

## THE TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT–SHUNT PROCEDURE FOR REFRACTORY ASCITES

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**Abstract Background.** Previous studies have suggested that the transjugular placement of an intrahepatic stent to establish a portosystemic shunt is an effective treatment of uncomplicated ascites accompanying variceal bleeding. We studied the stent shunt for use in patients with liver cirrhosis and ascites refractory to medical treatment.

**Methods.** Fifty of 62 consecutive patients with cirrhosis and refractory ascites were treated with the stent shunt — an expandable stent of metallic mesh placed between a major branch of the portal vein and one of the hepatic veins. Patients were followed for a mean ( $\pm$ SD) of  $426\pm 333$  days.

**Results.** The stent shunt was successfully placed in all patients and reduced the pressure gradient between the portal vein and the inferior vena cava by an average of 63 percent. Thirty-seven patients (74 percent) had complete responses (total remission of ascites within three months), and nine patients (18 percent) had partial responses. Four patients did not respond, including two who died within two weeks of shunt placement. After the procedure, 25 patients had hepatic encephalopathy, as compared with 20 patients before the procedure; although encephalopathy improved in 3 patients, new encephalopathy developed in 8 patients. In the

28 of the 33 patients followed for more than six months who were evaluated, the mean serum creatinine concentration was  $1.5\pm 0.09$  mg per deciliter ( $133\pm 8$   $\mu$ mol per liter) before placement of the stent shunt,  $1.5\pm 1.6$  mg per deciliter ( $133\pm 141$   $\mu$ mol per liter) one week after the procedure, and  $0.9\pm 0.3$  mg per deciliter ( $80\pm 27$   $\mu$ mol per liter) after six months ( $P=0.008$  for the comparison of concentrations before and six months after the procedure). Renal function did not improve in the six patients with organic kidney disease. Procedure-related complications developed in 16 patients. During follow-up, an additional 29 patients died — 10 of progressive liver disease and 19 of other causes. Survival for at least one year was associated with a patient's being under 60 years of age, having a serum bilirubin level before placement of the stent shunt of less than 1.3 mg per deciliter (22  $\mu$ mol per liter), and having a complete response.

**Conclusions.** Our findings in an uncontrolled prospective study suggest that the transjugular intrahepatic portosystemic stent–shunt procedure was an effective treatment for many patients with liver cirrhosis and refractory ascites, but mortality from underlying diseases was substantial. (N Engl J Med 1995;332:1192-7.)

**R**EFRACTORY ascites is the complication of portal hypertension that most severely affects both quality of life and long-term survival.<sup>1-5</sup> Depending on the patient's general clinical state and whether there are additional complications, such as renal insufficiency and variceal bleeding, the rate of survival at one year is 20 to 50 percent.<sup>6-9</sup> Survival has not been improved significantly by either paracentesis<sup>7,10,11</sup> or peritoneovenous shunting.<sup>12-18</sup>

Portal hypertension is a major contributor to ascites formation, and decompression of the portal vein by surgical shunts is a plausible treatment.<sup>19-22</sup> However, the procedure has not been shown to improve survival, probably because of the operative mortality of 5 to 39 percent,<sup>19-23</sup> and has therefore been more or less abandoned.

The transjugular intrahepatic portosystemic stent shunt is a nonsurgical side-to-side shunt consisting of a stented channel between a main branch of the portal vein and a hepatic vein.<sup>24-26</sup> The stent shunt has been shown to be an effective treatment of uncomplicated ascites accompanying variceal bleeding,<sup>24</sup> with an operative mortality of about 1 percent. We studied the use of this procedure for refractory ascites.

