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Journal

Seminars in Interventional Radiology, 35(05)

ISSN

0739-9529

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Publication Date

2018-12-01

DOI

10.1055/s-0038-1676092

Peer reviewed

Transhepatic Revision of Occluded Transjugular Intrahepatic Portosystemic Shunt Complicated by Endotipsitis

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Semin Intervent Radiol 2018;35:492–496

*CME credit is not offered for this article.

A rare but potentially lethal complication of transjugular intrahepatic portosystemic shunt (TIPS) creation is stent infection, referred to as “endotipsitis.”¹ This condition—due to microorganism colonization of a TIPS stent graft with biofilm formation—is associated with high morbidity and mortality rates, and requires aggressive management with antibiotic therapy and possible removal of the infected device. Herein, we present a case of endotipsitis attributed to transhepatic revision of an occluded TIPS created 3 years earlier, leading to refractory sepsis requiring prolonged antibiotic therapy and hospitalization, and ultimately orthotopic liver transplantation (OLT). We further provide an overview of endotipsitis, its diagnosis, incidence, and management.

Case Presentation

A 65-year-old man underwent OLT in 2002 for liver cirrhosis attributed to chronic hepatitis B and D virus infection. In 2012, he presented with cholangitis, and was found to have a high-grade stricture at the biliary duct-to-duct anastomosis, with associated choledocholithiasis and moderate intrahepatic biliary ductal dilation. He was treated with antibiotics, resection of the stricture, Roux-en-Y hepaticojejunostomy, and intraoperative choledochoscopy and lithotripsy.

In 2013, the patient presented with gastrointestinal (GI) bleeding and was found to have recurrent cirrhosis and bleeding gastric varices, refractory to endoscopic therapy. A 10 × 60 mm TIPS covered stent graft was created, bridging the right hepatic vein to right portal vein, and gastric and esophageal varices supplied by the left and posterior gastric veins were embolized with metallic coils.

In 2017, the patient was admitted for cholangitis. Magnetic resonance imaging demonstrated unchanged moderate intrahepatic biliary ductal dilation (–Fig. 1), TIPS occlusion, and peri-graft enhancement and T2 prolongation, raising the

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possibility of peri-graft inflammation and/or TIPS infection. Symptoms of cholangitis resolved with ursodiol, a 4-day course of intravenous (IV) piperacillin-tazobactam followed by a 14-day course of oral amoxicillin and clavulanate.

TIPS revision was then attempted via a transjugular approach to prevent variceal bleeding, but the intra-graft thrombus was firm and could not be cannulated. Therefore, after the administration of 2 g ceftriaxone IV, and under sterile technique, the TIPS was recanalized via a transhepatic approach (–Fig. 2).

In the hours after TIPS revision, the patient developed fevers, rigors, altered mental status, tachycardia, and hypotension; he was transferred to the intensive care unit for vasopressor support and further management of septic shock. A thorough evaluation for source of infection, including computed tomography of the chest, abdomen, and pelvis, and transthoracic echocardiography demonstrated no clear source of infection aside from chronic biliary ductal dilation. He was treated with IV vancomycin and piperacillin-tazobactam while blood cultures were pending; he was transitioned to ceftriaxone after blood cultures grew *Klebsiella pneumoniae* susceptible to this agent. Symptoms improved, bacteremia cleared, and the patient was discharged on a 14-day course of IV ceftriaxone. On follow-up in the interventional radiology (IR) clinic 2 weeks after discharge, the patient was stable, and the TIPS was patent on ultrasound.

One week later, the patient was brought to the IR suite for transvenous obliteration of gastric varices under general anesthesia. An 8-Fr sheath was introduced from a right internal jugular vein approach through the TIPS and into the portal vein; splenoportography demonstrated occlusion of left and posterior gastric veins from prior coil embolization, and gastric varices supplied by innumerable diminutive portosystemic shunts. Therefore, balloon-occluded retrograde transvenous obliteration was performed with a mixture of air, 3% Sotradecol

