

Pharmacologic Treatment of Portal Hypertension: Past, Present, and Future

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This is the 50th anniversary of the founding of the American Association for the Study of Liver Diseases. The celebration of the Society is also a celebration of the accomplishments of its members and others in the field of hepatology. Viral hepatitis and liver transplantation are clearly two areas in which there has been an explosion of knowledge leading to dramatic changes in how we manage patients with liver disease. Similarly, our understanding of portal hypertension and its complications also has changed, especially during the last 2 decades. One of the most significant advances has been the development of drug therapy for portal hypertension. To understand how far we have come, it is helpful to review where we were preceding the seminal observation in 1980 by Lebrecht et al.,¹ that an oral medication could lower portal pressure chronically. The impact of their finding on the management of patients with varices is the focus of this report. Pharmacologic therapies that prevent both the first episode of variceal bleeding as well as recurrent bleeding will be discussed; however, treatment of actively bleeding varices will be touched on only lightly. The status in 1980 of treatment of esophageal varices will be reviewed first. The current treatment of varices then will be discussed, followed by some thoughts on the potential for new pharmacologic therapies. The reader who is interested in more thorough discussions of current therapies for gastroesophageal varices is referred to several recent reviews.²⁻⁴

YEAR 1980

Drug therapy for portal hypertension in 1980 was limited to the intravenous use of agents, such as vasopressin, during an acute bleeding episode. Vasopressin lowers portal pressure by causing vasoconstriction in the splanchnic bed thereby decreasing portal flow. When vasopressin is given, decreases in portal pressure are modest (10% to 44%) and decreases in hepatic blood flow are slightly greater (33% to 54%). The efficacy of drugs such as vasopressin in controlling variceal bleeding was controversial, but most felt the use of vasopressin was associated with cessation of bleeding. Somatostatin also was being investigated as an agent to control acute

variceal bleeding.⁵ Other therapies used in the acutely bleeding patient were balloon tamponade, transhepatic embolization of varices, endoscopic sclerotherapy, surgical shunts, and various devascularization procedures.⁶⁻⁸

Although drugs were used in the patient with acutely bleeding varices, the prevention of bleeding was thought to require obliteration of the varices endoscopically, by transhepatic thrombosis of the varices or by surgical decompression of the portal venous system. Devascularization procedures or esophageal transection were used in patients who were not candidates for the above approaches (Table 1). Earlier studies had shown that portacaval shunts should not be used as primary prophylaxis in patients with varices.⁹ Because of the latter findings, in 1980 the only patients being entered into controlled trials were those who had bled at least once from their varices.

Sclerotherapy of esophageal varices was described in 1939. It received limited attention despite published data showing benefit until the late 1970s.¹⁰ Terblanche et al. in 1979 and Clark et al. in 1980 published 2 controlled trials showing that sclerotherapy was effective in preventing recurrent bleeding from varices.^{11,12} Their observations, plus improvements in the flexible endoscope, established sclerotherapy as an effective method for the treatment of acute and recurrent bleeding from varices. Surgical shunts were an established method for the control of recurrent bleeding in patients who had bled at least once from varices.⁶⁻⁸ The major debate at that time was whether the distal splenorenal shunt was better than the portacaval shunt in managing patients who had bled at least once from varices.¹³

Perhaps the best way to assess how patients with cirrhosis and varices were being managed in 1980 is to look at what textbooks included in chapters on portal hypertension. Two textbooks were published in 1982: Schiff's *Diseases of the Liver* and Zakim and Boyer's *Hepatology: A Textbook of Liver Diseases*. In the two chapters in Schiff's book on portal hypertension and cirrhosis and the chapter in Zakim and Boyer's book on portal hypertension, only shunts and to a lesser extent esophageal sclerotherapy and transhepatic thrombosis of varices were discussed as the way to prevent recurrent bleeding from esophageal varices.⁶⁻⁸ Similarly, 349 articles dealing with portal hypertension were published in 1979 to 1980. There were 57 articles on portacaval shunts, 21 articles on transhepatic thrombosis of varices, and only 11 articles on sclerotherapy (data were obtained from a Medline search using the subject headings "portal hypertension" and "adrenergic beta antagonists" or "portacaval shunts," "sclerotherapy," or "transhepatic thrombosis"). At the end of the 1970s, a surgical portal-systemic shunt was the procedure of choice in preventing recurrent bleeding from gastroesophageal varices.

Abbreviations: WHPV, wedged hepatic vein pressure; TIPS, transjugular intrahepatic portosystemic shunts; ET, endothelin receptors.

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TABLE 1. Therapies for the Primary and Secondary Prevention of Variceal Bleeding

Indication		1980	2000
Primary	None		Medical
			β -blockers Oral nitrates Banding
Acute	Medical		Medical
		Vasopressin	Octreotide/somatostatin
		Balloon tamponade	Vasopressin/nitrates
		Endoscopic sclerosis	Terlipressin Endoscopic therapy Balloon tamponade* TIPS
Secondary	Surgical		Surgical
		Emergency shunt/devascularization	Emergency shunt/devascularization*
		Medical	Medical
			Sclerotherapy Transhepatic thrombosis
Surgical	Shunts	Shunts	
	Devascularization*	Devascularization*	
	Esophageal transection*	Esophageal transection*	

*Use limited to patients with uncontrolled bleeding, failed TIPS, or with portal and splenic vein thrombosis.

