THERAPEUTIC APPROACHES TO THE PREVENTION OF VARICEAL HEMORRHAGE IN CIRRHOTIC PATIENTS

MEDICAL GRAND ROUNDS

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The liver is a highly vascular organ which receives 30-40% of the cardiac output. Blood is supplied to the liver by two afferent vessels: the hepatic artery with well-oxygenated blood, and the portal vein which drains blood from the splanchnic organs and the spleen. Both the terminal portal venules and hepatic arterioles deliver blood to the sinusoids through which this large volume of blood must flow before reaching the hepatic vein and returning to the systemic circulation. In chronic liver disease, an increase in resistance to flow through the sinusoids commonly occurs. In addition, circulatory changes develop in cirrhotic patients which commonly lead to a hyperdynamic splanchnic circulation with increased blood flow entering the portal system. The combination of these two factors leads to a rise in portal venous pressure (1). As shown in Table 1, lesions at a variety of other points in the portohepatic circulation can also lead to portal hypertension.

TABLE 1

SITES OF OBSTRUCTION OF PORTAL FLOW

Portal Vein, Extrahepatic
(1) Portal vein thrombosis
  (a) congenital
  (b) sepsis
  (c) trauma
(2) Malignant occlusion of portal vein

Portal Vein, Intrahepatic
(1) Congenital Hepatic Fibrosis
(2) Schistosomiasis

Sinusoids
(1) Cirrhosis
(2) Fulminant hepatitis
(3) Fatty liver disease

Hepatic Vein
(1) Veno-occlusive disease
(2) Budd-Chiari syndrome

With the development of portal hypertension, shunting of blood through a number of portal systemic anastomoses occurs. Such naturally occurring anastomoses between the portal and systemic circulation include periumbilical veins in the anterior abdominal wall, the inferior hemorrhoidal branch of the inferior mesenteric vein, retroperitoneal veins draining parts of the spleen, pancreas and colon, and the coronary (left gastric) and short gastric veins which

anastomose in the lower esophagus with branches of the azygos system. The veins of the lower 2-5 cm of the human esophagus are primarily located in the lamina propria rather than the submucosa. Anastomotic shunts or varices which occur in this area of the esophagus are especially vulnerable to rupture and bleeding.

However, portal hypertensive bleeding can also occur at the site of gastric varices, hemorrhoidal veins or even from varices formed at various points in the small intestine, colon or rectum. Finally, it has long been recognized that bleeding from "gastritis" is a common cause of morbidity in cirrhotic patients. More recent endoscopic/pathologic correlations have provided convincing evidence that after esophageal varices, "congestive" or "portal hypertensive" gastropathy may well be the next most common source of portal hypertensive hemorrhage (2-4).

As shown in Figure 1, the development of esophageal varices per se and occurrence of hemorrhage from esophageal varices in particular are associated with a poor prognosis. The survival data depicted in Figure 1 were compiled by Baker and coworkers in the early 1950s by following a group of liver disease patients found to have nonbleeding esophageal varices during esophagoscopy (5). The findings discovered in this study were in good agreement with other reports during this era which indicated that gastrointestinal bleeding in cirrhotic patients was associated with a 50-80% one year mortality rate.

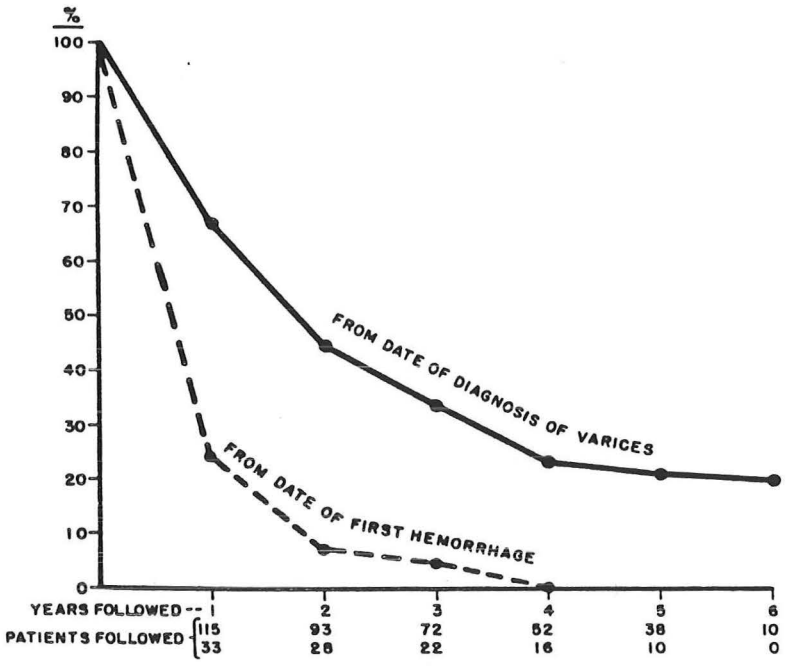


Figure 1. From Baker et al, Am. J. Med. 26:232

As shown in Table 2, the risk of death from the first episode of variceal hemorrhage has improved little if at all during the 30 years since the series of Baker et al. The data in this table have been gleaned from prospective studies in which cirrhotic patients with no prior history of GI hemorrhage but with "untreated" large varices were followed prospectively. Certainly, the observations contained in Figure 1 and Table 2 indicate that variceal hemorrhage is a very morbid event for cirrhotic patients. Such observations, in conjunction with the finding that survivors of an initial variceal hemorrhage have approximately a 65-80% risk of recurrence within several years of follow-up, have led to aggressive efforts to improve survival in patients with esophageal varices by intervening prophylactically (before first bleed) or therapeutically (during or after first bleed) with various treatments designed to stop or prevent variceal hemorrhage.

TABLE 2

RISK OF DEATH FROM FIRST VARICEAL HEMORRHAGE

Decade	First Author of Report	Number Deaths Number of First Bleeds	Mortality Attributed to First Variceal Bleed
1950's	**Baker (5)**	**11/33**	33
1960's	Jackson (6)	9/14	64
	Resnick (7)	5/12	42
	Conn (8)	8/14	57
	Conn (8)	5/7	71
	Overall	**27/47**	**57**
1980's	Witzel (9)	19/30	63
	Piai (10)	19/29	66
	Sauerbruch (11)	11/24	46
	Pascal (12)	18/30	60
	Italian Multicenter (13)	9/27	33
	Ideo (14)	4/11	36
	Grace (15)	3/11	27
	Overall	**83/162**	**51**

Much of the mortality associated with portal hypertensive hemorrhage is related to events occurring during or around the time of the acute hemorrhage. However, because of the hemodynamic instability of these patients and their unique susceptibility to a variety of infectious and metabolic complications during the hours or days surrounding a variceal hemorrhage, most controlled clinical trials of therapies directed at long-term management of portal hypertensive hemorrhage have been designed to intervene either prior to the first variceal hemorrhage or after a patient has been initially stabilized following an acute variceal bleed. The remainder of this grand rounds will focus on the review of such randomized prospective trials.

Why Randomized Prospective Trials

If an event such as variceal hemorrhage is associated with a 50% case mortality rate and a 75% recurrence rate, then it stands to reason that any therapy which can be performed with little procedure related mortality and which has significant efficacy in preventing recurrent hemorrhage should provide a dramatically improved survival rate. That such straight forward reasoning has been repeatedly shown to be incorrect is related to several characteristics of this disease.

One problem in evaluating the efficacy of therapies designed to prevent variceal hemorrhage is the great variability in the natural history of this disease in different subsets of patients. Smith and Graham published an analysis of survival in patients presenting with variceal hemorrhage to the Ben Taub General Hospital in Houston (16). In this analysis they have eloquently detailed the pitfalls inherent in retrospectively comparing therapeutically treated groups of patients to historical controls. As depicted in Figure 2, when one delays several days to several weeks after patient presentation to enroll "stabilized" patients in therapeutic trials, one pre-selects a subset of "survivors" who have significantly higher rates of long-term survival than does a population of unselected patients enrolled at time of presentation to the hospital. Thus, if a surgeon in a referral medical center predominantly operates electively on patients who are referred to him from outlying hospitals, he cannot analyze this survival data and compare it to a control group of patients enrolled at a large city hospital where almost all patient survival is calculated from time of initial presentation with a portal hypertensive bleed.

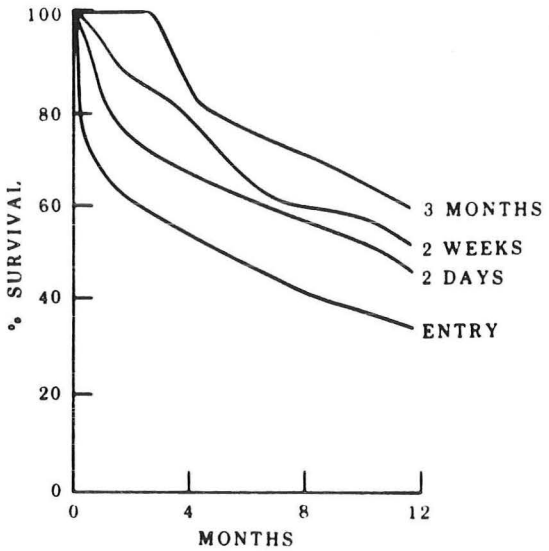


Figure 2. Comparison of the effect of varying "0" time from entry to 2 days, 2 weeks, or 3 months. From Graham et al, Gastroenterology 80:807, 1981.

A second, even more important factor in survival analysis is related to the fact that not all varices (or variceal hemorrhages) are associated with equal mortality risk. With the initial application of surgical therapies designed to relieve portal hypertension, it became clear that operative risk was highly correlated with the degree of underlying liver disease. Tables 3 and 4 detail two of the most popular classification systems for assessing operative mortality risk in patients with portal hypertension. Not only do such classification systems stratify patients according to operative risk, but they have also been found to stratify variceal hemorrhage patients into vastly different levels of risk for acute and long-term mortality.

TABLE 3

CHILD'S (17) CLASSIFICATION OF HEPATIC RESERVE

Criteria	Good Risk A	Moderate Risk B	Poor Risk C
Serum bilirubin (mg/dl)	>2	2-3	>3
Serum albumin (gm/dl)	>3.5	3-3.5	<3
Ascites	None	Controlled	Not Controlled
Encephalopathy	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor

TABLE 4

PUGH'S (18) MODIFICATION OF CHILD'S CLASSIFICATION

Criteria	Points Scored for Abnormality 1	2	3
Serum bilirubin*	1-2	2-3	>3
Serum albumin	>3.5	2.8-3.5	>2.8
Prothrombin time (sec. prol.)	1-4	4-6	>6
Ascites	Absent	Slight	Moderate
Encephalopathy (grade)	None	1-2	3-4
*For Primary Biliary Cirrhosis Serum bilirubin	1-4	4-10	>10

Good operative risk (Grade A) = 5 or 6 points; Moderate operative risk (Grade B) = 7, 8 or 9 points; Poor operative risk (Grade C) = 10-15 points.

