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Alimentary Tract

Long-term outcome of transjugular intrahepatic portosystemic shunt for portal hypertension in autosomal recessive polycystic kidney disease☆

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ABSTRACT

Background: Autosomal recessive polycystic kidney disease (ARPKD) with congenital hepatic fibrosis (CHF) causes portal hypertension and its complications. A transjugular intrahepatic portosystemic shunt (TIPSS) could serve as a symptomatic treatment for portal hypertension-related symptoms in these children.
Aims: To study the effect of TIPSS on portal hypertension, liver and kidney function and the long term complications.
Materials and methods: We report on 5 children with CHF treated with a TIPSS to manage severe portal hypertension related symptoms.
Results: Mean follow-up time was 7 years and 2 months. At the end of follow-up there was a reduction of spleen size ($p = 0.715$) and hypersplenism with a rise in platelet count ($p = 0.465$). Esophageal varices and ascites disappeared in all patients. Liver and kidney function remained stable. In two patients endotipsitis was suspected and two patients developed an in-stent stenosis. There was no sign of encephalopathy in our patients.
Conclusion: TIPSS using ePTFE-covered stent is a feasible and effective alternative for surgical portosystemic shunting in children with CHF, also on the long term. It can postpone the need of a liver transplantation but close monitoring remains important for early diagnosis of endotipsitis or stent dysfunction related to stenosis.

1. Introduction

Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutations in the PKHD1-gene on chromosome 6 and has an estimated incidence of 1 in 20,000 live births [1].

It is a ciliopathy affecting the kidneys and liver, causing congenital hepatic fibrosis (CHF) with or without biliary cysts.

Renal manifestations are characterized by cystic dilatations of the renal collecting ducts and can progress to end-stage renal disease. The phenotype and age of presentation are extremely variable. Patients diagnosed in the prenatal or neonatal period are more likely to have a severe renal disease with poor outcome. Furthermore, a frequent complication of the prenatal ARPKD presentation is the presence of oligohydramnios, leading to the "Potter sequence" with pulmonary hypoplasia and a high perinatal mortality. Patients diagnosed at adolescent or adult age typically have a milder renal involvement and more symptoms related to the hepatic fibrosis [2,3].

Hepatobiliary manifestations are associated with developmental defects of ductal plate remodeling. This results in dilatation of

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the intrahepatic bile ducts, CHF or a combination of both [4]. CHF can also occur on its own. It is a progressive portal tract fibrosis which leads to portal hypertension and its complications [5].

The clinical presentation of liver disease in ARPKD is dependent upon the presence of portal hypertension and the biliary disease. Patients with portal hypertension usually present with hypersplenism and varices, whereas ascites, hepatopulmonary syndrome and encephalopathy are relatively uncommon [6]. Patients with significant biliary abnormalities are more prone to cholelithiasis and cholangitis [7]. Synthetic liver function is usually not impaired until the later stages of the disease [1,5,8].

Therapy of the liver disease primarily focuses on the treatment of portal hypertension. For a long time, surgical portosystemic shunts have been the primary non-transplant option in treating portal hypertension related symptoms that cannot be controlled by medication alone. In adults, this has mostly been replaced by the less invasive transjugular intrahepatic portosystemic shunt (TIPSS) procedure.

In contrast to adults, there is a lack of experience using TIPSS in children. This might be due to the rarity of the disease and indication of TIPSS in children and the difficulty finding adequately sized endovascular material. Another concern is the lack of data on long-term outcome and the risk of stent dysfunction with the need for reintervention.

Specifically for children with ARPKD, it is worth noticing that the presence of multiple hepatic cysts is considered as a contra-indication for TIPSS placement because of the risk for procedural bleeding complication when puncturing the cyst [9].

Here we review our single center experience of TIPSS in children with ARPKD with long term follow-up.

2. Materials and methods

2.1. Patient selection

All consecutive patients (<18 years old) who underwent a TIPSS procedure between July 2000 and October 2015 were identified from the electronic patient records. Five patients (two boys, three girls) were included. This retrospective report was approved by the ethics committee of the University Hospitals Leuven, Leuven, Belgium.