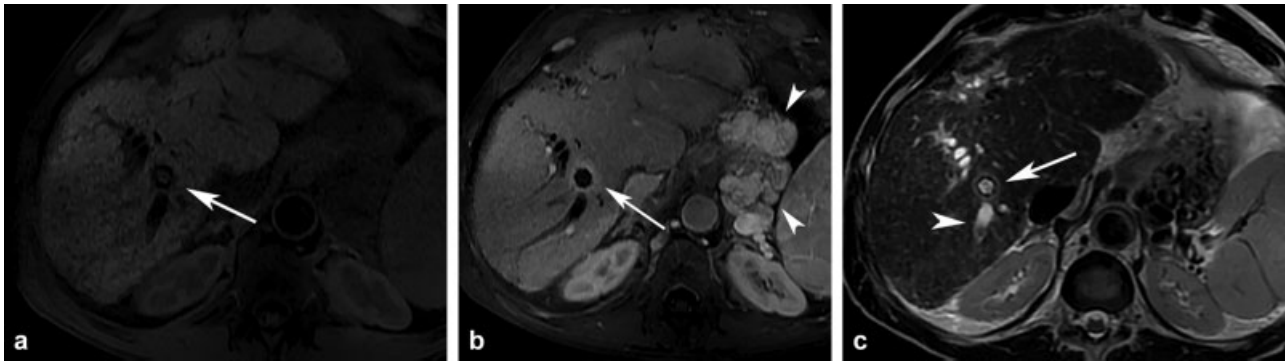


Fig. 1 Axial MR images of a 65-year-old man with history of OLT, with recurrent hepatitis B virus cirrhosis and TIPS creation 4 years earlier for variceal bleeding, admitted for cholangitis. An irregular T1-hypointense rim (*arrow*) adjacent to the TIPS is present on T1-weighted images with fat saturation (**a**) with corresponding peri-TIPS hyperenhancement (*arrow*) after administration of gadolinium contrast (**b**) and nonenhancement of the occluded lumen. Enhancing gastric varices are also present (*arrowheads*). T2-weighted images with fat saturation (**c**) demonstrate a corresponding irregular halo of T2 prolongation (*arrow*) adjacent to the TIPS; moderate intrahepatic biliary ductal dilation is also noted (*arrowhead*). In retrospect, peri-TIPS T2 prolongation and enhancement in the setting of TIPS occlusion and cholangitis is suggestive of endotipsitis.



Fig. 2 Transhepatic revision of occluded TIPS. Under sonographic and fluoroscopic guidance (**a**) the intrahepatic portion of the TIPS was percutaneously accessed with a 21-g needle directed toward the venous end, avoiding sonographically evident biliary radicals. A 0.018-in guidewire was advanced into the TIPS under fluoroscopic guidance, and the needle exchanged for a 4/6-Fr sheath. A 4-Fr catheter was coaxially introduced and a guidewire advanced into the inferior vena cava (IVC). Concurrently, a 10-Fr sheath was placed via the right internal jugular vein into the inferior vena cava. The guidewire from the transhepatic access was then snared (**b**) to obtain through-and-through access; a tandem 0.035-in guidewire was introduced via the right internal jugular vein sheath to cannulate the TIPS and gain access into the portal vein (**c**). A new 10 × 80 mm stent graft (Viatorr) was ultimately deployed within the prior TIPS and dilated to 8 mm and patent on portal venography (**d**); the resulting portosystemic gradient reduced from 10 to 6 mm Hg. The right internal jugular vein sheath was removed and hemostasis achieved with manual pressure; the 6-Fr sheath was removed and the transhepatic tract was occluded with microfibrillar collagen paste.

(AngioDynamics, Queensbury, NY), and Lipiodol (Guerbet, Princeton, NJ). He tolerated the procedure well without immediate complication and was admitted for observation. However, the following day, the patient developed fevers, chills, lactic acidosis, and worsening renal function. Blood cultures grew *Candida albicans*. A thorough evaluation again demonstrated no clear source of infection. He was initiated on micafungin and ultimately discharged on postoperative day 8 on a 14-day course of fluconazole.

Two weeks later, the patient presented to the emergency department with melena. He was found to be pancytopenic with iron-deficiency anemia. Upper GI endoscopy was obscured by blood in the stomach. Direct TIPS evaluation was performed via a right internal jugular vein approach; angiography demonstrated high-grade stenosis at the cephalad aspect of the shunt, in retrospect suggestive of a vegetation. This was treated with angioplasty with a 10-mm balloon (Mustang; Boston Scientific, Spencer, IN) with resolution of the stenosis and reduction of the portosystemic gradient from 21 to 12 mm Hg. That evening, the patient became febrile and was discharged the following day on antibiotics after symptoms resolved.

Follow-up ultrasound 1 week later demonstrated TIPS occlusion with recurrent ascites. Transjugular approach was again unsuccessful due to firm thrombus. The TIPS was successfully revised, again via a transhepatic approach with a final portosystemic gradient of 9 mm Hg. The patient became febrile immediately following the procedure with rigors, hypotension, and worsening renal function. Blood cultures grew *Enterococcus faecium* (vancomycin-resistant enterococcus). He was treated with fluconazole and daptomycin. The patient was discharged on linezolid in stable condition.

Considering all of the patients' aggregate events, endotipsitis was suspected due to sustained bacteremia with no other source identified, recurrent episodes of TIPS thrombosis, and worsening of sepsis following TIPS instrumentation. The patient was then listed for OLT with Model for End-Stage Liver Disease (MELD) score of 22. An application was made to the United Network of Organ Sharing (UNOS) Review Board for exception points for endotipsitis, and a MELD score of 26 was granted.