As shown in Table 5, the short and long-term risk of death in patients with variceal hemorrhage is correlated far more closely with level of hepatic dysfunction than it is with the presence or absence of bleeding itself. The degree to which liver dysfunction impacts on mortality is further emphasized by the fact that in the review by Fonkalsrud et al (22) of children with extrahepatic portal venous thrombosis (and no intrinsic liver disease), 62 of 62 children survived their initial variceal hemorrhage. Furthermore, despite multiple recurrent bleeds, only two died of hemorrhage during up to 25 years of long-term follow-up. Death from hemorrhage in adult patients with extrahepatic portal hemorrhage and variceal bleeding is also a relatively uncommon event (23,24). Therefore, while variceal hemorrhage clearly increases the baseline mortality rate in patients with chronic liver disease (Figure 1), it must also be stressed that extremely high mortality rates from variceal hemorrhage are only seen in the presence of significant decreases in hepatic function. Thus, even subtle differences in overall levels of hepatic function in various patient populations can greatly affect long-term mortality rates. Furthermore, any adverse effects of therapy on hepatic function can readily counteract any benefit realized from decreases in rates of variceal hemorrhage.

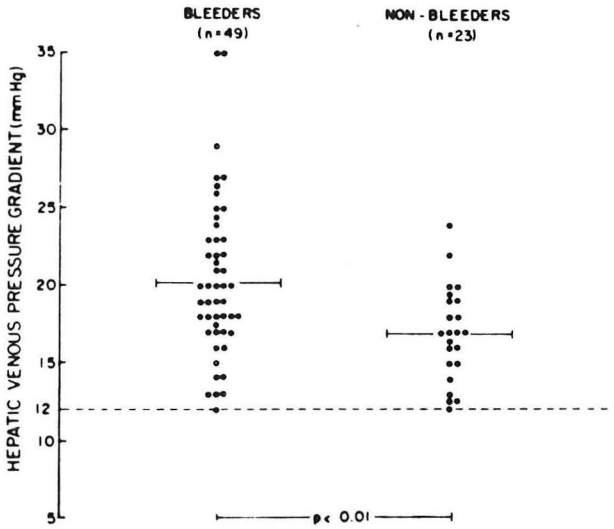
TABLE 5

MORTALITY RATES IN PATIENTS WITH VARICEAL HEMORRHAGE AND VARYING DEGREES OF HEPATIC RESERVE

Series	Acute Mortality From One Variceal Hemorrhage			5-Year Mortality Following Index Bleed		
	A	B	C	A	B	C
Burroughs (19)	9%	3%	51%	-	-	-
Soderlund (20)	-	5%	43%	-	-	-
Sauerbruch (21)	-	-	-	5%	45%	90%

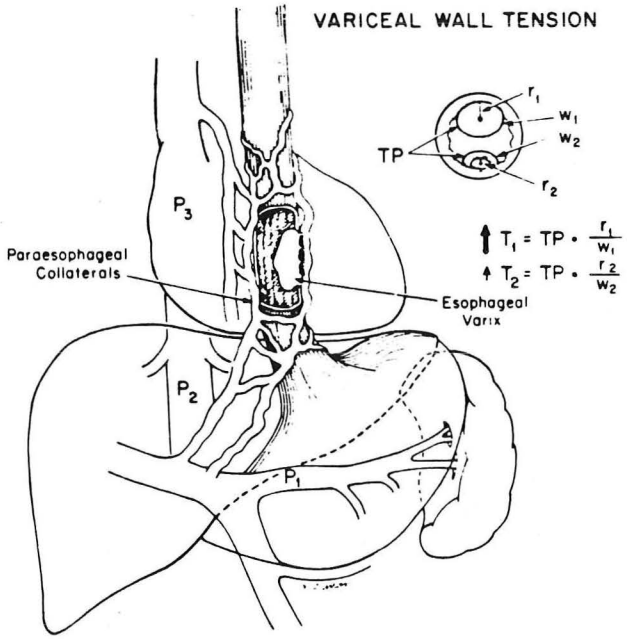
Why Do Varices Bleed?

As shown in Figure 3, all patients with varices have significant portal hypertension and a hepatic venous pressure gradient (usually calculated by subtracting free hepatic vein pressure from the wedged hepatic vein pressure) which exceeds 11.5 or 12 mmHg (25). However, in prospective studies of patients with varices, anywhere from 1/3 to 3/4 of patients never develop variceal hemorrhage (5-15). As demonstrated in Figure 3, while "bleeders" have on the average slightly more severe portal hypertension than do non-bleeders, there is considerable overlap between these two groups of patients. In most studies, virtually no level of portal hypertension has been found to absolutely predict future risk of hemorrhage.



Hepatic venous pressure gradient in alcoholic cirrhotics with gastroesophageal varices with and without variceal bleeding.

Figure 3. From Garcia-Isao et al, Hepatology 5:419.



Variceal wall tension: In varices with the same transmural pressure (TP) but different radii ($r_1 > r_2$) and wall thickness ($w_1 < w_2$), wall tension (T) will be greatest in the varix with the largest radius (r_1) and thinner (w_1) wall.

Figure 4. From Polio and Groszmann, Seminars in Liver Disease 6:319

As illustrated in Figure 4, the tension on the wall of a varix is dependent not only on the degree of portal hypertension or transmural pressure but is also a function of the radius or size of the varix and the wall thickness (25,26). The findings detailed in Figure 5 indicate that calculation of variceal wall tension produces a quantitative figure which provides much improved though not absolute discrimination between varices which bleed and those which do not (26). The importance of considering size of varices and wall thickness in estimating risk of bleeding has been confirmed by studies which have found that overall, levels of portal hypertension (hepatic venous pressure gradients) are similar in patients with small versus large varices (27). However, patients with large varices have a several fold higher risk of bleeding than do patients with small varices (27).

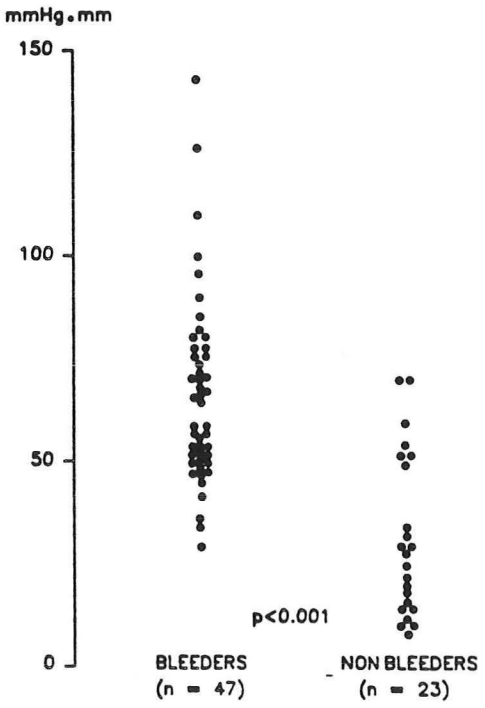


Figure 5. Values of calculated variceal wall tension in patients with and without previous variceal hemorrhage. From Rigau et al, Gastroenterology 96:877.

As there is no accepted, non-invasive technique for measuring transmural pressure in varices, or estimating this value by measurement of hepatic venous pressure gradients, it is fortuitous that other characteristics of varices are useful in estimating risk of bleeding. Table 6 details the parameters which have been found to predict risk of bleeding from varices (27-30). These parameters fall into three general categories: those which estimate severity of underlying liver disease, those which estimate size of varices, and those which probably

reflect thickness of varix walls as reflected by the ability to detect the color of blood underlying thin-walled varices or the red discolorations produced by varices eroding through overlying esophageal mucosa. Use of parameters such as those detailed in Figure 5 and Table 6 in assessing risk of variceal hemorrhage are crucial to the design and interpretation of prophylactic treatment trials as only patients fated to bleed will benefit from measures designed to prevent variceal hemorrhage, whereas all patients will suffer from any side effects induced by such therapies.

TABLE 6

RISK FACTORS FOR BLEEDING FROM VARICES

Size
- Large varices >> small varices
- Extension of varices into upper 2/3 of esophagus

Wall Thickness/Mucosal Erosions
- Blue varices
- Red wale markings
- Hematocystic spots "Red color sign"
- Cherry red spots

Extent of Liver Disease
- Child's C > Child's B > Child's A
- Ascites
- Low albumin
- Coagulopathy

Prevention of Initial or Recurrent Variceal Hemorrhage

Table 7 details some of the therapies which have been employed in an effort to prevent variceal hemorrhage and prolong survival in patients with portal hypertension. The very length of this list immediately suggests that no single therapy has gained widespread acceptance or has proven to have indisputable efficacy. As mentioned earlier in this grand rounds, the greatest mortality risk in these patients appears to not be associated with the presence of portal hypertension alone but rather with the significant degree of liver dysfunction manifested in the majority of such patients. Of all the techniques listed in Table 7, only the last, liver transplantation, addresses this major mortality risk factor.

Only four categories of therapies have been submitted to the scrutiny of prospective, randomized trials performed at more than one center. These therapies include non-selective portacaval shunt surgery, selective distal splenorenal shunt surgery, endoscopic sclerotherapy, and β-blocker therapy. Such trials have been performed in two settings: so-called therapeutic trials in patients who have presented with one or more episodes of variceal (or portal hypertensive gastropathy) bleeds and the prophylactic trials performed in patients with varices from which they have not yet bled.