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## METHODS

We studied 50 of 62 consecutive patients with refractory ascites who were treated between January 1989 and September 1993 and followed for a mean ( $\pm$ SD) of  $426\pm 333$  days. The characteristics of the patients are given in Table 1. All the patients had one or more additional liver-related complications (e.g., recent variceal bleeding) or severe accompanying disease. Renal function was impaired in about half the patients. In four patients who were undergoing hemodialysis, the reason for the stent–shunt treatment was to ameliorate arterial hypotension complicating hemodialysis and thus causing a fluid loss. The 12 patients who were excluded had advanced hepatic cancer (4 patients) or advanced extrahepatic cancer (2 patients), severe heart failure (2 patients), or severe liver failure (4 patients).

Refractory ascites was defined as tense ascites without a decrease in body weight during at least four weeks of a standard treatment consisting of saline restriction ( $<60$  mmol of sodium per day), spironolactone (300 to 400 mg per day), and furosemide (120 mg per day),<sup>6</sup> or with intolerance of the standard treatment (a serum sodium concentration of  $<125$  mmol per liter, a serum creatinine concentration of  $>2.4$  mg per deciliter [212  $\mu$ mol per liter], or allergy to spironolactone and furosemide). In patients with serum sodium concentrations of less than 125 mmol per liter, fluid intake was restricted to 1 liter per day. Mild and severe functional renal failure were defined by the repeated finding of serum creatinine concentrations of more than 1.2 and less than 2.4 mg per deciliter (106 and 212  $\mu$ mol per liter) and of 2.4 mg per deciliter or more, respectively, accompanied by urinary sodium concentrations of less than 10 mmol per liter in the presence of a central venous pressure of more than 8 cm of water. Organic kidney disease was excluded. Kidney function was tested during diuretic treatment in all patients except the 14 whose diuretic agents were withdrawn because of severe renal impairment (11 patients) or low serum sodium concentrations (3 patients). Renal function was not measured during the three days following large-volume paracentesis.

Table 1. Characteristics of the 50 Patients Studied.

CHARACTERISTIC	VALUE*	%
Age (yr)	56±9	
Sex (M/F)	34/16	68/32
Alcoholic cirrhosis	38	76
Budd–Chiari syndrome	5	10
Postnecrotic cirrhosis	4	8
Primary biliary cirrhosis	2	4
Genetic hemochromatosis	1	2
Child–Pugh score†	10.0±1.4	
Child–Pugh class B	18	36
Child–Pugh class C	32	64
Liver-related complication		
Refractory ascites	50	100
Infectious‡	7	14
Chylous	3	6
Variceal bleeding only within the previous 4 wk	16	32
Variceal bleeding no later than 4 wk before	10	20
Uncomplicated hernia	7	14
Complicated hernia or fistula§	10	20
Spontaneous bacterial peritonitis within the previous 4 wk¶	10	20
Occluded peritoneovenous shunt	3	6
Functional renal failure		
Mild: creatinine >1.2 and <2.4 mg/dl	11	22
Severe: creatinine ≥2.4 mg/dl	5	10
Hepatic encephalopathy within the previous 3 mo		
Stage 1–2	15	30
Stage 3–4	5	10
Accompanying disease		
Organic kidney disease (all patients/patients undergoing hemodialysis)	6/4	12/8
Chronic heart disease (New York Heart Association class II–III)	5	10
Hematologic disorders**	5	10
Tumor		
Hepatic	2	4
Extrahepatic	3††	6

\*Unless otherwise stated, values are the number of patients. Plus–minus values are means ±SD.

†Calculated according to Pugh et al.<sup>27</sup>

‡At the time of treatment these patients had infected ascites (>400 leukocytes per cubic millimeter, positive bacterial culture) due to complicated hernia or fistula.

§Five patients had spontaneous cutaneous fistula, and five had maceration.

¶These patients had >400 leukocytes per cubic millimeter with or without positive bacterial culture.

||All patients had diabetic glomerulosclerosis with a serum creatinine concentration of ≥2.4 mg per deciliter.

\*\*Three patients had polycythemia vera, one had paroxysmal nocturnal hemoglobinuria, and one had chronic lymphocytic leukemia.