One week later, the patient reported to the emergency department with abdominal distension, dyspnea on exertion, and lower extremity edema in the setting of decompensating cirrhosis. The patient was found to have *Klebsiella oxytoca* bacteremia. The patient was ineligible for OLT until bacteremia cleared. Increased velocities were noted within the TIPS graft on ultrasound suggestive of recurrent stenosis, but TIPS revision was deferred in favor of medical optimization for OLT. He was treated with imipenem, daptomycin, and oral vancomycin. By hospital day 17, the patient's MELD score increased to 36 and blood cultures had been negative for 11 days.

The patient then underwent OLT. Pathological and microbiological evaluation of the explanted TIPS demonstrated culture-positive vegetations, confirming the diagnosis of endotipsitis. Immunosuppressive agents were initiated conservatively due to the patient's high risk of infection. He recovered from the transplant and is doing well over 1-year postoperatively.

Discussion

Endotipsitis is a rare but highly morbid complication of the TIPS procedure, with an estimated incidence of approximately 1 to 10%¹⁻⁶ and estimated mortality of 32%.⁷ The range in incidence of this adverse event is due to the relatively unreported outcomes of the TIPS procedure. Six studies that describe retrospective analysis of all TIPS procedures and suspected endotipsitis cases in six distinct institutions each found a slightly different rate of incidence of the infection. In 1998, Brown et al reported on 314 patients who underwent TIPS procedures from 1990 to 1995, and the rate of endotipsitis due to one causative agent was found to be approximately 1%.³ Four patients were found to suffer from *Enterococcal bacteremia*, all with a thrombosed TIPS graft.³ Of the four bacteremic patients, one was found to have acute endocarditis which may have been responsible for the infection.³ Two of the patients died from the infection and the other two underwent successful repeat TIPS procedures.³ Other infective causes of bacteremia were not analyzed in this study.³ In 2000, DeSimone et al described a total of 99 TIPS procedures performed between 1992 and 1999.⁴ Ten of the 99 patients suffered from sustained bacteremia and 5 of those 10 were likely bacteremic due to infection in the TIPS graft, representing a 5% rate of endotipsitis.⁴ Of the five cases of endotipsitis, three patients had a patent stent and two had thrombus occluding the stent.⁴ All patients cleared the bacteremia on IV antibiotics. Two of these patients died later from multiorgan failure, one from hepatorenal syndrome, one was lost to follow-up, and one was alive when the study was published.⁴ In 2003, Armstrong and MacLeod detailed 180 TIPS procedures performed between 1992 and 2000, and three cases of endotipsitis were identified, representing an incidence of 1.7%.² One patient had a patent TIPS graft, one had an occluded graft, and one had an unknown graft patency.² Two of the three patients died from multiorgan failure several weeks after the procedure and one was cured of the infection and alive when the study was published in 2003.² In 2010, Kochar et al reported on 778 TIPS procedures performed from 1992 to 2006 and an additional 7 patients who had TIPS at outside institutions were followed up at this center.¹ Eight cases of endotipsitis were identified, or approximately 1% incidence.¹ Of the eight cases, four had a thrombosed graft, three had a patent graft, and one was not recorded as patent or occluded.¹ Five of the eight patients died within 3 years of the TIPS procedure; in four of those patients, endotipsitis was a contributing factor.¹ In 2011, Mizrahi et al described 96 TIPS procedures performed from 1996 to 2009 and 7 cases of endotipsitis were identified.⁶ This represents the highest incidence of the complication at 10.4%.⁶ Four of the seven patients had a thrombus in the TIPS stent graft.⁶ Four of the seven patients died from the infection, two died during treatment with negative cultures, and one was alive at the time the study was published in 2011.⁶

Endotipsitis has a variety of presentations, but nearly always includes fever. Other presenting symptoms may

include chills, anorexia, malaise, anemia, diarrhea, and shock.⁸ Early manifestation of endotipsitis (within 120 days of TIP creation) may be attributable to procedural graft seeding.^{6,8} However, as in the presented case, endotipsitis may present years after stent-graft implantation. Late infection is often associated with revision or manipulation of the TIPS stent graft.² One study found that the average time from TIPS creation to bacteremia in patients with endotipsitis was 210 days, with a range from 6 to 732 days,⁹ and since that study bacteremia within 24 hours has been reported as well.¹⁰ The endotipsitis literature is predominantly limited to case reports and small retrospective studies; a 2010 systematic review identified 36 reported patients.⁸ A review of the literature published in 2017 identified 56 cases of endotipsitis, concluding that the overall mortality of all reported cases at that time was 32%.⁷ The use of broad-spectrum prophylactic antibiotics in the TIPS perioperative period has been found to be an effective method to prevent infection and are widely used,^{4,6} though some institutions prefer to individualize the use of prophylaxis.^{2,3,9}