TABLE 7

THERAPIES EMPLOYED TO PREVENT VARICEAL HEMORRHAGE

A. Surgical Variceal Elimination
   (1) Transesophageal ligation
   (2) Esophageal or gastric transection
   (3) Gastroesophageal devascularization
   (4) Splenectomy - splenic devascularization

B. Shunt Surgery
   (1) Non-selective/portal venous diversions
      (a) End-to-side portacaval anastomosis
      (b) Side-to-side portococaval anastomosis
      (c) H-graft portacaval anastomosis
      (d) Mesocaval anastomosis
      (e) Central splenorenal anastomosis

   (2) Selective/portal venous maintaining
      (a) Distal splenorenal anastomosis
      (b) Corono caval anastomosis

C. Endoscopic Variceal Sclerosis

D. Percutaneous Transhepatic Variceal Obliteration

E. Pharmacologic Therapy of Portal Hypertension
   (1) β-adrenoreceptor blockade (Propranolol, Nadolol)
   (2) Verapamil
   (3) Prazosin

F. Liver Transplantation

The use of liver transplantation has never been assessed in any form of prospective, randomized fashion in patients with variceal hemorrhage. Furthermore, at present the majority of patients at risk for variceal hemorrhage are considered not to be candidates for liver transplantation secondary to either chronic alcoholism or to lack of medical insurance and/or great personal wealth. One small series from Taiwan has reported efficacy of verapamil in preventing rebleeding from esophageal varices, and one large series of reports from a single Japanese center has reported impressive survival and rebleeding rates in predominantly Childs A or B patients treated with esophageal transections and paraesophagogastric devascularization (31). This experience has not been reproduced, however, in US centers (32-33).

Surgical Approaches to the Prevention of Portal Hypertensive Hemorrhage

In 1877, Nickolai Eck first demonstrated that portacaval anastomosis could be performed in dogs without immediate fatality (34). Shortly thereafter, Pavlov and others described a syndrome of meat intoxication in dogs with Eck fistulas

(34). The full implications of these findings were not appreciated by surgical proponents of portacaval shunting until the results of the prospective randomized trials summarized in Tables 8 and 9 became available nearly a century later. No therapy yet devised, short of an orthotopic liver transplant, has been shown to be as efficacious as portacaval shunting in lowering portal pressures and preventing subsequent variceal (or portal hypertensive gastropathy) hemorrhage. The observations detailed in Figure 1 and Table 1 suggested that variceal hemorrhage in the cirrhotic patient was associated with a high degree of morbidity and mortality. It seemed intuitively obvious that the best way to improve on this grim outcome was to intervene before the first variceal hemorrhage.

TABLE 8
PROPHYLACTIC PORTACAVAL SHUNT SURGERY

Study	First Author	# Patients Enrolled		Variceal Hemorrhage	Mortality			Incidence of Portosystemic Encephalopathy
					Variceal Bleeding	Liver Failure	Total	
VA Coop.	Jackson (7)	Control	75	19%	9%	9%	28%	20%
		Shunt	37	16%	8%	16%	51%	38%
BILG	Resnick (6)	Control	45	27%*	11%	20%	42%	30%
		Shunt	48	2%	2%	25%	46%	52%
Yale-I	Conn (8)	Control	31	39%*	19%	6%	55%	-
		Shunt	25	4%	4%	36%	80%*	-
Yale-II	Conn (8)	Control	22	27%*	23%	5%	45%	0%[a]
		Shunt	19	11%	5%	26%	42%	19%*

*Values considered to be significantly increased compared to alternate therapy group.
(a) In combined analysis of these studies, chronic or spontaneous portosystemic encephalopathy was noted to occur in 19% of the surgical patients, and in none of the controls ($p<0.05$).

Several sobering conclusions were reached from the four major studies which have examined the use of prophylactic portacaval shunts in patients with varices that have not yet bled (6-8). First of all, the efficacy of this procedure in preventing death from variceal hemorrhage is counterbalanced not only by risk of acute peri-operative death but also by acceleration of liver failure and an

increased death rate from other complications of liver disease. In addition to an increased mortality rate from liver failure, it also became apparent that many patients were left in a predicament much like that of Pavlov's dogs with Eck fistulas. Whereas most control patients with chronic, stable liver disease experience encephalopathy only during periods of hepatic decompensation or when stressed by major infections or gastrointestinal bleeding, patients status post portacaval shunts were frequently found to have severe bouts of encephalopathy precipitated by little more than a high protein meal or by no apparent precipitating factors whatsoever. Moreover, in some of these patients, hepatic encephalopathy proved to be chronic and highly refractory to standard therapies. An example of such a complication is illustrated by the case of patient J.B., case #1 in the appendix.

Of note, whereas it might seem logical that portosystemic encephalopathy would be more likely to occur in Child's C patients with severe underlying liver disease, in many series which have examined this issue (6-8.35-38), it has been noted to occur nearly as frequently in Child's A patients such as patient J.B. Furthermore, even in adult patients with extrahepatic forms of portal hypertension or in schistosomiasis patients in whom underlying liver function is normal, 56% and 69% incidences, respectively, of post-shunt encephalopathy have been reported following nonselective portacaval shunt procedures (39,40). The important role of the portal vein in providing a variety of hormones and hepatotropic substances as well as the presence of nitrogenous wastes in the portal circulation which, when shunted past the liver, induce portosystemic encephalopathy have been offered as explanations for the dual problem of accelerated mortality from liver failure and increased incidence of severe hepatic encephalopathy seen after portacaval shunt surgery.

Certainly, as shown by the results compiled in Table 8, one of the major problems with the use of prophylactic shunt surgery is that only a minority (19-39%) of untreated patients with varices actually suffer from variceal hemorrhage during long-term follow-up (all patient series in Table 8 represent results of mean follow-up of >3 years and in some cases as long as 12 years). The often decreased (2 of 4 studies) long-term survival seen following prophylactic shunt surgery can therefore be attributed in large part to the complications of this procedure which are manifested in a large subset of patients who receive no potential benefit. The second Yale controlled trial was designed to address this problem by only enrolling patients with both varices and ascites and who were therefore expected to exhibit higher rates of variceal hemorrhage. This expectation unfortunately proved to be wrong.

It had long been noted that rebleeding rates were very high once patients initially bled from esophageal varices. Four studies summarized in Table 9 where performed to assess the value of "therapeutic" shunts in patients with one or more previous episodes of hemorrhage. The stated intent of the first 3 of the studies listed in Table 9 was to assess the value of therapeutic portacaval shunt in patients with prior episodes of bleeding from esophagogastric varices. In the study of Rueff et al, the intent was to assess the value of this therapy in patients with cirrhosis and portal hypertension (as evidenced by the presence of varices) in whom a major upper gastrointestinal hemorrhage of non-peptic ulcer origin had occurred. Thus, the latter study admittedly included both patients thought to have bled initially from varices as well as some patients in whom the

initial bleed appeared to be from "gastritis". However, as pointed out by Reynolds (38), in the other studies emergency endoscopy was rarely employed and many of the patients were only evaluated by UGI series. Therefore, almost certainly some patients were enrolled with initial bleeds from "gastritis" instead of from their co-existing varices. This point of difference has been used repeatedly by one reviewer to justify the manner in which he combines data from these trials to demonstrate efficacy of therapeutic shunt surgery in patients with a previous variceal hemorrhage.

TABLE 9

PROSPECTIVE, RANDOMIZED THERAPEUTIC TRIALS OF PORTACAVAL ANASTOMOSIS IN PATIENTS WITH PREVIOUS PORTAL HYPERTENSIVE HEMORRHAGE

Author		Patients Enrolled	Variceal Hemorrhage	Chronic Encephalopathy	Mortality[a]		
					Variceal Bleeding	Hepatic Failure	Total
Resnik (35)	Control	25[b]	70%*	4%[c]*	39%*	9%*	52%
	Shunt	46	9%	27%	4%	28%	43%
Jackson (36)	Control	77	65%*	22%[d]	19%*	19%	64%
	Shunt	67	6%	31%	3%	27%	45%
Reynolds (37)	Control	44	90%*	0%*	52%*	7%*	66%
	Shunt	41	0%	49%	0%	44%	63%
Rueff (38)	Control	49	71%*	0%*	24%	22%	47%
	Shunt	31	13%	24%	13%	35%	68%

* $p<0.05$

[a] 5 year mortality rates are given for the first two studies, 5 to 12 year rates for Reynolds study, and 3 year survivals for Rueff's series.

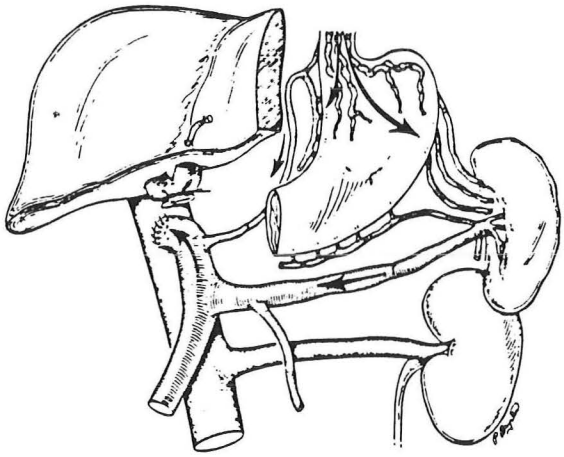
[b] Two patients lost to follow-up.

[c] Excludes patients shunted after rebleed but before encephalopathy.

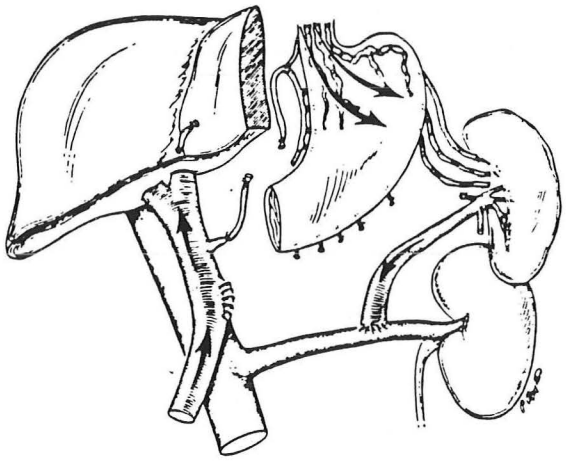
[d] Excludes patient with encephalopathy precipitated by hemorrhage.