††One patient had breast cancer, one had thyroid cancer, and one had a large adenoma of the colon with malignant transformation.

A complete response was defined as a total remission of ascites within three months. A partial response was defined as the presence of sonographically detectable ascites without the need for paracentesis. An absent response was defined as the persistence of severe ascites requiring paracentesis.

All patients in the study were hospitalized for at least four weeks before treatment to establish the diagnosis of refractory ascites or functional renal failure. Before the stent–shunt procedure, the following procedures were performed: urinalysis, including measurement of creatinine clearance and daily sodium and protein excretion, as well as ascitic-fluid analysis; an assessment of hepatic encephalopathy (including a number-connection test and a mental-status test); and duplex and abdominal sonography. Before treatment, ascitic fluid was removed by paracentesis, with albumin substituted intravenously (8 g of albumin per liter of fluid removed). Lactulose, antibiotics, dopamine, and other cardiac or pulmonary medications were given as warranted. After the implantation of the stent shunt, diuretic treatment was gradually reduced, the rate of reduction depending on

the urinary output or the reduction in body weight. Patients were sent home from the hospital when their hepatic and renal functioning was stable or improving. Subsequently, they were seen after four weeks and then at three-month intervals. No patient was lost to follow-up.

The technique of placing a transjugular intrahepatic stent to establish a portosystemic shunt and the postprocedural management (e.g., anticoagulation) have been described previously.<sup>24,26</sup> After mild intravenous sedation and analgesia (50 to 100 mg of meperidine and 1 to 5 mg of midazolam), a puncture needle was advanced transjugularly in a catheter through the inferior vena cava into one of the three hepatic veins. Subsequently, an intrahepatic branch of the portal vein was punctured and the shunt was established by the implantation of either the Palmaz stent (Johnson and Johnson Interventional Systems, Warren, N.J.), which was used in 36 patients (2.4±1.0 stents per patient) or the Wallstent (Schneider, Büllach, Switzerland), used in 14 patients (1.2±0.4 stents per patient). (A lengthy shunt path may require multiple stents.) The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

### Statistical Analysis

Differences in the survival curves were determined by Kaplan–Meier analysis and the log-rank test (Cox–Mantel). Comparative results of repeated and serial measurements were analyzed by the paired t-test and the Wilcoxon–Wilcoxon test, respectively. The significance of changes in the severity of ascites was analyzed with the statistical sign test (Dixon–Mood). All the tests were two-sided, with a significance level of P=0.05. The statistical analyses were performed with Winstat 3.0 software (Kalmia, Cambridge, Mass.).

### RESULTS

The stent shunt was successfully established in all 50 patients. The portal venous pressure gradient was reduced by an average of 63 percent, partly as a result of an increase in the inferior vena caval pressure (Table 2). A total of 20 complications occurred in 16 patients and included intraabdominal bleeding requiring blood transfusions (2 patients), stent dislocation and subsequent placement of the stent in the right iliac vein (1 patient), septicemia (*Staphylococcus aureus*, 1 patient) or a temperature above 38.5°C (4 patients), cardiac arrhythmia requiring treatment during the procedure (sinus tachycardia, 2 patients; sinus bradycardia, 1 patient), and malaise and vomiting after the procedure (3 patients). Six patients had transient deterioration of their renal function induced by the contrast medium

Table 2. Portal and Vena Caval Pressure before and after the Stent–Shunt Procedure as Determined during the Procedure in the 50 Patients.

	BEFORE PROCEDURE	AFTER PROCEDURE	CHANGE	P VALUE
	<i>centimeters of water</i>			
Inferior vena cava				
Mean ±SD	10±5	17±5	+7±6	<0.001
Range	0–22	7–27		
Portal vein				
Mean ±SD	40±10	28±7	–12±8	<0.001
Range	22–73	10–40		
Pressure gradient*				
Mean ±SD	30±10	11±6	–19±10	<0.001
Range	14–55	2–30		

\*The pressure gradient is the portal pressure minus the inferior vena caval pressure.

