

## Transjugular Intrahepatic Portosystemic Shunt Infection: A Case Study of Bacteraemia caused by *Escherichia Coli*

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Received: 09 Jan 2022

Accepted: 21 Jan 2022

Published: 28 Jan 2022

J Short Name: JJGH

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### Citation:

Qin JP, Transjugular Intrahepatic Portosystemic Shunt Infection: A Case Study of Bacteraemia caused by *Escherichia Coli*. Japanese J Gastro Hepato. 2022; V8(3): 1-5

### Keywords:

Transjugular intrahepatic portosystemic shunt; Infection; Bacteraemia; *Escherichia coli*.

## 1. Abstract

### 1.1. Background

It is widely believed that liver transplantation is the only way to cure hepatic cirrhosis. However, due to limited funds and liver donors, liver transplantation is seldom performed in Asia, especially in China. For patients who have experienced oesophageal and gastric varices bleeding and waiting for a liver transplant, transjugular intrahepatic portosystemic shunt (TIPS) has proven to be an ideal treatment procedure. However, TIPS may lead to severe complications. At present, TIPS infections remain a rare complication, and the definition remains controversial. Specific pathogenesis has not been elucidated. In the literature, no pathogenic bacterium has been confirmed as a major pathogen of TIPS infection, and no infections have been attributed to the placement of TIPS. Whether or not such infections are all associated with stent implantation of TIPS remains a question that needs to be answered. We report a case involving successful treatment of this patient that potentially can be used as a reference in clinics.

**1.2. Case Summary:** we report a case of a 64-year-old male patient with hepatic cirrhosis who underwent repeated bacterial culture of blood  $\leq 24$  hours after TIPS that showed an *Escherichia coli* infection. The patient was successfully cured. Informed consent was obtained from the patient to publish the case details and images.

**1.3. Conclusion:** It should become less likely for neoplasm or thrombi combined with infection to occur after TIPS in stunts made from Viatorr® stents (WL Gore and Associates) and their increasing use in clinics. Therefore, intestinal bacterial translocation may

eventually become the main cause of TIPS infection. A multi-centre randomized controlled study would be required to determine if postoperative use of antibiotics is effective in preventing TIPS infections.

**1.4. Core Tip:** It is widely believed that liver transplantation is the only way to cure hepatic cirrhosis. However, due to limited funds and liver donors, liver transplantation is seldom performed in Asia, especially in China. For patients who have experienced oesophageal and gastric varices bleeding and waiting for a liver transplant, transjugular intrahepatic portosystemic shunt (TIPS) has proven to be an ideal treatment procedure. However, TIPS may lead to severe complications. In the opinions of researchers, TIPS infection is a serious and even lethal complication. Here, we report a case of a patient with hepatic cirrhosis who underwent repeated bacterial culture of blood  $\leq 24$  hours after TIPS that showed an *Escherichia coli* infection. The patient was successfully cured. Informed consent was obtained from the patient to publish the case details and images.

## 2. Introduction

In recent years, postoperative complications associated with TIPS have gradually become less of a problem among patients with hepatic cirrhosis, and TIPS infection has become a rare postoperative complication [1]. However, if a Walls tent (10 × 60 mm) is used to build a shunt, it has been reported that infection with *Enterococcus faecalis* caused the death of patients due to postoperative stent dysfunction [2]. In the opinions of researchers, TIPS infection is a serious and even lethal complication. Here, we report a case of a patient with hepatic cirrhosis who underwent repeated bacterial culture of blood  $\leq 24$  hours after TIPS that showed an *Escherichia coli*

infection. The patient was successfully cured. Informed consent was obtained from the patient to publish the case details and images.

### 3. Case Presentation

#### 3.1. Chief complaints

A 64-year-old male patient was admitted to the hospital because of recurrent haematemesis and melena.

#### 3.2. History of present illness

He experienced repeated hematemesis, black stool for over 3 years, endoscopic and conservative treatments in many hospitals but with no relief, then he was referred to our hospital.

#### 3.3. History of past illness

The patient had alcoholic cirrhosis combined with EVB and Acute Variceal Bleeding Accompanied.

#### 3.4. Personal and family history

No special personal history or family history.

#### 3.5. Physical examination

The preoperative physical examination showed anaemia, and the spleen could be touched 2 cm below the costal margin. No positive signs were detected in other areas.

#### 3.6. Laboratory examinations

The preoperative laboratory examination revealed moderate anaemia, a Child-Pugh score of Grade B, and a MELD score of 12.

#### 3.7. Imaging examinations

Enhanced abdominal computed tomography (CT) revealed portal hypertension with collateral circulation in cirrhosis.