In none of these trials was a significant difference seen in long-term survival of shunt versus control groups. In all studies, shunted patients had a lesser rate of recurrent hemorrhage and a lesser incidence of fatal hemorrhage, but a greater incidence of severe portosystemic encephalopathy and a higher mortality rate from hepatic failure. However, in the first three trials, there was a trend towards increased survival in the shunted patients during the first 5 years of follow-up, whereas in the study of Rueff et al, there was a trend towards improved survival in the control group. Of note, in the third study (Reynolds et al), an early trend favoring surgery had reversed by the end of the

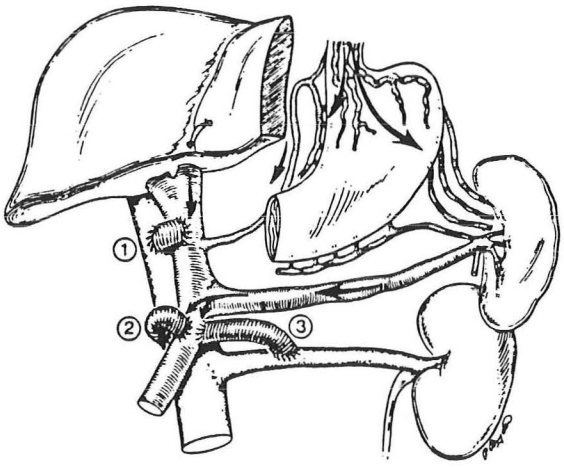
trial. If one takes the liberty of pooling the data from all four trials, there is no statistically significant difference in long-term survival between patients receiving shunt surgery and those randomized to non-surgical care (38). However, in an often quoted analysis by Conn (41), the data from only the first three trials has been pooled (the fourth being excluded because of "differences in design"), and when statistical analysis is performed, an increased survival in shunted patients is noted at the 4th and 5th year follow-up points. Even this contrived difference is small (50% vs. 38%) and is counterbalanced by the significant increase in patients with chronic severe encephalopathy (34% vs. 9%). When variation in length of follow-up is considered, the overall rate of recurrent hemorrhage and the rate of death from hemorrhage in the study of Rueff et al was comparable to that seen in the other three studies. Furthermore, as "design differences" were more a matter of definition than practical outcome, the selective nature of Conn's analysis of this data seems highly questionable. The results of the studies outlined in Table 9 also re-emphasized the deleterious effects of non-selective portacaval shunts on hepatic function and mental status. In light of these findings, a host of alternative surgical procedures have been employed in the treatment of portal hypertension. Some of the more popular procedures are illustrated in Figure 6.



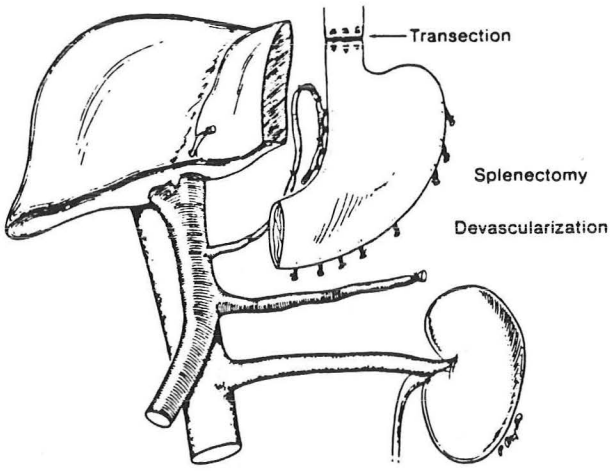
End-to-side portacaval shunt



Distal splenorenal shunt



Interpositon H-graft shunts



Ablative procedures

Figure 6

Most uncontrolled series have reported major problems related to shunt occlusion or high encephalopathy rates following the various forms of interposition grafts. However, the distal splenorenal shunt procedure pioneered by Warren and Zeppa gained rapid popularity in the U.S. as the surgical procedure of choice. In Japan, the Sugiura procedure of esophageal transection and paraesophagogastric devascularization came into widespread use (31). Series of selected, nonrandomized patients have been reported to excellent long-term survival following either of these procedures when performed in Zeppa, Warren or Sugiura's respective institutions (31,42,43).

Of these procedures, only the selective distal splenorenal shunt of Warren and Zeppa has been widely assessed in prospective randomized trials. Unfortunately, no study has compared this therapy to an untreated control group. However, a host of studies have now compared the results of distal splenorenal shunts to those of nonselective shunts in prospectively randomized patients. The results of these studies are summarized in Table 10. Despite the exceptional survival figures quoted for nonrandomized recipients of this procedure (42,43), when the distal splenorenal shunt has been compared to a variety of non-selective shunt procedures in a prospective randomized fashion, no benefit with respect to long-term survival has been demonstrated in any of the 6 series in which these procedures have been compared in cirrhotic patients (44-49) or the one series composed of patients with portal hypertension secondary to schistosomiasis (50).

TABLE 10

PROSPECTIVE, RANDOMIZED COMPARISONS OF THE EFFICACY OF A SELECTIVE SHUNT (DISTAL SPLENORENAL SHUNT) VERSUS NON-SELECTIVE SHUNT PROCEDURES (44-50)

Author	Years Follow-up	Patients Enrolled	Incidence of Chronic (Spontaneous) Encephalopathy	Incidence of Recurrent Variceal Hemorrhage	Relative Mortality Rates
Millikan	10	DSRS 26	27%	8%	58%
		HGIS 29	76%*	14%	72%
Langer	5.5	DSRS 38	12%	8%	53%
		ESPCS 40	33%*	0%	48%
Fischer	2-5	DSRS 23	0%	4%	22%
		CSRS 19	0%	0%	0%
Reichle	2-8	DSRS 13	+	0%	31%
		MCS 14	+*	0%	29%
Harley	5	DSRS 27	39%	27%*	57%
		ESPCS 27	32%	4%	69%
Grace	3-11	DSRS 43	47%	18%	46%
		PCS 38	45%	12%	68%
Silva[b]	2	DSRS 30	7%	7%	0%
		CSRS 32	26%*	13%	6%
		EGDS 30	0%	13%	0%

DSRS = Distal splenorenal shunt; HGIS = H-graft interposition graft; ESPCS = End-to-side portacaval shunt; CSRS - central splenorenal shunt; MCS = mesorenal shunt; SSPCS = side-to-side portocaval shunt; EGDS - esophagogastric devascularization with splenectomy.

a Reported in patient months, 3.75 months for mesocaval shunt and 0,75 months for DSRS

b This study was performed in patients with portal hypertension secondary to schistosomiasis without apparent instrinsic liver disease; * $p<0.05$

As the major goal in design of the distal splenorenal shunt procedure was to maintain portal perfusion and thereby preserve hepatic function and prevent an excess incidence of portosystemic encephalopathy, a major focus of such trials has been to carefully observe patients for the development of chronic or spontaneous encephalopathy during follow-up after surgery. In the two series of Millikan et al (44, Warren's Emory Group) and Langer et al (45), the incidence of chronic encephalopathy in DSRS patients has been 12-16% at 5 years of follow-up and 27% after 10 years of follow-up. In these two series, the incidence of encephalopathy in the nonselective shunt recipients was significantly higher at similar time points. In a very small study by Reichle et al (47), a significantly decreased incidence of chronic encephalopathy was also noted in the DSRS group. Finally, in a prospective randomized trial performed in Brazilian schistosomiasis patients by Silva et al (50), a DSRS was found to entail significantly less risk (though not 0% risk) of chronic encephalopathy than did a central splenorenal shunt procedure. As historical series using standard portacaval shunt techniques have reported even higher incidences of post-shunt encephalopathy in schistosomiasis patients, it is possible that the incidence of this complication after central splenorenal shunt procedures is reduced to an intermediate degree. This might also explain the results of the study of Fisher et al (46) in which chronic encephalopathy was not seen in recipients of either type of splenorenal shunt. However, the results of Harley et al (48, USC) and Grace et al (49, Boston-New Haven Collaborative Liver Group) are dramatically different in that no significant difference between total or severe encephalopathy rates could be demonstrated following selective distal splenorenal shunts or non-selective portacaval shunts.

When these studies have been scrutinized regarding nature of patient selection, relative severity of underlying liver disease, or classification of grades or types of encephalopathy, no means can be found to rationalize the disparate results of the Millikan and Langer studies versus those of the Harley and Grace trials. Proponents of the distal splenorenal shunt procedure have pointed out that proper performance of a selective distal splenorenal shunt requires more than just a simple splenorenal anastomosis. Careful dissection of three major pathways of potential venous bridging between the portal and splenic vein which form in the pancreatic, mesocolic and gastric vascular beds, respectively, is also thought to be very important. It has been suggested that a long learning curve is necessary to acquire the skills necessary to perform a "proper" Warren shunt (50). The Harley and Grace studies have been criticized because in the former study (48), distal splenorenal shunts were performed by a series of "senior vascular fellows" albeit under the supervision of a single senior faculty surgeon, while in the latter series of Grace et al (49), eleven different surgeons were involved in performance of the 43 distal splenorenal shunts (51). It has also been noted that in 3 of the 43 DSRS patients in the series of Grace et al, the gastroesophageal devascularization aspect of the procedure was omitted. However, defendants of the trials of Harley et al and Grace et al point out that the experience of their surgeons in performing these procedures is likely to be no less than that available in the average U.S. medical community.

Several definitive conclusions can be drawn from the data contained in Table 10. Most important, perhaps, is the observation that use of the distal splenorenal shunt procedure does not prolong survival relative to that seen in

recipients of non-selective portacaval shunt procedures. Since portacaval shunts have not been shown to prolong the life of patients with a history of variceal hemorrhage, it also follows that prolongation of survival is not one of the benefits of the distal splenorenal shunt. A second major point is that even in the best of hands, chronic, nonprecipitated encephalopathy appears to be a complication of the distal splenorenal shunt procedure in approximately 15% of patients after 5 years of follow-up and in approximately 25% of patients after 10 years. That such encephalopathy is not merely related to progression of underlying liver disease is suggested by two observations. The development of encephalopathy in 7% of schistosomiasis patients within 2 years of a distal splenorenal shunt (Table 10, Silva series) is not at all inconsistent with the rate seen in Warren's Childs A or B cirrhotic patients. Furthermore, Warren and other investigators have noted, especially in patients with alcoholic liver disease, that portal perfusion often significantly deteriorates within a year after a distal splenorenal shunt (52-54). A decrease in the caliber of the portal vein with development of huge collateral venous channels that connect directly with the distal splenorenal shunt has been described in many such patients. Indeed, the loss of portal perfusion during late follow-up of recipients of this procedure has been so frequent in some series as to raise the question of why there is not a much higher incidence of late onset encephalopathy after performance of a distal splenorenal shunt. An example of a patient with such spontaneous encephalopathy following distal splenorenal shunt is detailed in case #2 in the appendix. A final important conclusion contained in Table 10 should also be noted. In the hands of some surgeons, the incidence of recurrent variceal hemorrhage is significantly higher after distal splenorenal shunt than after portacaval shunt surgery (see series of Harley, et al, Table 10). However, in the hands of most surgeons, the distal splenorenal shunt operation does achieve a very satisfactory reduction in risk of recurrent portal hypertensive hemorrhage.