2.2. TIPSS placement

Before the procedure, ultrasonography was performed in each patient to evaluate portal vein and hepatic artery patency. In all patients, the TIPSS was placed under general anesthesia by an experienced interventional radiologist (GM). In one patient (No. 1) a bare metal stent (Wallstent, Boston Scientific, Natick, MA, USA) was used, in the other patients a Viatorr ePTFE-covered stent (WL Gore and Associates, Flagstaff, AZ, USA).

Vascular access was obtained through the right internal jugular vein, followed by catheterization of the right hepatic vein. Wedged CO_2-venography was used to map the portal venous system. Intrahepatic puncture was performed from the right hepatic vein to the right portal vein. The puncture tract was then dilated using an angioplasty balloon (diameter 5 mm) and the expendable stent was inserted from the portal vein up to the confluence of the right hepatic vein and the inferior vena cava. After stent insertion, further dilatation was obtained using a larger angioplasty balloon (diameter 8 mm). Shunt placement was considered successful when portosystemic gradient was reduced to 10 mmHg or less [11].

Patients were not on prophylactic anticoagulant therapy after TIPSS placement.

2.3. Follow-up

During admission after TIPSS placement, Doppler ultrasonography was performed on day 1 and day 7. After discharge, follow-up occurred every 3–6 months.

During our follow-up, we evaluated liver function by platelet count, bilirubin, albumin, INR and transaminases. Spleen size was measured on ultrasound. Endoscopic evaluation was systematically performed within one month after TIPSS placement. When there were no residual varices, follow-up endoscopy was only performed when clinically indicated or when stent dysfunction was suspected. On endoscopy, varices were graded based on two criteria (confluence of varices around the esophageal wall and flattening by insufflation of air).

1) Small varices: not confluent around the esophageal wall, flatten with air insufflation.
2) Medium varices: not confluent around the esophageal wall, do not flatten with air insufflation.
3) Large varices: confluent around the esophageal wall, do not flatten with air insufflation.

MELD score was calculated. Kidney function was assessed by means of clinical examination, blood samples and imaging. Blood pressure and the use of antihypertensive medication were monitored, ophthalmologic screening was provided. Laboratory assessments included creatinine, ureum and proteinuria. Ultrasonography with measurement of kidney size was performed every 3–6 months and (51)Cr-EDTA clearance was used in patients with a low estimated GFR.

Monitoring for the development of encephalopathy was done through patient history, clinical examination and ammonia measurement. School results were monitored and, when necessary, neuropsychological testing was performed using the Wechsler Intelligence Scale for Children (WISC) with measurement of verbal IQ, performance IQ and total IQ.

2.4. Statistical analysis

All data are reported as means and ranges. Student t-test was used to evaluate the significance of changes in data before and after TIPSS placement. Statistical tests were performed on SPSS. Statistical significance was established at $p \leq 0.05$. A p value <0.1 was considered as a trend towards statistical significance.

3. Results

3.1. Patient characteristics

Five patients (two boys, three girls) were included. The patient characteristics are listed in Table 1.

Four patients were diagnosed with ARPKD based on genetics and liver biopsy. One patient (No. 5) was diagnosed with CHF on liver biopsy without renal involvement. In this patient, genetic screening of the PKHD1 gene is ongoing. All but one patient (No. 1) underwent TIPSS placement at our institution. This patient was referred to our center after TIPSS placement for follow-up. In three patients (No. 2, 4 and 5), the technical details of the TIPSS placement have been previously reported [10].

Mean follow-up time was 7 years, 2 months (range 0.14 months to 194 months). In two patients (No. 1 and 5), follow-up of TIPSS placement was short because of liver transplantation.

In patients No. 1 and 5, TIPSS was placed because of uncontrollable variceal bleeding. In the other three patients, indication of TIPSS placement was a combination of varices with suspected

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Table 1
Patient and procedure characteristics of TIPSS placement.