#### 3.8. Final Diagnosis

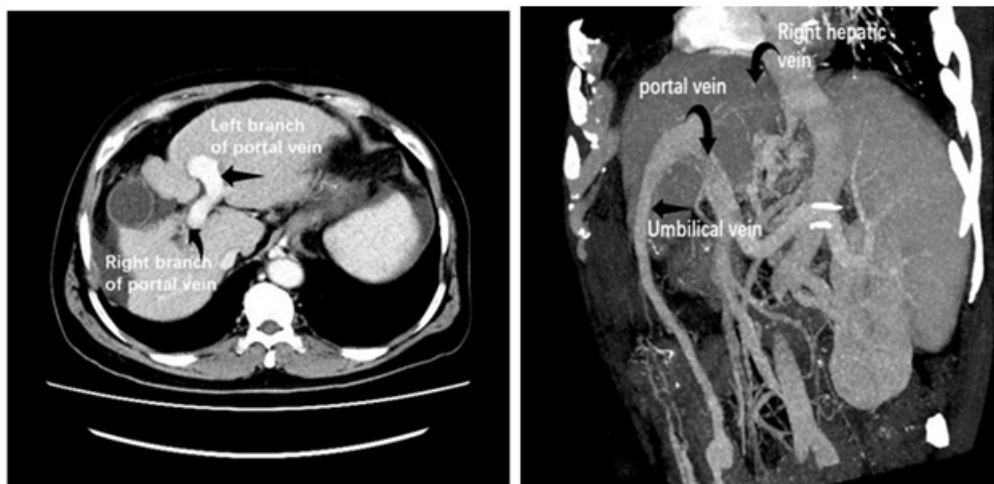
The diagnosis was alcoholic cirrhosis combined with EVB, which conformed with the indications presented in the TIPS instructions in America [3]. The patient and his family were informed of the diagnosis and proposed treatment procedure and signed informed consent forms.

### 3.9. Treatment

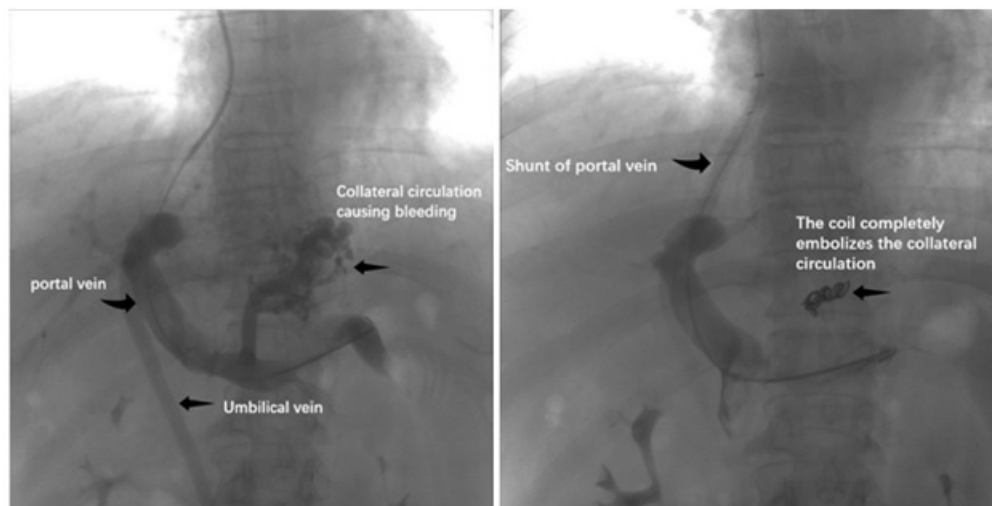
(1) Tomography (CT) imaging of the liver and three-dimensional reconstructed radiography of the hepatic and portal veins showed a portal branch puncture (Figures A–B). Details of the imaging procedures have been previously reported [4].

(2) TIPS: On the basis of the findings from the contrast-enhanced CT of the liver and three-dimensional reconstructed radiography of the hepatic and portal veins, we used a RUPS-100 puncture system (Cook Medical, Bloomington, IN) after making a right jugular vein puncture to puncture the portal branch from the superior vena cava and right atrium to the right hepatic vein or hepatic inferior vena cava. After successful portal branch puncture and determination by radiography that the puncture was accurately and safely performed, the pressure of the portal vein and postcava was determined. For collateral circulation vessels with oesophageal and gastric varices caused by embolism, a balloon (inner diameter: 8 mm) was used to expand the corresponding puncture channel, and then an 8-mm Viatorr® (WL Gore and Associates) stent was placed. Subsequently, portography was performed again, and then the pressure of the portal vein and postcava was also determined (Figures C–D). Details of the operation have been previously published [4].