(iopromide). Two of these patients required hemodialysis for one to two weeks.

### Ascites and Shunt Function

Overall, 46 patients (92 percent) responded to the treatment. Thirty-seven (74 percent) had complete responses, and nine (18 percent) had partial responses. In those with partial responses, the responses were limited by recurrent spontaneous bacterial peritonitis (six patients) and severe organic kidney disease (three patients). There was no response in four patients — one with recurrence of tumor-induced portal-vein thrombosis, one with treatment-resistant peritonitis, and two who died within two weeks of the procedure, while still in the hospital (one of myocardial infarction, the other of diffuse gastrointestinal hemorrhage and disseminated intravascular coagulation after hemodialysis). All the patients who responded (excluding those who were undergoing hemodialysis) required low doses of diuretics (e.g., 100 mg of spironolactone or 40 mg of furosemide per day, or both) to maintain their responses and to treat peripheral edema. Two of the four patients who were undergoing hemodialysis before the stent–shunt procedure had complete responses, one had a partial response, and the fourth died of septicemia two weeks after the procedure.

The severity of ascites during the first three months of follow-up is shown in Figure 1. Significant improvement was seen within one week ( $P<0.001$ ). At three months, 8 of the 36 patients who were alive had mod-

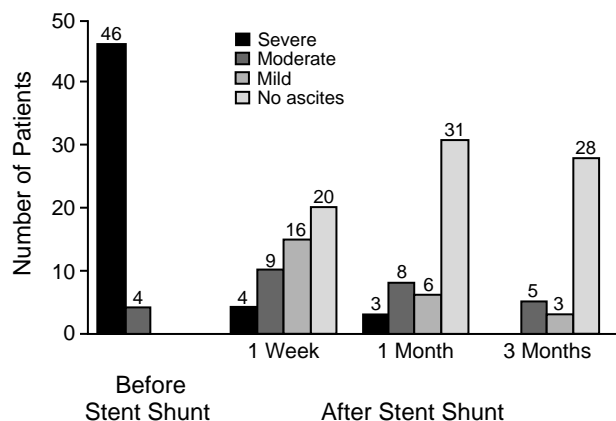


Figure 1. Severity of Ascites before and after the Stent–Shunt Procedure.

Ascites was graded by ultrasound as severe or tense ascites, moderate ascites with fluid in the flanks, or mild ascites with fluid around the liver and in Douglas's and Morison's pouches.

Table 3. Serum Creatinine Concentration, Creatinine Clearance, and Urinary Sodium Excretion before and after the Stent–Shunt Procedure in Patients without Organic Kidney Disease.

VARIABLE*	BEFORE PROCEDURE	1 WK AFTER PROCEDURE	6 MO AFTER PROCEDURE	P VALUE
	<i>mean ±SD</i>			
Patients followed for more than 6 mo†				
Serum creatinine concentration (mg/dl)	1.5±0.9	1.5±1.6	0.9±0.3	0.5‡ 0.008§
Creatinine clearance (ml/min)	41±29	43±38	88±62	0.5‡ 0.03§ <0.001
Urinary sodium excretion (mmol/day)	20±36	78±23	—	<0.001
Patients who died within the first 6 mo¶				
Serum creatinine concentration (mg/dl)	1.2±0.4	1.1±0.5	—	0.5
Creatinine clearance (ml/min)	26±11	22±13	—	0.8
Urinary sodium excretion (mmol/day)	21±18	62±41	—	<0.001

\*To convert values for creatinine to micromoles per liter, multiply by 88.4.

†Because of incomplete follow-up, serum creatinine concentration was measured in 28 of the 33 patients, and creatinine clearance and urinary sodium excretion were measured in the same 15 patients.