Patient characteristics							
Patient No.	1.	2.	3.	4.	5.	Mean	p-value
Gender	F	M	F	F	M		
Age (year, month)	9 years 2 months	4 years 8 months	6 years 3 months	11 years 4 months	14 years 4 months	10 years 10 months	
Length (cm)	117	106	122.2	130	179.7	130.98	
Weight (kg)	23	16	24.1	26	77.4	33.3	
Follow-up (months)	23	124	91	194	0.14	86.4	

Procedure characteristics								
Patient No.		1.	2.	3.	4.	5.	Mean	p-value
Stent type		Wallstent	Viatorr	Viatorr	Viatorr	Viatorr		
Length/diameter (mm)		66/8	70/8	70/8	60/8	80/8		
Procedure time (min)		NA	105	180	135	90	127.5	
Portal pressure (mmHg)	Pre	32	21	25	19	38	27	
	Post	24	9	16	7	17	14.6	0.042
PSG (mmHg)	Pre	15	14	16	18	25	17.6	
	Post	10	2	5	6	7	6	0.042
Portal flow	Pre	NA	15	11	14	31	17.75	
Velocity (cm/s)	Post	50	28	61	25	80	48.8	0.068
HARI	Pre	NA	0.8	0.71	0.73	0.74	0.745	
	Post	0.74	0.63	0.64	0.68	0.86	0.71	0.465

NA = not available, PSG = portosystemic gradient, HARI = hepatic artery resistance index.

bleeding and hypersplenism with deep thrombopenia in two patients (No. 3 and 4).

3.2. TIPSS placement

The technical success rate of TIPSS placement was 100%. Technical data are reported in Table 1.

All patients had an uncomplicated recovery, except for one (No. 3). This patient showed respiratory distress and lung edema immediately after the procedure. Intubation was necessary for one day, followed by antibiotic treatment. There was a fast and complete recovery.

3.3. Effect on portal hypertension

Before TIPSS placement, all patients had clinically significant portal hypertension with esophageal varices and were treated with propranolol (2 mg/kg/day). Two patients (No. 1 and 5) had clinical signs of acute variceal bleeding with hematemesis and anemia. One patient (No. 2) had grade 3 esophageal varices that were treated with sclerotherapy once, followed by TIPSS placement one week later because of suspected variceal bleeding. The two other patients (No. 3 and 4) had grade 2–3 varices treated with sclerotherapy multiple times. In these patients, TIPSS was eventually placed because of recurrent esophageal varices with occult blood loss in combination with hypersplenism and deep thrombopenia.

Endoscopic evaluation was performed within one month after TIPSS placement. Varices had disappeared and propranolol was stopped in all patients.

In two patients therapy with beta blockers was restarted because of arterial hypertension. In none of the patients there was evidence of recurrence of esophageal varices at the end of follow up.

Splenomegaly was initially present in all patients. Spleen size and mean platelet count did not decrease significantly. Data are summarized in Table 2.

3.4. Effect on liver function

Before TIPPS placement, 4 out of 5 patients had a small amount of ascites on ultrasonography but without clinical sign of refractory ascites. One year after TIPSS this number had decreased to 1 out of 5 patients and at the end of follow-up none of the patients had free fluid on ultrasonography.

During follow-up, laboratory assessment (including albumin, bilirubin, INR and transaminases) showed a stable liver function in all of the patients. Data on the evolution of AST, MELD score and Child Pugh score are summarized in Table 2.

None of the patients showed any clinical symptoms of encephalopathy after TIPSS placement.

3.5. Effect on hypertension and kidney function

There was no clear change in arterial hypertension or kidney function after TIPS placement. Blood pressure, creatinine, GFR and kidney size remained stable during follow-up (Table 2). None of the patients were on dialysis during our follow-up.

3.6. Long-term outcome

None of the patients developed heart failure related to higher preload or symptoms of hepatic encephalopathy. Ammonia levels remained within normal range (Table 2). In two patients, neuropsychological testing (using the WISC-III) was needed due to learning difficulties. In one of them (No. 2), results were below average with a total IQ of 84, verbal IQ of 86 and performance IQ of 86 but the testing was non-suspicious for hepatic encephalopathy. In the other patient (No. 1), testing was normal (total IQ of 105, verbal IQ of 98 and performance IQ of 112).

Two patients (No. 3 and 4) currently have no indication for liver transplantation and remain under clinical follow-up for 7 years, 7 months and 16 years, 2 months respectively.

Three patients underwent a liver transplantation during follow-up. In these patients TIPSS served as a bridge to transplantation. One patient (No. 5) underwent liver transplantation only 4 days after TIPSS placement. He was already on the transplant list and underwent an urgent TIPSS placement because of uncontrollable variceal bleeding. The TIPSS effectively controlled this bleeding until a donor organ was available. In another patient (No. 1) a transplant was needed after 2 years. Initially a Wallstent was successfully placed in this patient but after 14 months she presented with TIPSS stenosis in combination with recurrent episodes of sepsis, potentially related to endotipsitis. Urgently, she underwent a

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Table 2
Effect of TIPSS placement on portal hypertension, liver function and kidney function.