(3) At 24 hours after the operation, the patient became intolerant of cold and had a high fever, with increased white blood cell count, C-reactive protein level, and procalcitonin level. Through repeated bacterial blood culture, *E. coli* was detected. Ultrasonic testing of the portal system and TIPS stent permeability evaluation showed no neoplasm or thrombogenesis, and blood-flow velocity in the stent was normal. Meropenem (0.5 g) was used at a dose of 1.0 g per 18 h, and body temperature and inflammatory indicators gradually returned to normal. After 5 days, the drug was discontinued. Two days after drug withdrawal, the patient again developed a high fever. Repeated bacterial blood culture showed the presence of *E. coli*. Meropenem again produced a good clinical effect, but 5 days later, it was replaced with Rifaximin, an oral antibiotic.



**Figures A-B:** Portal vein branch puncture under the guidance of preoperative liver enhanced computed tomography and three-dimensional reconstruction of the hepatic and portal veins.



**Figures C–D:** Portal vein angiography was repeated and portal pressure gradient was measured simultaneously.

### 3.10. Outcome and Follow-Up

After TIPS, the portal venous pressure gradient (in mmHg) dropped from 25.3 before the operation to 11.2 after the operation. At 2 weeks after the operation, the Child-Pugh score was Grade B and the MELD score was 13. After a calm postoperative period, the patient was discharged from the hospital and reported no further complications.

### 4. Discussion

TIPS infection, a rare and severe complication, clinically shows symptoms of infection and definite bacteraemia (cold intolerance, high fever, positive results in repeated blood culture) that are combined with thrombus/neoplasm in the stent. In this case, the term endotipsitis was coined and defined by Sanyal and Reddy [5]. An early case of lethal bacteraemia with TIPS infection was reported by Schiano TD [2]. The corresponding pathogenesis remains unclear, although it is thought to be caused by TIPS stent infection and a neoplasm formed due to a biliary fistula. Moreover, lesion localisation by imaging failed. In such cases, the part of the liver that contains the TIPS stent must be excised so that the neoplasm can be extracted and incubated to determine the corresponding pathogenesis. There have been two reported autopsy cases with thrombi in the TIPS stents that proved to be the source of infection [6]. In addition, a patient with a TIPS infection underwent a TIPS stent intima biopsy, and a biopsy specimen indicated pulmonary infiltration with eosinophilia [7]. Even if a clear diagnosis is made, anti-infective therapy is still an unsolved problem. Considering that the stent is not removable, a patient with repeated infections requires urgent attention. Since the TIPS shunts are Teflon™ (Chemours Company Wilmington, DE)-coated stents, there are individual cases in which covered stents were used in a TIPS/biliary system for fistula sealing [8]. Patients who have received anti-infective therapy in this way during hospitalisation have remained in stable condition. Mizrahi M et al [9]. Analyzed the literature on TIPS infections and found that application of covered stents improved TIPS shunt patency, lowered occurrence rates of hepatic en-

cephalopathy and stent dysfunction, and avoided TIPS intervention. Therefore, such applications can reduce the possibility of TIPS infection. At present, TIPS has an increasing number of indications, and postoperative complications of TIPS have gradually decreased [10-11]. Especially, the tectorial membrane of stents used for TIPS (e.g. Viatorr®, WL Gore and Associates) is not exposed to bile from the liver parenchyma segment of the shunt. Therefore, the problem of TIPS stent dysfunction is basically settled, and it is unlikely for local biliary tract infections to involve blood in the systemic circulation [12].

Outside of China, a total of four TIPS surgeries have been reported in the medical records [8, 13-15], in which the incidence rate of TIPS infection was about 1.5% (range: 0.6%–5.5%). Although most patients with TIPS infection had experienced alcoholic cirrhosis, we still cannot confirm whether the sex of the patient and pathogenesis of hepatic diseases are independent risk factors of TIPS infection. In our centre, Viatorr® stents (WL Gore & Associates) have been used to perform TIPS for 486 patients since March 2016. The aim of this case report was to describe the first patient with a TIPS infection. The infection rate in this patient was 2%, far below that reported in the literature outside of China. There are two possible major reasons for this finding. First, viral hepatitis type B is the major pathogen of hepatic cirrhosis in China, whereas alcoholic cirrhosis and non-alcoholic fatty cirrhosis play a major role in Europe and America, which involve different patient conditions. As pointed out by Komshian SV [16] and Connolly JP [17], it is much more likely for bacteraemia to occur among patients undergoing cancer, diabetes, or alcoholism or who have an indwelling catheter and in other patients who receive long-term antibiotic therapy. The male patient in this case report had alcoholic cirrhosis. We assume that his pathogenesis may be one of the causes of his TIPS infection. Second, scholars outside of China recommend preoperative antibiotics to prevent infection [2, 18-19]. According to the latest version of the TIPS guidelines in North America [12], the use of preoperative antibiotics depends

on the specific risk factors in patients, such as previous biliary tract examinations. There is insufficient evidence proving that routine use of antibiotics in the perioperative period can reduce infective complications after TIPS. All of the patients receiving TIPS in our center take antibiotics (i.e., third-generation cephalosporins at conventional doses for 3 days) postoperatively, but no antibiotics are taken preoperatively. As demonstrated by clinical practice in the centre, postoperative antibiotics are beneficial, especially for patients with alcoholic cirrhosis or with hepatic cirrhosis combined with diabetes.