‡For the comparison of measurements obtained before the procedure with those obtained one week after it.

§For the comparison of measurements obtained before the procedure with those obtained six months after it.

¶Serum creatinine concentration and creatinine clearance were measured in all 10 patients, but because of incomplete follow-up, urinary sodium excretion was measured in 4.

erate or mild ascites. The patients with complete responses had a mean ( $\pm$ SD) decrease in body weight of  $10.7\pm6.1$  kg ( $P<0.001$ ). The 31 patients with complete responses who were followed for more than six months had an initial decrease in mean body weight from  $74.5\pm13.6$  kg to  $64.8\pm11.7$  kg ( $P<0.001$ ), and then an increase to  $69\pm15$  kg ( $P<0.001$ ). We attributed the increased weight to a visible improvement in the nutritional status of the patients.

The response to treatment could not be predicted on the basis of the serum creatinine concentration before the stent–shunt procedure, the serum or ascites albumin concentration, or the portal and caval pressures or the portal venous pressure gradient before or after the procedure. Thrombotic occlusion of the stent shunt occurred within two weeks in 5 patients, and later shunt insufficiency occurred in 16. Later shunt insufficiency was indicated by the recurrence of ascites after complete remission (in 12 patients) and variceal bleeding (in 1), respectively. In three patients, shunt stenosis was diagnosed by duplex sonography without the reappearance of ascites and did not require reestablishment of the shunt. In the other patients, the shunt was reestablished, in all but one patient with tumor thrombosis, by local thrombolysis, balloon dilatation, and placement of additional stents.

### Renal Function after the Stent–Shunt Procedure

Table 3 shows the results of kidney-function tests before and after the stent–shunt procedure in patients without organic kidney disease. In the 33 patients followed for more than six months, the serum creatinine concentration and creatinine clearance did not change during the first week after the procedure, whereas urinary sodium excretion improved significantly. After six months, however, both the serum creatinine concentration and the creatinine clearance improved significant-

ly. Early effects were similar in the 10 patients who died during the first six months. In the six patients with organic kidney disease (data not shown), the stent shunt did not improve renal function, and hemodialysis had to be continued in four patients. Dialysis was facilitated by decreased arterial hypotension, allowing more fluid to be removed.

#### Liver Function and Hepatic Encephalopathy

In the 31 patients followed for more than six months for whom data were complete, the mean serum bilirubin concentration worsened significantly ( $P=0.006$ ) during the first month, from  $2.5\pm 0.3$  to  $3.2\pm 0.3$  mg per deciliter ( $43\pm 5.1$  to  $55\pm 5.1$   $\mu\text{mol}$  per liter), but improved during the subsequent five months to  $2.1\pm 0.3$  mg per deciliter ( $36\pm 5.1$   $\mu\text{mol}$  per liter). The mean serum albumin increased by 20 percent (from  $3.0\pm 0.6$  to  $3.6\pm 0.7$  g per deciliter,  $P<0.001$ ) within the six-month observation period. This increase may be attributed to decreased ascites and to the fact that paracentesis was not performed, and may only in part reflect improved hepatic function.

The number of patients with hepatic encephalopathy increased from 20 patients before the stent–shunt procedure to 25 after it; the condition of 3 patients improved after the procedure, but new hepatic encephalopathy developed in 8. Hepatic encephalopathy was debilitating in 8 of the 25 patients and resistant to medical treatment. Progressive liver failure developed in all these patients, and all died. Two other patients with chronic hepatic encephalopathy received liver transplants, 1 and 11 months, respectively, after the stent–shunt procedure.

#### Mortality

In addition to the 2 patients who died in the hospital, 29 died during follow-up, 10 of them from progressive liver failure 34 to 260 days after the stent–shunt implantation. An increase in the bilirubin concentration of more than 100 percent within one month and continued heavy drinking of alcohol were significantly correlated with progressive liver failure. Other causes of death were infection (five patients), heart disease (five), hepatocellular carcinoma (three), nonvariceal upper gastrointestinal bleeding (three), and unknown causes (three).

