ( $P < 0.001$ , adjusted OR 10.682, 95% CI: 2.22-51.3). In the group that was highly suspected of endotipsitis 4/7 patients did not receive prophylaxis. The reduction in the number of bacteremias, was attributed mainly to prevention of early staphylococcal infections. 17/24 (70%) of infections in the group with bacteremia that did not receive prophylaxis were due to staphylococcal infections (13 *Staphylococcus aureus* and 4 coagulase-negative *Staphylococci*) that occurred within 120 d of the procedure ( $P < 0.002$ , as compared to late infection).

There was a linear increase in the number of positive blood cultures following TIPS with increased duration of procedure ( $P < 0.001$ , adjusted OR 1.015; 95% CI: 1.001-1.030).

Two other variables associated with increased risk of bacteremia were HCV and hypothyroidism. There were 31 HCV patients in our cohort, 18 (60%) had bacteremia as compared with 5/17 (30%), 3/10 (30%) 5/18 (27%), 8/21 (38%), in the HBV, Budd-Chiari and cryptogenic cirrhosis, NASH and miscellaneous groups ( $P < 0.005$ ) respectively. There were 30 patients with hypothyroidism in our cohort. Patients were considered to have hypothyroidism if they had the diagnosis in their medical charts, if they were treated with thyroid hormone replacement or if they were found to have elevated thyroid stimulating hormone (TSH) levels in their laboratory results. 24/30 (80%) had bacteremia (single and persistent) as compared with 15/66 (22%) in the euthyroid patients ( $P < 0.00003$ , adjusted OR 15.67; 95% CI: 2.94-83.47).

## DISCUSSION

Bacteremia is a serious complication following TIPS. "Endotipsitis" is the term used to describe persistent bacteremia stemming from endovascular infection of the TIPS stent. The incidence and risk factors associated with bacteremia and/or endotipsitis following TIPS are currently unknown<sup>[25]</sup>. We retrospectively identified 39 episodes of bacteremia in 96 patients who underwent TIPS in a single center over a 13-year period. We identified seven cases of persistent bacteremia highly suspected for endotipsitis and 32 episodes of non-persistent bacteremia.

Multivariate analysis identified 4 variables as independent risk factors for bacteremia following TIPS. To the best of our knowledge this is the first longitudinal study to assess variables associated with this previously under-reported and poorly understood entity.

We first looked at bacterial isolates from patients with bacteremia following TIPS. The majority of pathogens isolated were staphylococci and enterococci species. These pathogens are consistent with isolates reported in previously published data and with data from other endovascular infections<sup>[19,20]</sup>.

The median length of time between TIPS and the first bacteremia was 38 d. We did not find a correlation between re-intervention such as "TIPSogram", stent angioplasty or re-stenting following the initial procedure and the occurrence of bacteremia. Previous reports have suggested that endotipsitis can occur at any time following the initial procedure with periods reported in the literature ranging from 6 d to 10 years<sup>[19]</sup>. It was also previously suggested that the pathogens identified following TIPS may differ between early (less than 120 d following the initial procedure) and late episodes (more than 120 d following the initial procedure). In the present study 24 (62%) of the bacteremia episodes were within 60 d of the procedure. The majority of early isolates were *Staphylococcus aureus*; however, due to the small numbers of other bacterial species, this did not reach statistical significance. Therefore, although there was no correlation between type of bacterium and the timing of bacteremia following the initial procedure, it is possible that *Staphylococcus* will emerge as the predominant bacterium in early post-TIPS bacteremia.

We identified four variables that were independent risk factors for bacteremia following TIPS. Failure to use prophylactic antibiotics was associated with increased risk of bacteremia. During the 1996-2000 period we did not routinely use prophylactic antibiotics before the procedure. From 2000 onwards, based on reports by Gulberg *et al* and Dravid *et al*<sup>[8,26]</sup>, we started using a single dose of cefazolin for ambulatory patients, or a single dose of vancomycin for hospitalized patients. Following the initiation of prophylactic treatment we observed a marked reduction in the incidence of bacteremia. This reduction was mainly attributed to a reduction in early staphylococcal infection.

There are no formal recommendations regarding antibiotic prophylaxis prior to TIPS. However, if we draw comparison from other endovascular infections, the recent guidelines of the American Heart Association concerning prevention of endocarditis state that prophylaxis is needed when prosthetic material is present during the first 6 mo after the procedure<sup>[27]</sup>. Several reports suggest that portions of the TIPS stent do not undergo endothelialization and remain exposed indefinitely. These exposed segments may form areas of attachment for bacteria<sup>[28,29]</sup>. We therefore currently use prophylaxis during the initial procedure and during repeated TIPS manipulations. A single prior report assessed the efficacy of a second generation cephalosporin as prophylaxis prior to TIPS and found that it did not

decrease the incidence of infection, thereby casting doubt on the efficacy of prophylaxis<sup>[21]</sup>. However antibiotic prophylaxis is nowadays considered standard care<sup>[30,31]</sup>. Our results strongly support the use of prophylaxis as a means to decrease early infections post-TIPS.

Of interest is the question of whether use of coated versus uncoated stents alters the prevalence, course or susceptibility to bacteremia and endotipsitis. Use of polytetrafluoroethylene coated stents was first reported in 1995<sup>[32]</sup>, however their widespread use has only been recent. Covered stents improve TIPS patency, reduce the rate of encephalopathy and the need for re-intervention<sup>[33,34]</sup>. It is therefore possible that they alter the susceptibility to bacteremia and the development of endotipsitis. We had only 4 patients with covered stents in our cohort (none had bacteremia) and cannot assess its impact on bacteremia in patients following TIPS procedure. This variable will have to be assessed in future randomized prospective studies.