Effect on portal hypertension								
Patient No.		1.	2.	3.	4.	5.	Mean	p-value
Spleen size/SD (cm)	Pre	15/6.22	10.6/3.2	21/15	19/9.48	25/16.95	18.1/10.2	
	Post	15/5.05	9/0.57	17.7/10.5	17.2/7.74	NA	14.7/5.96	0.109/0.068
	End FU	12.8/3.2	16.4/5.4	16.4/6.9	14.9/4.9	NA	15.1/5.1	0.715/0.144
Platelet count (×10*9/L)	Pre	186	159	48	40	67	100	
	Post	173	214	70	60	NA	129.3	0.144
	End FU	151	103	122	238	NA	153.5	0.465
Effect on liver function								
Patient No.		1.	2.	3.	4.	5.	Mean	p-value
AST	Pre	58	45	33	30	84	50	
	Post	57	44	32	36	NA	42.52	0.705
	End FU	35	24	25	36	NA	30	0.144
MELD/Child Pugh	Pre	43291	43257	43260	43230	43260	8.8/6	
	Post	43290	43226	43229	43228	NA/NA	8/5.5	0.18/0.157
	End FU	43259	43226	43231	43227	NA/NA	8/5.3	0.414/0.083
NH3	Pre	NA	NA	35	NA	NA	35	
	Post	51	75	37	45	NA	52	
	End FU	28	43	85	36	NA	48	
Effect on kidney function								
Patient No.		1.	2.	3.	4.	5.	Mean	p-value
Creatinine	Pre	0.49	0.73	0.4	0.73	0.69	0.61	
	Post	0.86	0.59	0.33	0.62	NA	0.6	0.875
	End FU	0.85	0.64	0.45	0.69	NA	0.66	0.875
Kidney size/SD (cm) left	Pre	11.5/2.7	10.5/5.3	11.2/4.2	10.7/1.7	12/2.5	11.2/3.3	
	Post	11.9/3.3	11.7/6.6	11.6/5.2	11.2/0.89	NA	11.6/4.0	0.098/0.375
	End FU	12.8/4.4	13.7/5.9	13/4.3	12.4/2.4	NA	13/4.2	0.125/0.125
Kidney size/SD (cm) right	Pre	11.5/2.7	10.2/5.3	10.6/4.8	10.3/1.1	10/0.22	10.6/2.8	
	Post	11.3/2.6	11.6/6	12.5/6.5	10.7/0.32	NA	11.5/3.9	0.25/0.875
	End FU	10.5/1.6	13/4.8	14.3/6	13/3.1	NA	12.7/3.9	0.25/0.625

NA = not available, SD = standard deviation, End FU = end of follow-up.

TIPSS revision with a Viatorr stent, received IV antibiotic treatment for over a month and was placed on the transplant list. Because of declining kidney function, there was an indication for combined liver and kidney transplantation. She underwent combined liver–kidney transplantation 9 months later. In the meantime there were no problems with the newly placed Viatorr stent, in particular no sign of recurrent sepsis of recurrent in-stent stenosis. The third patient (No. 4) needed liver transplantation 15 years after the TIPSS procedure. In the months before transplantation she suffered from recurrent cholangitis with sepsis and acute respiratory distress syndrome. Radiographic imaging (ultrasound, CT and PET-CT scan) showed the development of multiple small liver abscesses. One of the abscesses was located at the anterior side of the proximal part of the TIPSS. Due to the severity of the infections and the fact that endotipsitis could not be excluded, she was placed on the transplant list and received a liver transplantation two months later.

In one child (No. 2), a TIPSS revision was needed 10 years after the initial procedure. There was a recurrence of portal hypertension with esophageal varices and cavernous transformation of the portal vein on ultrasound, MRI and catheter-angiography (Fig. 1a). The lumen of the stent was narrowed at the hepatic venous side (Fig. 1b) and the stent was thought to be outgrown by the now adult size liver. TIPSS revision was done by placing another Viatorr stent in the already existing stent, making the distal ending 1.5 cm longer (Fig. 2). Pressure gradient successfully dropped from 15 mmHg to 5 mmHg.

No other long-term complications occured.