Endoscopic Variceal Sclerosis

Over the past decade, the literature has been inundated with a plethora of manuscripts (>500 papers by most estimates) dealing with the use of endoscopic sclerotherapy in the control and prevention of esophageal variceal hemorrhage. As in the case of the surgical literature, however, the number of well controlled prospective, randomized trials evaluating this technique is much smaller. In addition, while I have chosen to not review the general topic of management of acute variceal bleeding in this grand rounds, it should be pointed out that endoscopic sclerotherapy has become generally accepted as the best therapy in management of acute variceal hemorrhage. Controlled, randomized prospective trials have shown that emergency sclerotherapy is superior to balloon tamponade and/or pitressin in controlling acute variceal bleeding (56-58), and in some series emergency sclerotherapy has also been shown to decrease acute mortality (56).

The variations in techniques employed to sclerose varices via an endoscope are almost as varied as those employed to surgically decompress portal hypertension. Some studies have employed paravariceal injections whereas others have attempted to limit sclerosant injections exclusively to an intravariceal site. A wide variety of sclerosants, including ethanolamine oleate, polidocanol,

sodium morrhuate, tetradecylsulfate, and absolute ethanol have been proposed as the ideal agent(s) for this purpose. The spacing of chronic sclerotherapy sessions has varied from 3 day to six week intervals. Most patients probably end up with combinations of paravariceal and intravariceal injections and it has been difficult to distinguish between the relative efficacy of the more popular sclerosing agents. Similarly, it has been difficulty to deduce the optimal spacing of sclerotherapy from the results of the various prospective trials (reviewed in references 59 and 60).

Table 11 details the results of 5 randomized controlled trials comparing the results of sclerotherapy to that of "standard" supportive therapy. In one of these trials, that of Terblanche et al (60), the control group also received emergency sclerotherapy at the time of any acute variceal hemorrhage. Thus, the only difference between the two groups was in the use of emergent and chronic (elective) obliterative sclerotherapy in one group versus only emergent sclerotherapy in the other. In the remaining four trials detailed in Table 11, acute bleeding in the control groups was managed by pitressin and/or balloon tamponade. Thus, as the Terblanche study showed no long-term survival benefit of sclerotherapy, the question must be raised as to whether the improved survival demonstrated in 3 of the other 4 trials listed in Table 11 is related predominantly to the benefits of emergency sclerotherapy.

TABLE 11

OUTCOME OF RANDOMIZED TRIALS (61-65) OF CHRONIC ENDOSCOPIC VARICEAL SCLEROSIS IN PREVENTION OF RECURRENT HEMORRHAGE

Study	Follow-up	Patient Number		Rebleeding	Mortality		
					Liver Failure	Bleeding	Total
Terblanche	3-5 years	Control	38	73%*	11%	NS	63%
		EVS	37	43%	8%	NS	62%
Copenhagen Project	9-52 mo.	Control	94	138 episodes**	NS	NS	78%**
		EVS	93	64 episodes	NS	NS	65%
Westaby et al	19-68 mo.	Control	60	80%	10%	42%*	53%*
		EVS	56	55%	18%	9%	32%
Korula et al	3-34 mo.	Control	57	mean 13.2 Units*	7%	25%	33%***
		EVS	63	mean 3.5 Units	11%	11%	33%
Soderlund et al	1 mo.-5 yr.	Control	50	0.16 bleeds/mo.*	8%	26%	66%
		EVS	57	0.05 bleeds/mo.	10%	5%	51%

NS = Not stated
* $p<0.05$
** $p<0.05$ when bleeding and mortality rates after day 40 analyzed separately.
*** $p<0.05$ when shunted patients removed from both groups (improved survival in sclerotherapy recipients by life table analysis)

In further evaluation of the results detailed in Table 11, it should be noted that in all 5 trials chronic sclerotherapy was found to significantly decrease total incidence or volume of rebleeding. However, the efficacy of this therapy in preventing rebleeding is far less than that of shunt surgery (see Tables 9 and 10). Yet in spite of a relatively decreased efficacy in preventing recurrent hemorrhage, endoscopic sclerotherapy has been found to significantly improve some measure of long-term survival in three of these trials whereas no form of shunt surgery has ever been shown to achieve this goal.

It should be noted, however, that in the study of Korula et al (64), prolongation of survival could only be demonstrated when patients receiving shunt surgery (28% of controls versus 6% of sclerosis patients) were removed from life table analysis at the time of surgery. Total length of follow-up was also quite brief in many of the patients in this study. In the Copenhagen Esophageal Varices Sclerotherapy Project, mortality rates were quite high in both groups of patients and statistically significant differences in survival were only noted when deaths occurring more than 40 days after randomization were analyzed separately. Only in the study if Westaby et al (63) from the King's College Liver Unit was overall long-term survival clearly statistically improved ($p<0.01$) in the recipients of sclerotherapy. When one examines the life table analysis of this study in Figure 7, it would appear that most of this survival advantage was apparent within 6 months of presentation, with long-term survival curves being relatively parallel from this point onward. Thus, endoscopic sclerotherapy is the first approach to treatment of variceal hemorrhage which has been shown in more than one randomized, prospective trial to significantly improve survival in patients with previous variceal hemorrhage. It can be argued that much of this benefit may derive from the use of this therapy in acute management of variceal hemorrhage. Chronic sclerosis does, however, decrease rebleeding rates and one trial (the Copenhagen project, in which survival benefit was only seen during long-term follow-up) argues that it may have a modest additional benefit with respect to long-term survival.

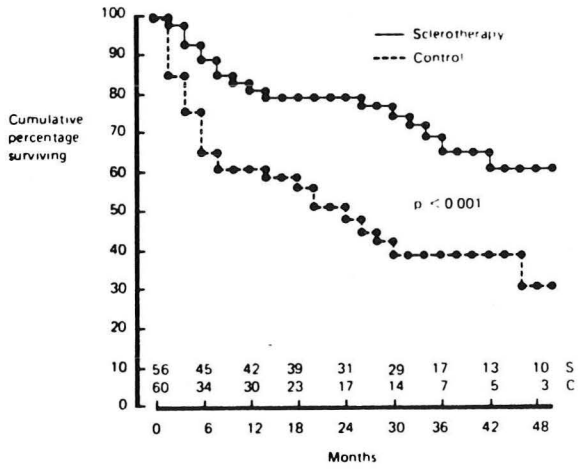


Figure 7. From Westaby et al, Hepatology 5:829.

Unlike portacaval shunt surgery, endoscopic variceal sclerosis has been found to have no negative effects on the incidence of portosystemic encephalopathy or death from hepatic failure. However, this therapy clearly does entail a unique set of complications. The nature of complications resulting from sclerotherapy is listed in Table 12, along with the incidence of these complications as reported in the trials detailed in Table 11. Esophageal ulceration (14-70% incidence), esophageal stricture (3-18% incidence) and bleeding from esophageal ulcers or injection sites (9-21%) are the most common complications of this therapy. In addition, a several percent risk of potentially fatal esophageal perforations or aspiration pneumonias were also noted in these series. Thus, therapy is not without significant morbidity. However, all trials of endoscopic sclerotherapy have shown a decreased frequency of recurrent hemorrhage, several have shown a significant benefit with respect to acute and/or long-term survival, and none have shown a detrimental effect of this therapy in long-term survival or functional status. This approach to prevention of recurrent variceal hemorrhage has become, therefore, the standard of care for such patients during the 1980s.

TABLE 12

COMPLICATIONS OF ENDOSCOPIC VARICEAL SCLEROSIS

Frequency Complication	Terblanche (61)	Copenhagen Project (62)	Westaby (63)	Korula (64)	Soderlund (65)
Esophageal ulcer	42%	NS[a]	33%	70%	14%
Esophageal stricture	11%	NS	18%[b]	3%	18%
Esophageal perforation	0%	10%	4%[b]	3%	4%
Bleeding from ulcers or injections	-	11%	9-21%	NS	9%
Pulmonary aspiration	-	6%	-	6%	-
Fever >101°F	-	NS	-	14%	-

[a] NS = Not stated

[b] From an earlier report (66).

In light of these positive results, a number of groups of investigators have examined whether this technique is of benefit in prevention of death from initial variceal hemorrhage. The results of eight prospective, randomized trials of prophylactic sclerotherapy are detailed in Table 13. Two of these (70,71) have only been reported in abstract form at this point in time. At first glance, the results of these trials are quite disparate. Results of three trials indicated that prophylactic sclerotherapy resulted in a dramatic (2 to 3 fold), statisti-

cally significant decrease in mortality rates (9,10,67). Four studies, however, showed no statistically significant benefit of sclerotherapy with respect to either incidence of major hemorrhage or survival, and one large American cooperative study actually demonstrated an excess mortality rate in recipients of sclerotherapy (70).

TABLE 13

USE OF SCLEROTHERAPY IN PROPHYLAXIS OF VARICEAL BLEEDING: RESULTS OF 8 PROSPECTIVE CONTROLLED RANDOMIZED TRIALS

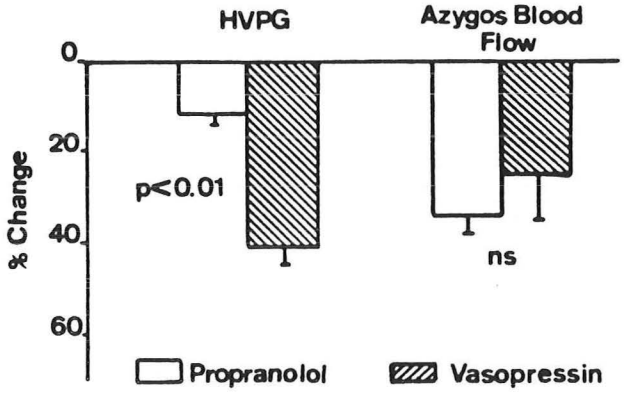
First Author	Mean Duration of Follow-up	Patients Enrolled	Incidence of Major Hemorrhage	Mortality	
				Bleeding	Total
Paquet (67)	3 years	Control 33	88%*	64%*	64%*
		EVS 32	5%	0%	19%
Witzel (9)	25 months	Control 53	57%*	36%*	55%*
		EVS 56	9%	4%	21%
Koch (68)	36 months	Control 30	30%	20%	33%
		EVS 30	17%	0%	37%
Santangelo (69)	13 months	Control 46	15%	4%	24%
		EVS 49	35%*	18%*	24%
Sauerbruch (11)	22 months	Control 65	37%	17%	46%
		EVS 68	40%	15%	35%
Piai (70)	2 years	Control 69	57%*	28%*	56%*
		EVS 71	18%	7%	30%
Gregory (71)	11 months	Control 139	16%	NS	17%
		EVS 143	22%	NS	29%*
Potzi et al	3 years	Control 41	37%	NS	54%
		EVS 41	32%	NS	34%