The second independent risk factor for bacteremia was the duration of the procedure. This variable, which has not been previously reported as a risk factor associated with TIPS, has been shown to be an independent risk factor for bacteremia in numerous other surgical procedures including lung surgery<sup>[9]</sup>, total abdominal hysterectomy<sup>[35]</sup>, and others<sup>[36]</sup>, as well as in non-surgical interventions such as percutaneous transluminal coronary angioplasty<sup>[37]</sup>.

The two final variables associated with an increased risk of bacteremia were hypothyroidism and HCV. We could not find a direct association between hypothyroidism and infection. However, it has been previously reported that hypothyroidism decreases portal venous flow in animal models, and may be associated with a hypercoagulable state. These effects may increase the risk of bacterial adhesion to the stent thereby increasing the risk of infection as well as stent thrombosis<sup>[38,39]</sup>.

The association between HCV and infection has been previously suggested<sup>[40]</sup>. Bacterial infections are very common in patients with HCV cirrhosis, accounting for up to 15% of hospitalizations<sup>[41]</sup>. Recently HCV was shown to be associated with an increased rate of bacteremia in hemodialysis patients with tunneled catheters<sup>[42]</sup>.

We found no difference in survival between patients with persistent bacteremia, non-persistent bacteremia and without bacteremia. This finding may be attributed to the high overall mortality in our cohort of patients with very advanced liver disease, as well as to the size of our persistent bacteremia group which was not large enough to detect small changes in survival rates.

Our study has several limitations. It is retrospective and suffers from inherent problems associated with this study design. Some of the patients that underwent TIPS in our hospital may have presented with TIPS-related infections in other hospitals. Some of the data collection was incomplete. However the majority of the data was parametric and collected using computerized systems, and we specifically noted any missing data. Finally, due to the rarity of bacteremia and endotipsitis, it is unlikely that

prospective studies to assess its incidence and risk factors will ever be conducted.

In summary, bacteremia and “endotipsitis”, following TIPS is an emerging and probably under-recognized infectious disease. We identified four independent risk factors for bacteremia following TIPS including, lack of prophylactic antibiotics, prolonged procedure, HCV and hypothyroidism. As was previously shown the bacteremia and specifically endotipsitis can present as an early infection within days or weeks after TIPS or as a late infection, appearing months to years after the initial procedure. Multiple causative agents were implicated without a single bacterium emerging as a predominant pathogen. Endotipsitis should be considered in any patient with a TIPS and a persistent bloodstream infection that is not clearly attributable to another source. Antibiotic prophylaxis and an effort to shorten procedure duration should reduce the risk of endotipsitis.

## COMMENTS

### Background

Transjugular intrahepatic portosystemic shunting (TIPS) is a procedure that uses minimally invasive image guided techniques to decompress the portal system and reduce portal hypertension. The most common indications for TIPS are for the treatment of variceal bleeding, and refractory ascites, other less common indications include: Budd-Chiari syndrome, hepatorenal syndrome, veno-occlusive disease hepatic hydrothorax, non-variceal bleeding and pre-operative portal decompression. Systemic complications of TIPS procedure include hepatic failure, encephalopathy, sepsis and death. Local complications are less frequent but include laceration of vessels, massive hemorrhage and pneumothorax, as well as prosthesis-associated complications such as occlusion, migration and misplacement. Bacteremia associated with endovascular infection of TIPS stents is an infrequently reported serious complication.

### Research frontiers

The widespread use of the TIPS procedure has led to the recognition of multiple complications, both systemic and local, with more frequent reports of bacteremia following TIPS procedure.

### Innovations and breakthroughs

In the area of TIPS and bacteremia a lot of details are missing as prospective randomized control trials are impossible. For this reason, any trial prospective or retrospective is valuable for understanding the prevalence and outcome of bacteremia complications.

### Applications

In this study 49 men and 47 women were included with a mean age was 55.8 years (range 15-84). Indications for TIPS included variceal bleeding, refractory ascites, hydrothorax and hepatorenal syndrome. Positive blood cultures after TIPS were found in 39/96 (40%) patients at various time intervals following the procedure. Seven patients had persistent bacteremia fitting the definition of endotipsitis. Staphylococcus species grew in 66% of the positive cultures, Candida and enterococci species in 15% each of the isolates, and 3% cultures grew other species. Multi-variate regression analysis identified 4 variables: hypothyroidism, HCV, prophylactic use of antibiotics and the procedure duration as independent risk factors for positive blood cultures following TIPS ( $P < 0.0006$ , 0.005, 0.001, 0.0003, respectively). Prophylactic use of antibiotics before the procedure was associated with a decreased risk for bacteremia, preventing mainly early infections, occurring within 120 of the procedure. Our data comprise the largest cohort presented to date and provide readers with insight into the risk factors for bacteremia and ways in which such complications can be prevented.

### Terminology

Transjugular intrahepatic portosystemic shunting (TIPS) is a procedure that uses minimally invasive image guided techniques to decompress the portal system and reduce portal hypertension. TIPS was first described as a research technique in 1969 and gained clinical acceptance in the early 1990s

**Peer review**

This study is of interest because it introduces new knowledge regarding the risk factors for bacteremia post TIPS procedure.

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