Survival for at least one year after establishment of the stent shunt was associated with a patient's being under 60 years of age, having a serum bilirubin concentration before the stent–shunt procedure of less than 1.3 mg per deciliter (22  $\mu\text{mol}$  per liter), and having a complete response to treatment (Table 4). Overall survival was not related to renal function before the stent–shunt procedure, although patients with severe functional renal failure (creatinine concentration  $\geq 2.4$  mg per deciliter) did better than patients with organic kidney disease. There was no correlation between survival and the Child–Pugh class, the cause of liver disease (al-

Table 4. Kaplan–Meier Estimates of Survival According to Age, Child–Pugh Class, Response to Treatment, and Bilirubin and Creatinine Concentrations before the Stent–Shunt Procedure.

CHARACTERISTIC	NO. WHO DIED*/		P VALUE
	TOTAL NO.	1-YR SURVIVAL	
Age (yr)			
<60	12/27	0.66	0.03
$\geq 60$	17/23	0.39	
Child–Pugh class			
B	9/18	0.66	0.62
C	20/32	0.46	
Response			
Complete	16/37	0.75	<0.001
Partial or none	13/13	0.0	
Bilirubin before procedure (mg/dl)†			
<1.3	4/11	0.82	0.008
$\geq 1.3$	15/22	0.31	
Renal function before procedure			
Serum creatinine (mg/dl)‡			
<1.3	15/28	0.60	0.16
$\geq 1.3$	14/22	0.42	
Type of kidney disease			
Organic	5/6	0.14	0.008
Severe functional renal failure (serum creatinine $\geq 2.4$ mg/dl)	0/5	1.0	

\*Values represent the total numbers of deaths recorded throughout the study.

†Patients with organic kidney disease, those with liver transplants, and those in whom the actual bilirubin concentration did not reflect hepatic function (e.g., patients seen in the emergency room with acute variceal bleeding and patients with Budd–Chiari syndrome without cirrhosis) were excluded.

‡To convert values for creatinine to micromoles per liter, multiply by 88.4.

coholic versus nonalcoholic), or the presence of hepatic encephalopathy before or after the stent–shunt procedure. Figure 2 shows the Kaplan–Meier survival estimates for all patients and for patients according to their responses to treatment. Median survival for all patients was estimated to be 382 days. For those who had complete responses, median survival was estimated to be 558 days, as compared with 75 days for those with partial or no responses.

#### DISCUSSION

In an uncontrolled prospective study, we found that the transjugular intrahepatic portosystemic stent shunt was an effective treatment for refractory ascites and that 74 percent of the patients had complete responses. These results may be due to both decompression of the portal system and improved renal function. Improved renal function may be related to increased vascular filling, as indicated by a marked increase in the central venous pressure and a decrease in hyperaldosteronism, which has been reported with surgical<sup>20,22</sup> and transjugular<sup>28</sup> shunts. Most of the patients gained weight. This well-known effect of portosystemic shunts<sup>20,22,29</sup> may be due to improved absorption of nutrients and shunt-induced hyperinsulinism.

In some patients, functional renal failure and organic kidney disease may have contributed to the formation of ascites. Improvement in both ascites and renal function was seen in all 16 patients with functional renal failure, regardless of severity, but not in the 6 patients with organic kidney disease. Improvement in functional renal failure with the stent shunt has also been suggest-