When the characteristics of the control groups in these trials are examined, a bimodal distribution of patient outcomes is seen. In the three trials showing positive benefit of sclerotherapy, annualized rates of major hemorrhage ranged from 27.3% to 29.3% with cumulative rates at 2 and 3 years, respectively, being 57% and 88%. Similarly, annualized mortality rates in the control groups in these trials ranged from 21.3% to 28% with cumulative mortalities at 2 and 3 years, respectively, being 53%-56% and 64%. In contrast, in the trials showing no benefit or negative benefit of sclerotherapy, annualized rate of first hemorrhage varied from 10.6%-20.2% and cumulative rates of hemorrhage after 3 years of follow-up were only 30-37%. Furthermore, annualized mortality rates in the control groups enrolled in these studies averaged only 18.9%. Thus, studies showing benefit from sclerotherapy seem to have managed to select study populations with exceptionally high rates of subsequent variceal hemorrhage and associated mortality. All studies reported some incidence of esophageal erosion, strictures and sclerotherapy-induced bleeding. It can be anticipated that

complications will be shared by all members of a therapy group whereas benefit occurs only in those who would otherwise have bled had their varices not been eradicated. Thus, it is not surprising that in populations with high bleeding frequencies, prophylactic sclerotherapy shows benefit while in populations with very low bleeding rates, any benefit is negated by the complications of this therapy. It also should be noted that the study of Paquet, which showed the greatest margin of benefit, has been criticized because the control patients were denied benefit of emergency sclerotherapy following any variceal bleeds. As mentioned earlier, emergency sclerotherapy has been adopted widely as the standard of care in acute variceal hemorrhage and its use in the control patients who bleed in most of the other studies may have contributed to lessening of mortality in control groups. Indeed, the 73% mortality rate from acute hemorrhage seen in Paquets group is the highest in any of the trials included in Table 13 and in excess of that reported in any of the older studies summarized in Table 2. Thus, until such time as a widely accepted method is available for predicting which patients will eventually bleed from their varices, use of prophylactic sclerotherapy cannot be recommended.

Pharmacologic Therapy of Portal Hypertension

While multiple forms of pharmacologic therapy for systemic hypertension have long been accepted as efficacious, only recently have such forms of therapy been evaluated in the treatment of portal hypertension. Only non-selective β-blocker therapy, and especially propranolol therapy, have been assessed extensively as therapy for portal hypertension. Propranolol appears to reduce portal hypertension by a reduction in splanchnic blood flow (72,73). This is a result of both a reduction in cardiac output (β-1- adrenergic blockade) and splanchnic vasoconstriction (β-2-adrenergic blockade). As shown in Figure 8, when compared to vasopressin, propranolol has a relatively modest effect on the hepatic venous pressure gradient (the most commonly used indirect measurement of portal hypertension). In contrast, propranolol has a more dramatic effect on azygous blood flow which is reduced to comparable levels by these two agents.



Comparison of the effects of oral propranolol administration and intravenous vasopressin infusion on the hepatic venous pressure gradient (HVPG) and azygos blood flow.

Figure 8. From Bosch et al, Seminars in Liver Disease 6:314

Unlike therapy of systemic hypertension, it is not generally feasible to directly titrate propranolol doses to desired levels of reduction in portal pressures. Most investigators have used indirect measures of β-blockade such as a 25% reduction in resting pulse rate to adjust propranolol dosage. However, when administered in this fashion, most investigators find that reduction in hepatic venous pressure gradients have been unpredictable with some patients showing no reduction, others showing only very modest (10-20%) reductions and only approximately 30% of patients responding with a >20% reduction in hepatic venous pressure gradients (reviewed in reference 73). When measurements of azygous blood have been used to assess the therapeutic effects of propranolol, it has been noted that the fraction of azygous blood flow to cardiac output was significantly decreased in Pughs Class A and Class B cirrhotics but not in Pugh's Class C cirrhotics (74). Thus, there is a good deal of physiologic data to suggest that the therapeutic effects of propranolol might be sporadic, especially in Pugh/Child Class C cirrhotics.

Perhaps with some advance knowledge of the nature of propranolol's effects on portal hypertension in patients with varying degrees of liver disease, the first major prospective randomized trial of propranolol therapy in patients with previous portal hypertensive bleeding was performed in a highly selected population of nonascitic, predominantly Child's A cirrhotics. As shown in the first row of Table 14, the results of this trial indicated the propranolol therapy significantly reduced portal hypertensive hemorrhage and mortality in this population of cirrhotic patients (75). Of note, in keeping with the long-standing belief by this group of investigators that in patients with varices, bleeds from gastritis and esophageal varices are of common underlying etiology and significance, this study enrolled both patients with previous variceal bleeds and those patients with large varices and previous bleeds from "gastritis". This inclusion criteria seems somewhat justified in that of control patients enrolled after initial gastritis bleeds, 37.5% manifested rebleeding from varices and 37.5% from gastritis. However, in patients initially enrolled after variceal bleed, 54% experienced rebleeding from varices and only 7% from gastritis. Thus, these two populations of patients are not completely overlapping. However, propranolol proved to be efficacious in preventing both types of bleeding in patients enrolled by either initial criteria.

TABLE 14

PROSPECTIVE CONTROLLED RANDOMIZED TRIALS (75-79) OF β-ADRENORECEPTOR BLOCKADE IN PREVENTION OF RECURRENT PORTAL HYPERTENSIVE HEMORRHAGE

Study	Length of Follow-up	Patients with Ascites	Patients Enrolled		Frequency of Bleeding			Mortality	
					Varices	"Gastritis"	Total	Bleeding	Total
Lebrec	2 years	Nil	Placebo	36	50%*	14%*	64%*	17%*	43%*
			Propranolol	38	13%	3%	16%	0%	10%
Burroughs	21 months	+	Placebo	22	50%	NA	-	9%	23%
			Propranolol	26	46%	NA	-	15%	15%
Villeneuve	2 years	+	Placebo	37	81%	NA	-	NA	37%
			Propranolol	42	76%	NA	-	NA	46%
Gatta	0.5-2.8 yrs	Nil	Placebo	12	71%*	NA	-	17%	25%
			Nadolol	12	25%	NA	-	8%	8%
Colombo	1 year	Nil	Placebo	30	27%	3%	47%	10%	23%
			Atenolol	32	22%	0%	31%*	3%	9%
			Propranolol	32	9%*	0%	25%*	3%	13%

*p<0.05

Following the initial report of efficacy of propranolol in reducing rebleeding and mortality after portal hypertensive hemorrhage, two other randomized trials of this therapy were performed. Both trials (see Burroughs et al (76) and Villeneuve et al (77), Table 14) included a significant fraction of Child's Class B and C patients and both trials assessed only effects on variceal hemorrhage. Neither of these trials found any benefit of propranolol therapy in preventing repeat hemorrhage or in improving survival of portal hypertensive patients.

The small size of these two studies makes it possible that a modest benefit of propranolol therapy was missed by a type II error. However, extensive meta-analysis of these trials (80) has suggested that this cannot be the only explanation for the disparity between the positive results of Lebrec et al (75) and the negative results of Burroughs et al (76) and Villeneuve et al (77). It has been suggested that major differences in the composition of the patient populations or other unperceived differences in trial design or execution must be involved. Indeed, benefits of β-blocker therapy in preventing recurrent hemorrhage have been noted in two more recently reported trials in which all ascitic patients and/or all Child's C patients were excluded (see Gatta et al (78) and Colombo et al (79), Table 14). Neither trial showed any significant benefit of propranolol, atenolol, or nadolol in improving survival. However, the small size, and the low control group mortality rate in these trials makes detection of improvement in survival quite difficult. As both trials show apparent trends towards improved survival in β-blocker recipients, it is possible that these conclusions will change after longer follow-up.

After the reports of Burroughs et al (76) and Villeneuve et al (77), most authorities in the field of portal hypertension have expressed a great deal of skepticism regarding the benefits of β-blocker therapy in preventing recurrent variceal hemorrhage. Furthermore, although complications of β-blocker therapy have generally been much less frequent or severe than after endoscopic sclerosis or shunt surgery, some notable complications have been reported. In addition to the expected complaints of asthenia and sexual dysfunction early in the course of propranolol therapy and the occasional precipitation of congestive heart failure or bronchial wheezing, two other forms of complication have been noted. Villeneuve (77) and Burroughs (76) each reported two patients in whom isoprotereal infusions were required to maintain pulse rates and blood pressures in patients with hemodynamically significant bleeds while on propranolol. Only one episode of severe encephalopathy was reported in a propranolol recipient during the course of these five trials. However, in this patient, encephalopathy resolved after discontinuation of the drug and recurred with rechallenge. Other isolated cases of encephalopathy induced by propranolol challenge and re-challenge have been reported as well. Thus, induction of encephalopathy appears to be a rare but true complication of β-blocker therapy. Of note, no other reported detrimental effects of propranolol on hepatic function have been reported. Indeed, two prospective randomized trials have noted a beneficial effect of propranolol therapy on either serum albumin levels (79) or on skin fold thickness (81) in cirrhotic patients. A final particularly insidious complication which may be another potential explanation for the apparent discrepancy between trial results has been reported to occur during propranolol therapy (82,83). An example of this complication may have occurred in patient case #3, detailed in the appendix. A number of authors have noted that within the first days or weeks

after patient or physician initiated propranolol discontinuation, an inordinately high rate of recurrent hemorrhage from varices or gastritis appears to occur (82,83). This suggests that such bleeding might indeed be related to rebound phenomenon in which a hyperadrenergic state induces levels of portal hypertension of even greater severity than existed prior to initial therapy. Thus, inclusion of non-compliant patients with intermittent intervals of excess bleeding risk may negate the benefits of this agent in compliant patients. Some investigators have also noted that an inordinately high percentage of repeat hemorrhages during propranolol therapy occur in non-abstinent alcoholics (79,82). Thus, the careful selection of predictably compliant patients for trial enrollment (75) may have contributed to the success of this therapy in the hands of some investigators.