Recent case reports suggest that among the most fatal infections documented include *Staphylococcus aureus* with 63% mortality and *Candida* species with 67% mortality on the basis of a retrospective analysis of seven patients with *S. aureus* and eight patients with candida infection.^{10,11} Two of the eight patients with candida-associated endotipsitis responded to antifungal therapy, while the remaining six patients died from infection.¹⁰ These microorganisms can create a biofilm on the graft that may not be eradicated by antibiotics.¹² In the case of recurrent infection or infection refractory to treatment, ultimately only a liver transplant may be curative.^{8,9,11}

Stent grafts for TIPS were introduced in 1995, and are now commonly utilized for the procedure.^{8,13,14} The term “endotipsitis” was introduced in 1998 by Sanyal and Reddy who identified eight cases meeting specific criteria. Though the incidence is estimated to be 1 to 10%,¹⁻⁶ it is likely that TIPS-related infections have been underreported, in part because there has not been a commonly accepted identification or classification of the infection.^{2,4,7,15} In their 1998 publication, Sanyal and Reddy define endotipsitis as follows:

Definite infection: continuous, clinically significant (fever and positive blood cultures) bacteremia, with vegetations or thrombi inside the TIPS

Probable infection: sustained bacteremia and unremitting fever in a patient with an apparently normal TIPS, and no other obvious source of infection.¹⁶

Another definition was proposed by Armstrong and MacLeod in 2003, as follows, “sustained bacteremia in a patient with a TIPS device, with or without thrombus, plus either no other identifiable infective focus or an identifiable infective focus that is not considered to be the source of the bacteremia after an exhaustive workup. “Sustained bacteremia” is defined as greater than or equal to 2 blood cultures positive for the same organism, the first and last being separated by greater than or equal to 7 days.² This definition was challenged by DeSimone, who agreed with the majority of the definition but disagreed that the positive blood

cultures needed to be at least 7 days apart.¹⁷ Both authors agreed that to have a definitive infection of the TIPS stent graft a thrombus does not need to be present, which was part of the original definition of definite infective endotipsitis proposed by Sanyal and Reddy.

Despite these proposed definitions, there are still not universally accepted criteria for diagnosis and treatment of endotipsitis. An argument to adopt diagnostic criteria similar to Duke’s criteria for the diagnosis of endocarditis has been made by some scholars.^{2,10,11,17} Both endotipsitis and prosthetic valve endocarditis are endovascular infections of prosthetic materials that are challenging to remove and difficult to treat without removal once colonized due to ingrowth of tissue.^{11,18} It is thought that not all of the graft becomes endothelialized, leaving uncovered portions that serve as areas of attachment and are more susceptible to colonization by bacteria and fungus.^{6,12} While a sample from the graft may be the ideal method to diagnose endotipsitis, this is not always possible. Sampling the thrombus, if present within the graft, is another way to assess for infection.¹⁸

In the patient presented herein, endotipsitis was suspected when the patient had recurrent episodes of bacteremia with a negative workup for any other source in the setting of a thrombosed TIPS graft. Sepsis occurred after each intervention through the TIPS after the patient initially presented with cholangitis and TIPS occlusion. The bile ducts were dilated and colonized, leading to contamination of the TIPS stent graft from cholangitis, or during transhepatic access for recanalization. The patient had undergone a hepaticojejunostomy, inevitably penetrating the colonized ducts and contributing to the spread of infection. Biliary fistulas and cholangiolithiasis have been the suspected source of TIPS infection in several studies.^{5,6,8,18} Biliary intervention of any type increases the risk of infection.

Clearance of bacteremia and fungemia from the infected stent graft was not achieved in the case described earlier, despite prolonged antimicrobial therapy and the patient was ultimately cured with liver transplant. Pathologic and microbiological analysis of the TIPS stent graft from the explanted liver found that the graft was colonized, confirming endotipsitis. On culture, the stent grew polymicrobial species, including *E. faecium*, *K. oxytoca*, *C. albicans*, and *C. gabralata*. Colonization and vegetation formation lead to recurrent, rapid thrombosis of the graft and the bacteremia that the patient suffered following interventions through the TIPS.

Conclusion

Infection, while rare, can colonize a TIPS stent graft, leading to recurrent bacteremia and/or sepsis. In patients with a TIPS stent graft who experience unexplained recurrent bacteremia and fever, a diagnosis of endotipsitis should be considered.^{6,8,9} Endotipsitis is associated with high morbidity, with mortality rates reported at 32%.⁷ While prolonged antimicrobial therapy may resolve the infection, liver transplant may be required.

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