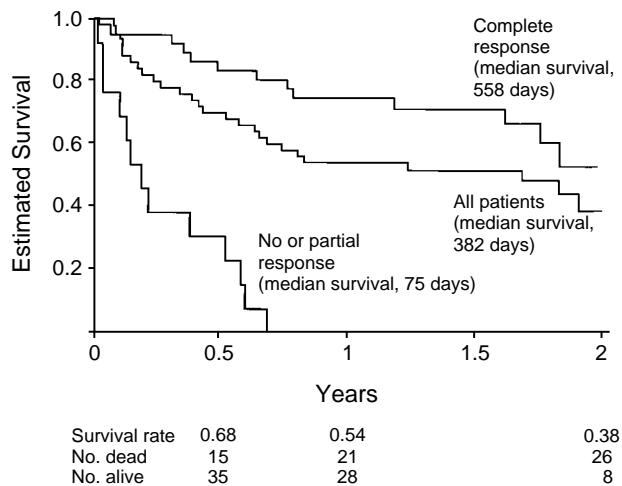


Figure 2. Kaplan-Meier Survival Analysis of All Patients and of Patients According to Their Responses to Treatment.

ed by others.<sup>30</sup> In a preliminary study,<sup>31</sup> the stent shunt decreased plasma endothelin-1, which is thought to have a key role in the pathogenesis of functional renal failure.<sup>32</sup> Other treatments of refractory ascites, such as peritoneovenous shunting and paracentesis, are ineffective or may aggravate functional renal failure.<sup>33</sup>

As expected, the stent shunt led to a considerable increase in the incidence of hepatic encephalopathy, which was debilitating in eight patients who died of liver failure. We believe that shunt reduction (achieved by inserting a reduced-diameter stent into the original stent tract)<sup>34</sup> or liver transplantation must be considered in those patients unless shunt stenosis or occlusion occurs spontaneously. In patients with spontaneous shunt insufficiency and previous shunt-induced encephalopathy, the reestablishment of the stent shunt is not indicated. In patients with insufficient shunting and no reappearance of ascites, we believe that attempts to improve the shunt are also not indicated. In these patients, transient decompression may have been sufficient for long-term control of ascites.

Some patients had transient deterioration of renal function induced by the contrast medium. Otherwise, no severe technical complication developed. There were no deaths from procedure-related complications. The small number of deaths (two) while patients were in the hospital may be explained in part by rapid improvement in renal function and ascites, which may have reduced the risk of further episodes of spontaneous bacterial peritonitis.<sup>35</sup> Variceal bleeding or repeated bleeding is another common cause of death in such patients. Only 1 of 16 patients with recent variceal bleeding had repeated episodes of bleeding.

Surgical shunts and the transjugular intrahepatic portosystemic stent shunt share the therapeutic principle of decompression of the portal system and therefore may have a comparable efficacy. Surgical shunts, however, complicate liver transplantation. The early

mortality rate after the placement of surgical shunts is reported to range from 5 to 39 percent.<sup>19-23</sup> Controlled, randomized trials will be necessary to compare survival after the transjugular stent-shunt procedure with that after other procedures.

In contrast to our findings, the transjugular intrahepatic portosystemic stent shunt in an earlier study led to complete resolution of ascites in only 7 of 14 patients with refractory ascites.<sup>36</sup> Treatment failed predominantly in patients in Child-Pugh class C — that is, in those with very high Child-Pugh scores (more than 11). This association with Child-Pugh class was not confirmed by our results.

In our study, being under 60 years of age, having a low pretreatment serum bilirubin concentration (<1.3 mg per deciliter), and having a complete response to treatment were all associated with survival for at least one year. Patients with organic kidney disease had a poor prognosis. We believe that such patients should not receive this treatment. Liver transplantation should be considered for patients with early increases in the bilirubin concentration of more than 100 percent or patients with incomplete responses to the stent shunt.

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**CORRECTION**

**The Transjugular Intrahepatic Portosystemic Stent–Shunt Procedure for Refractory Ascites**

The Transjugular Intrahepatic Portosystemic Stent–Shunt Procedure for Refractory Ascites . On page 1197, the journal cited in reference 34 should have been *Radiology*, not *Interventional Radiology*, as printed. We regret the error.