TABLE 15

PROPHYLACTIC USE OF β-ADRENORECEPTOR BLOCKADE IN PREVENTION OF INITIAL PORTAL HYPERTENSIVE HEMORRHAGE (12-15)

Trial	Length of Follow-up	Patients with Ascites	Patients Enrolled		Incidence of Bleeding			Mortality	
					Variceal	Gastritis	Total	Bleeding	Total
Pascal	2 years	+	Placebo	112	-	-	61%*	16%	49%*
			Propranolol	118	-	-	26%	8%	28%
Italian Multicenter	2.5 years	+	Placebo	89	-	-	37%**	-	~~41%~~ 26%
			Propranolol	85	-	-	26%	-	~~26%~~ 41%
Ideo	2 years	Nil	Placebo	49	16%	6%	22%*	8%	22%
			Nadolol	30	3%	0%	3%	0%	6%
Grace	16 months	Nil	Placebo	51	22%*	-	-	6%	22%
			Propranolol	51	4%	-	-	4%	10%

* $p<0.05$

** $p<0.05$ if all ascitic or all Child's B/C patients excluded.

Overall, propranolol therapy has proven to have relatively low levels of side effects in non-ascitic cirrhotics. In light of the lesser apparent risk of side effects during propranolol versus shunt or sclerosis therapy, a number of groups have now investigated the use of propranolol in prevention of initial variceal hemorrhage. The results of four randomized controlled prospective trials of this therapy have been summarized in Table 15. Of note, all 4 trials have shown efficacy of propranolol in preventing initial portal hypertensive hemorrhages. However, only one study showed a statistically significant benefit of propranolol therapy on survival. It is curious that in this study by Pascal et al (12), statistically significant improvement in survival was most dramatic among Child's C patients. Furthermore, this beneficial effect was dependent not only on a decreased incidence of death from hemorrhage but also on a decreased frequency of death from liver failure. In contrast to the results of Pascal et al (12), the Italian multicenter study (13) noted statistically significant reduction by propranolol in rate of hemorrhage only in Child's A cirrhotics. In

this study and those by Ideo et al (14) and Grace et al (15), a trend towards improved survival in non-ascitic patients on β-blocker therapy was noted but did not achieve statistical significance. Of additional note, the incidence of encephalopathy was 1/118 and 3/85, the incidence of severe hypotension or bradycardia 1/118 and 3/85, and of resistant ascites 0/118 and 3/85 in the two studies giving detailed reports of complications. Thus, unlike shunt surgery or sclerotherapy, propranolol therapy does not appear to exact an excess morbidity or mortality rate which negates the benefits of reduced bleeding rates. Furthermore, in patient populations with low rates of variceal bleeding, arguments can be made that prophylactic propranolol therapy might be of net benefit. It will be of interest to see whether trends towards improved survival among β-blocker recipients in the latter three trials listed in Table 15, indeed, achieve statistical significance during longer term follow-up.

Comparison of Various Forms of Therapy for Prevention of Recurrent Portal Hypertensive Bleeding

An ever increasing number of randomized controlled trials have attempted to compare the efficacy of various forms of therapy designed to prevent recurrence of variceal hemorrhage. The results of such trials have been listed in Tables 16 and 17. In Table 16, the results of trials comparing either distal splenorenal shunt or portacaval shunt therapy with endoscopic sclerotherapy are detailed. The last study listed in this table, that of Cello et al, included only Child's C patients and tends mainly to re-emphasize the bleak outlook which exists in this patient population, regardless of therapy utilized to decrease rate of recurrent hemorrhage. This trial also included extensive analysis of costs of medical care until time of patient death and noted that cost per patient (mean ± SEM) in the sclerotherapy group was $23,077 ± 3,375 while that in the shunt surgery group was $28,043 ± 2,920 (no significant difference). The other three trials which compared distal splenorenal shunt surgery to sclerotherapy generally included patients with much better initial hepatic function.

TABLE 16

COMPARISON OF ENDOSCOPIC SCLEROTHERAPY AND SHUNT SURGERY IN PREVENTION OF RECURRENT VARICEAL HEMORRHAGE: RESULTS OF RANDOMIZED TRIALS

Study	Follow-up	Patients Enrolled	Recurrent Hemorrhage	Spontaneous Encephalopathy	Mortality
Warren (53)	4 years	DSRS 35	3%	16%	40%*
		EVS 36	53%*	12%	16%
Rikkers (84)	25 months	DSRS[a] 27	19%	16%	35%
		EVS 30	57%*	7%	39%
Teres (85)	2-5 years	DSRS 43	14.3%	24%*	29%
		EVS 51	37.5%*	8%	32%
Cello (86)	3.3 years	PCS 32	0%	NA	100%
		EVS 32	38%	NA	85%

NA = Not assessed; DSRS = Distal splenorenal shunt; PCS = Emergent portacaval shunt; EVS = endoscopic variceal sclerosis

[a] Four patients received portacaval shunts

All four series clearly showed that either form of shunt surgery was clearly superior to sclerotherapy in preventing recurrent variceal hemorrhage. However, the only treatment group to demonstrate significantly improved survival in comparison to an alternate therapy was the endoscopic sclerotherapy recipients in the study of Warren et al (53). This survival benefit was attributed by the authors of this study to the greater preservation and/or improvement in hepatic function seen in the patients who did not receive a portacaval shunt during their presenting hospitalization. Of note, 9 of the sclerotherapy group eventually did receive shunt surgery after recurrence of variceal hemorrhage. Only one sclerotherapy patient died as a direct consequence of recurrent bleeding in this trial. In contrast, in the trial of Rikkers et al, 8 patients in the sclerotherapy group died of recurrent hemorrhage including several who died at outlying hospital before transfer back to a University Medical Center could be arranged. Differences in patient access to tertiary medical care in these studies which were performed in a primarily large city (Warren et al) versus small town rural (Rikkers et al) patient populations have been suggested as potential explanations for the differences in outcome in these two trials.

Two trials have now compared the efficacy of sclerotherapy to that of propranolol (see Fleig et al (87,88) and Alexandrino et al (89) in Table 17). Neither has noted a significant difference in overall bleeding rates or mortality rates between patients receiving either of these forms of therapy. While in both studies sclerotherapy was shown to be superior to propranolol in preventing recurrent hemorrhage from esophageal varices, bleeding rates from other sites (gastritis, gastric varices) was higher in sclerotherapy recipients than in propranolol recipients. A Japanese study (90) has compared endoscopic sclerotherapy to transhepatic obliteration of varices and a significant decrease in rate of rebleeding and a significant improvement in survival was noted in recipients of endoscopic sclerotherapy.

TABLE 17

COMPARISON OF PROPRANOLOL AND SCLEROTHERAPY IN RANDOMIZED CONTROLLED TRIALS

Study	Follow-up	Patients Enrolled	Patients with Recurrent Hemorrhage			Mortality
			Esophageal Varices	Other	Total	
Fleig (87,88)	1.5-5 years	P 50	48%*	12%	52%	32%
		EVS 55	31%	27%*	45%	36%
Alexandrino (89)	17-57 months	P 34	62%*	12%	74%	46%
		EVS 31	29%	26%	55%	31%
Terabayashi (90)	36 months	EVS 33	9%	9%	18%	15%
		PTO 33	61%	3%	64%*	58%*
Westaby (91)	6 months	P+EVS 26	-	-	27%	34%
		EVS 27	-	-	30%	26%
Jensen (92)	6 months	P+EVS 15	-	-	20%	NA
		EVS 16	-	-	75%*	NA
O'Connor (93)	2 years	P 31	-	-	65%	81%*
		EVS+P 31	-	-	45%	55%

P = propranolol; EVS = endoscopic variceal sclerosis; PTO = percutaneous transhepatic obliteration

* $p<0.05$

Several studies have begun to assess whether combinations of propranolol and sclerotherapy are superior to use of either therapy alone. In one study, Jensen et al (92) noted a statistically significant advantage to combination therapy over sclerotherapy alone in the prevention of recurrent hemorrhage. However, this difference was not found in the study of Westerby et al (91). Relative rates of esophageal variceal hemorrhage versus bleeding from gastric sources were not clearly delineated in either of these studies. Finally, in a study population composed largely of Child's C cirrhotics, O'Connor et al (93) noted a statistically significant improvement in survival in patients treated with propranolol plus sclerotherapy when compared to those treated with sclerotherapy alone.

Liver Transplantation

One obvious conclusion from the data reviewed thus far is that all therapies aimed primarily at prevention of recurrent variceal hemorrhage have at best a modest beneficial effect on long-term survival in cirrhotic patients with portal hypertensive bleeding. Almost certainly this is related to the fact that the major limiting factor with respect to long-term survival is the extent of underlying liver disease and not the intrinsic risk of variceal bleeding. In some patients, abstinence from alcohol, treatment of iron or copper overload or use of steroids to treat autoimmune liver disease may permit improvement in overall hepatic function but will not, of course, reverse an established cirrhosis. For most patients the only direct way to both relieve portal hypertension and improve level of hepatic function is to perform a liver transplant. Use of liver transplantation in specific treatment of patients presenting with variceal hemorrhage has never been assessed in a prospective manner. However, in the case of Child's C patients with variceal hemorrhage, the choices seem rather straight forward. Even when one considers the selection bias involved in examining the outcome in only those Child's C patients who can be stabilized long enough for a transplant to be arranged, no series of Child's C cirrhotics status post variceal hemorrhage achieves anything close to a 50% 5-year survival following surgical or non-surgical therapy of portal hypertension. As currently quoted 5 year survival rates following adult liver transplantation for various underlying disorders range from 55-85% (94), liver transplantation would appear to be the best option in such patients. Alternatively, many series achieve long-term survival rates in Child's A patients with are equal to or better than that seen after liver transplantation and thus initial use of other therapies seems indicated in this subset of patients. It must be noted, however, that many patients with variceal hemorrhage are not considered to be reasonable candidates for this therapy because of ongoing alcoholism.

Another point which should be made with respect to liver transplantation is that successful outcome of this procedure appears to be very dependent upon good portal venous flow into the transplanted organ. Previous portacaval shunt procedures may make recipient portal vein anastomosis to the donor liver difficult if not impossible. While previous distal splenorenal shunt surgery does not usually prevent subsequent successful liver transplantation, the decreased portal vein caliber and presence of spontaneously formed portosplenic vein shunts may make liver transplant surgery more difficult (96,97). Thus, if a liver transplant appears to lie in a patients' future, most transplant surgeons

recommend that shunt surgery be avoided or if such surgery is performed, they suggest that distal splenorenal shunts be used (96,97).

Recommendations

The field of portal hypertension has been both blessed and cursed by the availability of large numbers of prospective, randomized, controlled trials of therapy. The presence of multiple trials is of benefit in that virtually all therapies have been assessed in multiple clinical settings with varied patient populations. The presence of multiple trials is, however, also a disadvantage in that many small single center trials rather than several large multicenter trials have been performed. Because of the typically small numbers of patients enrolled in these small trials, the chance of missing small levels of benefit or differences in outcome by a type II error is high. Most physicians faced with making a decision regarding therapy in this situation are perplexed by the apparent contradictions present in this literature. Why is it that shunt surgery is clearly the best, definite approach to prevention of initial or recurrent portal hypertensive hemorrhage, yet shunt surgery is the only form of therapy in which prolongation of survival has never been demonstrated by scientifically valid techniques? Why is it that in every case in which a therapeutic approach has been shown to be of survival benefit, another, equally well designed and executed study can be produced which demonstrates no apparent benefit from this therapy? In my reading of this literature, I have reached three general conclusions which I think at least partially explain these apparent paradoxes. These are:

(1) Hemorrhage alone is not the major contributing factor to poor long-term survival in most patients with portal hypertensive bleeding. For most patients, the major predictor of mortality is the extent and activity of underlying liver disease.