4. Discussion

TIPSS has been accepted as a valuable treatment for refractory ascites and uncontrollable of recurrent variceal bleeding caused by portal hypertension in adults [9,12]. However, it is less studied in children.

While some small case series on the use of TIPSS in children with multiple underlying liver diseases have been reported [13–19], we focus our report on long-term outcome after TIPSS in children with congenital hepatic fibrosis (CHF) due to ARPKD. In contrast to other causes of portal hypertension, CHF does not affect the synthetic liver function [1,5,8]. Therefore TIPSS placement might be a more long-term solution in these patients instead of only serving as a bridge to transplantation.

Only 7 other children with CHF who underwent TIPSS placement were reported in the literature [13–18,20]. Characteristics of these patients are listed in Supplementary Table 1.

The mean published follow-up time of TIPSS in children is only 14.8 months, even in reports of TIPSS placement in children for other indications. With a mean follow-up time of 85 months and a maximum follow-up time of 188 months, another goal of our current report is to document the long-term feasibility and efficacy of TIPSS placement. This is important because growth and the resulting relative reduction of stent size is one of the main concerns for TIPSS placement in children compared to adults, which has not yet been evaluated.

TIPSS placement is effective, as ascites and esophageal varices disappeared in all of our patients. We could not demonstrate any

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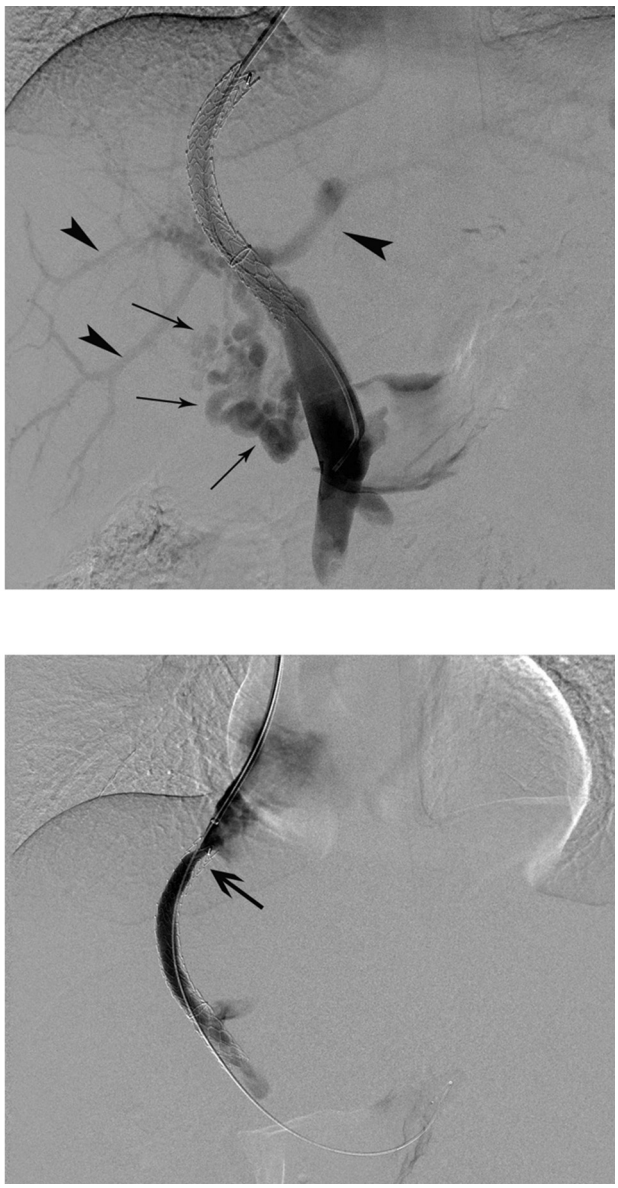

Fig. 1. (a) Catheter-directed direct portography reveals a patent TIPS-stent and tortuous collaterals (small arrows) draining into the intrahepatic portal veins (arrowheads). (b) Retrograde contrast injection through an 8 French long sheath reveals a clear stenosis (arrow) at the proximal end of the covered stent.