After using a Viatorr® (WL Gore and Associates) stent to build the TIPS shunt for our patient, he became intolerant of cold and developed a high fever  $\leq 24$  hours after the surgery. Repeated bacterial blood culture confirmed *E. coli*, which was inconsistent with the TIPS infection initially diagnosed. A possible reason for this inconsistency may be that no neoplasm or thrombogenesis forms in TIPS stents. We speculated that pathogenic bacteria in our patient may have originated from his intestinal tract. In the literature [20], the amounts of Enterobacteriaceae, Alcaligenaceae, Streptococcus, Veillonella and Fusobacteriaceae all increase in patients with hepatic cirrhosis, indicating that the composition of intestinal flora changes in these patients. Early research in our centre [4] suggested that a patient who has undergone a TIPS operation may experience hemodynamic 'rebalance' between the portal veins and whole body; moreover, the hemodynamic 'rebalance' may be achieved in 3–6 months after surgery. As speculated, revascularisation in the intestinal tract after TIPS improves intestinal mucosal circulation, which affects intestinal flora. For this reason, some conditional pathogens may enter the portal vein system via hepatointestinal circulation. Additionally, some blood could directly flow into the systemic circulation due to the established hepatic portal vein shunt, which would cause bacteraemia.

The definition of TIPS infection remains controversial. Through evaluation of patients with a fever after TIPS, Sanyal AJ [5] found that TIPS infection occurred  $\leq 284$  days on average after an operation, and the corresponding diagnostic basis can be either fever, positive blood culture results and thrombi/neoplasm in stents, or continuous bacteraemia provided that no other sources of infection are detected through extensive examinations. In the study described above, eight patients showed symptoms conforming to the diagnostic standards of TIPS infection. Specifically, two patients underwent TIPS infections  $\leq 10$  days after operation; seven of them were infected with aerobic Gram-negative bacteria in the oral and intestinal tracts, and one was infected with *Candida albicans*. Moreover, all patients responded to antibiotics, although two of them died, one of myocardial infarction and the other of alcoholic hepatic failure. In addition to three other new patients reported by Bouza E [7], a retrospective analysis was performed on the existing 23 cases of TIPS infection. The average time for them to be infected was 210 days (range, 6–32 days) after the operation. Their overall incidence

rate of TIPS infection was 1.33%. The pathogenic bacteria that were identified were Gram-positive bacteria (18 patients), Gram-negative bacteria (10 patients) and fungi (3 patients). Although 20 patients responded well to antibiotic therapy, 6 died of infection. In the literature, no pathogenic bacterium has been confirmed as a major pathogen of TIPS infection, and no infections have been attributed to the placement of TIPS. Hepatic cirrhosis patients, especially those with alcoholic cirrhosis or primary biliary cirrhosis, may suffer progressive decline of the hepatic reservation function as the disease progresses after TIPS [21]. Considering that these patients frequently also have severe hypersplenism, it is much more likely for various concurrent infections to occur. Whether or not such infections are all associated with stent implantation of TIPS remains a question that needs to be answered.

In the CCI clinical practice guidelines on the management of TIPS for portal hypertension (2019 edition) [22], no problems involving TIPS infection are referred to. At present, TIPS infections remain a rare complication, and the definition remains controversial. Specific pathogenesis has not been elucidated. As noted in the present report, it should become less likely for neoplasm or thrombi combined with infection to occur after TIPS in stents made from Viatorr® stents (WL Gore and Associates) and their increasing use in clinics. Therefore, intestinal bacterial translocation may eventually become the main cause of TIPS infection. A multi-centre randomized controlled study would be required to determine if postoperative use of antibiotics is effective in preventing TIPS infections.

## 5. Conclusion

It should become less likely for neoplasm or thrombi combined with infection to occur after TIPS in stents made from Viatorr® stents (WL Gore and Associates) and their increasing use in clinics. Therefore, intestinal bacterial translocation may eventually become the main cause of TIPS infection. A multi-centre randomized controlled study would be required to determine if postoperative use of antibiotics is effective in preventing TIPS infections.

## 6. Author Contributions

Yao X performed the operation and wrote the paper; Yang XL, He PP, Qi Q and Wang LJ collected the data; Tang SH collected the data; Qin JP participated in and guided the operation, conceptualized the idea, and finalized the manuscript.

## 7. Conflict of Interest

The authors declare that they have no conflict of interest.

## 8. Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent Informed consent was obtained from all individual participants included in the study.

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