(2) The adjectives "small" or "modest" are probably the most appropriate terms in describing the survival benefits afforded by presently available therapies for prevention of portal hypertensive bleeding. Thus, the difficulty in consistently demonstrating benefit in small trials is to be expected.

(3) Finally, the individual skills and enthusiasm of the physician involved as well as the demographic characteristics of the patients enrolled probably do play a role in the variability in outcome of apparently similarly designed prospective, randomized controlled trials.

Physicians can respond in a variety of ways to the conflicting nature of the results of the clinical trials reviewed in this grand rounds. One can take a nihilistic approach and decide that since no therapy has been consistently shown to be of benefit in prolonging survival, and since all therapies induce significant complications, we should only provide general supportive care for such patients. In response to this, it should be noted that in patients who have had an initial variceal hemorrhage, no study has ever shown that shunt surgery, sclerotherapy or β-blocker therapy actually decreases survival and many studies have shown efficacy with respect to decreased bleeding or prolonged survival. Because of the apparently conflicting nature of the results of trials attempting to compare efficacy of various forms of therapy, it is relatively easy to

selectively quote studies which indicate that the efficacy of portacaval shunt surgery = efficacy of distal splenorenal shunt surgery = efficacy of sclerotherapy = efficacy of propranolol. It is therefore tempting to believe that we are faced with the equivalent of "dealer's choice" with respect to therapy selection, and it is therefore acceptable for surgeons to recommend shunt procedures in all patients, for gastroenterologists to sclerose every varix in sight, and for the die-hard internist to either push Inderal or to plead "primum non nocere" and do nothing. My response to this viewpoint is that, in fact, there is a considerable amount of data upon which one can begin to make decisions regarding selection of the therapeutic approach for individual patients. From reviewing the studies detailed in this grand rounds and carefully considering the opinions expressed by the multiple "experts" who have written recent reviews on this topic, my approach to therapy selection can be summarized as follows:

(1) With the exception of a single trial of propranolol therapy, all studies showing survival benefit following therapeutic intervention after variceal hemorrhage have incorporated use of emergent sclerotherapy in the acute management phase. Endoscopic sclerotherapy is a treatment modality which can be employed readily in virtually all categories of patients and, therefore, probably should be used routinely in the initial management and stabilization of patients presenting with variceal hemorrhage.

(2) Almost all the data summarized in this review addresses treatment of complications of portal hypertension in the cirrhotic. However, in initial evaluation of a patient with an apparent portal hypertensive bleed, it is important to assess the etiology of the patient's disease. Does he have a more localized form of portal hypertension, such as that caused by splenic vein thrombosis, which can be easily managed by more limited approaches such as splenectomy? Does the patient have intrinsic liver disease or does he have extrahepatic portal hypertension? Even if the patient has portal hypertension initially caused by cirrhosis, has he maintained patency in his portal vein? What is the extent of his underlying liver, and to what extent can it be improved by abstinence from alcohol, nutritional support, or treatment of metal storage or autoimmune liver disease? Once such an initial evaluation has been performed, the approach to patients with different degrees of hepatic dysfunction should probably be individualized as follows:

Child's C patient. If a patient is a solid Child's C with little hope for immediate improvement in liver function, the first question to address is whether the patient is a transplant candidate. If the answer is yes, then one should arrange for a liver transplant. If not, I would probably proceed with chronic sclerotherapy and supportive care. Shunt surgery of any form is likely to only hasten the deterioration of liver function in such patients, and the presently available data suggest that propranolol will probably cause more harm than benefit.

Child's A patient. Such a patient is not yet ready for a transplant unless all reasonable efforts to control recurrent hemorrhage fail. If the patient has active liver disease (i.e. active alcoholic hepatitis, etc.), I would follow the advice of Warren et al (53,95) and proceed with chronic sclerotherapy while encouraging abstinence from alcohol and/or evaluation

and treatment, if possible, of the patient's underlying liver disease. If the patient has inactive Child's Class A cirrhosis, then there are some valid reasons to consider all therapeutic options. In discussing these options with the patient, I would inform him of the risk/benefit ratios of each therapy. If I were the patient, I would rank life itself and a clear mind as my number 1 and number 2 criteria for a good outcome, and I would proceed with chronic sclerotherapy. If there is any reason to suspect that gastric varices and/or hypertensive gastropathy might be contributing to bleeding risk, an argument can be made to add β-blocker therapy as well. I would, however, avoid use of propranolol in patients likely to be noncompliant.

If repeated and/or massive rebleeding occurs on sclerotherapy/propranolol, I would propose shunt surgery as an option. My first choice of surgical therapy at this point would be a distal splenorenal shunt performed by a methodical and experienced surgeon. If a patient is anatomically unsuited for a splenorenal shunt and recurrent bleeding were frequent and massive, I would probably give careful consideration to a liver transplant rather than opt for a non-selective shunt procedure.

There are clearly individual cases of Child's A/B cirrhotics in which good arguments can be made for different approaches. One major philosophical consideration has to do with the fact that for 80+% of such patients, shunt surgery tends to be a one-time quick and permanent fix. Sclerotherapy, on the other hand, may seem like a life sentence of repeated physician visits, tube swallowing, dysphagia, and occasional trips to the emergency room for hopefully small recurrent bleeds. Even propranolol may cause depression, sexual dysfunction, and if one does not pay careful attention to compliance, may leave a patient vulnerable to paradoxically increased periods of bleeding risk following even brief intervals off the medication. For some patients, especially those living in areas remote from ready access to gastroenterologic or surgical care, it may not be unreasonable to consider shunt surgery as an early option. However, one must be honest in informing such patients of the lack of proven survival benefit following this therapeutic approach and in advising the patient of the very real risk, even in Child's A patients, of trading off bleeding risk for the risk of developing chronic encephalopathy.

Child's B patient. This is the most difficult patient to assess with respect to risk/benefit of pursuing early liver transplantation. In some studies (see Table 5), Child's B patients seem to have a lesser 3-5 year survival than do adult recipients of liver transplants. However, one must not forget that there will usually be at least a several week delay between an initial bleed and performance of transplant surgery. When one makes adjustments for this selection bias (see Figure 2), the survival rates appear much more similar. Furthermore, in most series of Child's B variceal bleeders, some deaths undoubtedly occur from hepatic failure in patients who have progressed gradually to Child's C status. A present best approach to such patients might be to temporize with sclerotherapy while getting to know the patient and his disease. If at any point the patient appears to be Child's B(-) with ongoing deterioration, I would explore the option of liver transplantation if the patient is a reasonable candidate.

Otherwise, I would treat the patient much like the hypothetical Child's A patient detailed above.

What About the Cirrhotic with Varices that Have Not Yet Bled?

At present, all thoughts of prophylactic shunt surgery or sclerotherapy should be discouraged. However, the recent data regarding prophylactic β-blocker therapy seems very promising. A major problem to consider in implementing such an approach is the difficulty in deciding which patients should be screened and how they should be screened. As only one of four trials actually demonstrates a significant survival benefit, since screening is likely to be expensive, and because only a small subset of patients with varices can be expected to benefit, it is probably wise at this point to wait for further data from these trials before initiating widespread implementation of prophylactic propranolol therapy in cirrhotic patients with varices.

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APPENDIX

Patient Case #1

J.B. presented to a local hospital in 6/88 at age 51 with hematemesis. Endoscopy revealed bleeding esophageal varices. He received a 6 unit transfusion of packed RBC's and stabilized. Evaluation revealed cirrhosis of unknown etiology. The patient had no history of ethanol abuse. Two months later he was admitted to Parkland Memorial Hospital to be evaluated for a shunt procedure. Admission laboratory evaluation revealed a total bilirubin of 1.7 mg/dl, alkaline phosphatase of 348, AST of 39, albumin of 3.9 mg/dl and prothrombin time of 12.5 seconds. He had no ascites and no history of encephalopathy. On 8/3/88 a side-to-side portacaval shunt was performed. Mild confusion was noted postoperatively but he was felt to be ready for discharge on the 6th postoperative day. Ten days later the patient presented with confusion and asterixis. No evidence was found for infection or bleeding. Arterial ammonia levels were markedly elevated. He initially appeared to respond well to lactulose and a low protein diet. However, even on chronic lactulose therapy and a protein restricted diet, he has continued to have intermittent episodes of confusion over the past seven months and has been unable to return to work.

Patient Case #2

D.H. presented in 1980 at age 41 with variceal hemorrhage which was felt to be related to alcoholic liver disease. In 1981 a distal splenorenal shunt procedure was performed. The patient remained abstinent from alcohol and did well for 7 years. In 1988 he presented with confusion, asterixis and an arterial ammonia level of 240 mg/dl (normal <80), total bilirubin of 0.4, alkaline phosphatase of 67, AST of 81, albumin of 4.2 g/dl, prothrombin time of 11.5 seconds. There was no evidence of gastrointestinal hemorrhage or infection. On chronic lactulose therapy the patient has managed to maintain full-time employment, but continues to note periods of slowed mentation.

Patient Case #3

M.R. presented in 1982 with variceal hemorrhage felt to be secondary to alcoholic liver disease. Initial liver function testing revealed a total bilirubin of 3.7 mg/dl, albumin 2.8 g/dl, and prothrombin time of 14 seconds. The patient refused sclerotherapy and was begun on propranolol therapy. The patient discontinued all ethanol intake and remained compliant with medication use and medical follow-up for the ensuing 4 years. At this point she developed hypoxemia which was eventually attributed to intrapulmonary shunting. However, because of concerns about some element of bronchospasm, propranolol was discontinued. Within one week the patient noted onset of melena which persisted for three days. She did not seek immediate medical evaluation but subsequent endoscopic assessment revealed that esophageal varices were the only likely source of bleeding. Another episode of variceal hemorrhage occurred several months later. The patient was enrolled in a chronic sclerotherapy program and has had no further bleeding during an additional three years of follow-up. The patient does, however, complain of chronic dysphagia. Current liver function tests include a total bilirubin of 1.8 mg/dl, serum albumin of 3.3 g/dl, and a prothrombin time of 13.8 seconds.