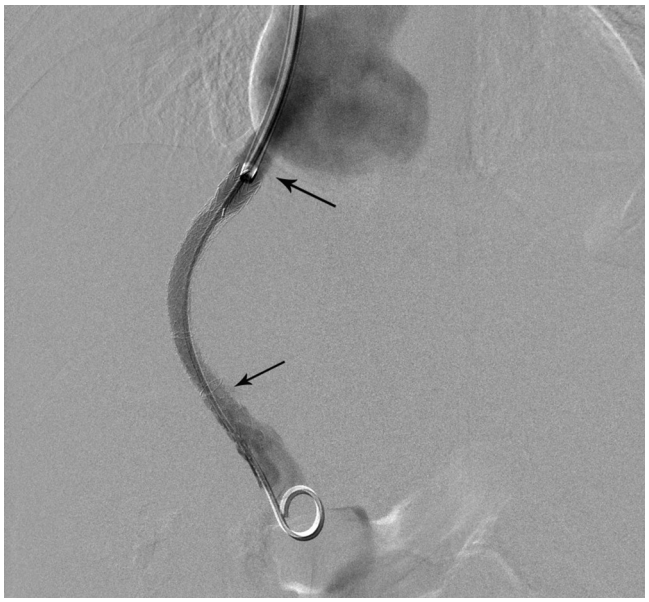

Fig. 2. Direct portography after stent-graft extension (small arrows) shows absence of collaterals in the hilum of the liver or opacification of intrahepatic portal vein branches. The TIPS stent-graft is fully patent.

significant changes in liver and kidney function in our data. When we combine our findings with the already existing literature (online Supplementary Table 1), there is a significant decrease in spleen size (17.6 cm to 14.7 cm, p 0.043) and standard deviation (+9.1SD to +5.5SD, p 0.028). In the combined data we also find a significant reduction of hypersplenism with increase of platelet count ($97.7 \times 10^*9$/L to $122.3 \times 10^*9$/L, p = 0.028). Both findings are in contrast with what other reports on TIPSS placement in children have previously suggested [15,16].

There was an in-stent stenosis in two patients (No. 1 and 4). The first patient is the only one in whom a bare metal stent (Wallstent) was placed. In the other patients, an ePTFE-covered stent (Viatorr) was used. In adults, it has been clearly demonstrated that the use of ePTFE-covered stents improves the shunt patency [21,22]. In children, multiple case reports tend to confirm this assumption [10,18,23]. When we combine our patients with the patients already described in the literature (online supplementary Table 1), there is a total of 12 children with CHF who underwent TIPSS placement. Of these children, 6 received a bare metal stent, followed by stenosis in 4 of them. The other 6 children received an ePTFE-covered stent. In these patients, only 1 stenosis was described. Therefore we can assume that an ePTFE-covered stent might be associated with lower risk for stent dysfunction as demonstrated in the cirrhotic adult population [24,25].

The second patient (No. 4) developed a stenosis ten years after initial placement. We believe the stent had become relatively too small for the growing liver. Elongation and dilatation of the stent successfully solved the problem.

From the above we can conclude that, when using an ePTFE-covered stent, TIPSS placement is not only feasible but also effective in patients with portal hypertension due to CHF, even on the long term. When using a stent in growing children, regular follow-up of stent function remains necessary.

We monitored for hepatic encephalopathy and long-term complications. During the follow-up period, none of the patients developed overt hepatic encephalopathy. In two patients (No. 1 and 4) endotipsitis was suspected, confirmed by PET-CT in one patient. Endotipsitis has previously been defined as a clinically significant continuous bacteremia with vegetations or thrombus inside the TIPS or a sustained bacteremia and fever in a patient with an apparently patent TIPS and no other obvious source of infection [26,27]. It is a rare complication of TIPS placement in adults and until now, there have been no reports of endotipsitis in children [26].

Limitations of our study are the small group of patients and retrospective data collection. Nevertheless, our patients were closely monitored during follow-up. Apart from that, our study is the only report documenting the long-term follow-up of TIPSS placement using ePTFE-covered stents in children.

In conclusion, when using an ePTFE-covered stent, TIPSS is a valuable tool to treat children with portal hypertension due to CHF, also on the long term. It is feasible in children and has an important effect on the complications of portal hypertension with disappearance of ascites and esophageal varices and a reduction of spleen size and hypersplenism with an increase in platelet count.

The use of TIPSS can postpone the need for a transplantation for quite some time. When patients are closely monitored for complications, TIPSS can safely be used in children.

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Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.03.009.

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