As mentioned previously, somatostatin was known to lower portal pressure, and one theory for this effect was that it caused a fall in cardiac output.⁵ Beta-blockers were known to lower cardiac output. Therefore, Lebrec et al. administered propranolol intravenously to 6 patients with cirrhosis to determine if this agent would lower portal pressure. They observed that cardiac output fell 32%, and corrected wedged hepatic vein pressure (WHVP) fell 19%.⁵ The same group next administered propranolol orally to 8 cirrhotic patients at increasing doses until their heart rate was reduced by 25%. Another 8 patients received a placebo. WHVP was measured before and 1 month after the administration of propranolol or placebo. The WHVP decreased in all treated patients with an average decrease of 25%. There was no change in the corrected WHVP in the control group. From this small study the investigators concluded that "this effect of propranolol might be useful in preventing recurrent bleeding due to ruptured oesophageal varices in patients with portal hypertension."¹ The observations of Lebrec et al.¹ in concert with the findings of Groszmann et al. that intravenous nitroglycerin also lowers portal pressure,¹⁴ set the stage for how we currently use drugs to prevent bleeding from esophageal varices.

YEAR 2000

Within 1 year of the first report by Lebrec et al. that propranolol lowers portal pressure, a controlled trial was published showing that propranolol also significantly reduced the risk of rebleeding from esophageal varices.¹⁵ That initial trial contained 74 patients. Twenty years later, thousands of patients have been entered into studies, which examined the efficacy of numerous treatments in the primary and secondary prevention of bleeding from gastroesophageal varices.²⁻⁴ β -Blockers have been compared with placebo, oral nitrates, and endoscopic therapy for primary prevention of bleeding

and with placebo, nitrates, endoscopic therapy, and transjugular intrahepatic portasystemic shunts (TIPS) in the secondary prevention of bleeding. It is a testimony to the hepatology community at large that so many controlled trials have been performed to define the role of β -blockers and other therapies in the prevention of bleeding from gastroesophageal varices. It is important to note that the effective lowering of portal pressure by β -blockers requires blockade of both β_1 -cardiac receptors and β_2 -splanchnic receptors.^{2,16,17} Therefore, only nonselective β -blockers (propranolol, nadolol, and timolol) are effective in lowering portal pressure significantly, and it is the first two agents that have been used in the controlled trials.

Primary Prophylaxis

At least 9 controlled trials comparing nonselective β -blockers as primary prophylaxis for varices to controls who received no active treatment have been published.^{2,4} Based on meta-analysis, there is a significant decrease in the adjust risk difference for bleeding and a smaller, but not significant, decrease in mortality in the β -blocker-treated patients. Ten patients need to be treated to prevent one episode of bleeding. If only studies in which medium or large varices are included in the analysis then the effect of β -blockers on the bleeding rate is greater and the number treated to prevent an episode of bleeding is reduced to 8. The reason β -blocker therapy is not more effective is because as many as two thirds of the patients do not respond to treatment with a 20% decrease in portal pressure or a decrease in the portal-hepatic vein gradient to below 12 mm Hg.^{3,17} If the portal-hepatic vein gradient does not fall at least 20% or to less than 12 mm Hg, then the use of β -blockers is ineffective in preventing bleeding.² There are no noninvasive tests available that measure the response of portal pressure to therapy in an accurate and reproducible manner. Only by performing a WHVP measurement twice, which requires catheterization of the femoral vein, can the response to therapy be determined. Identifying and treating only those patients who responded to therapy would increase the efficacy of β -blocker therapy. However, the invasive nature of the WHVP measurement and its cost make this an impractical approach at this time.

A cost-effectiveness analysis of primary prophylaxis with β -blockers has been performed.¹⁸ Treatment with propranolol was shown to be cost effective compared with no treatment in all groups as defined by Child's status and size of varices. Use of sclerotherapy or surgery in these patients was not cost effective. When the cost for patients with high- or low-risk varices and good or poor hepatic function was estimated, it was the Child's class C patient with high-risk varices who was most likely to benefit from therapy. For example, if one treats a group of Child's class A cirrhotic patients with low-risk varices, 50 patients need to be treated at a cost of \$76,640 to prevent 1 episode of bleeding. In contrast, treating a group with Child's class C cirrhosis and high-risk varices, only 5 need to be treated at a cost of \$12,775 to prevent 1 episode of bleeding.

Oral nitrates have also been used to lower portal pressure and decrease bleeding from varices. Nitrates alone lower portal pressure, and when given in combination with β -blockers, the fall in portal pressure is greater than with β -blockers alone.^{14,19} Nitrates appear to be as effective as β -blockers in preventing bleeding, although the number of studies is quite small and there is concern about an increase in mortality in

the nitrate-treated patients.² There are a number of studies comparing the combination of oral nitrates (isosorbide-5-mononitrate) plus β -blockers against β -blockers alone. Analysis of these studies shows a small increase in efficacy of combination therapy (a difference of 5%) with a significant increase in the incidence of side effects in the combination therapy groups.^{2,3} More recently, a long-term study of combination versus monotherapy suggests that combination therapy may be better with no increase in side effects.²⁰ Further studies are required to prove that nitrates add significantly to the efficacy of β -blockers. A recent report suggests that variceal ligation is better than β -blockers in the prophylaxis of varices.²¹ However, the number of patients in the study was small (89) and the bleeding rate on β -blockers was high (43%) compared with other studies that average about 15%.² Therefore, more studies are required before band ligation replaces β -blockers as the initial form of treatment.²² Finally, the effect of pharmacologic therapy on the risk of bleeding from large gastric varices is unknown. If large fundal varices are found, then treatment with β -blockers is warranted pending the publication of studies that define better how to manage these patients.

Based on the above studies the following recommendations are made (Fig. 1). Patients who are at risk for large varices should be screened. A recently published report suggests that patients with cirrhosis, splenomegaly, and/or a platelet count of less than 88,000 are most likely to have large varices and therefore are an appropriate group to endoscope.²³ If medium or large varices are found then the patient should be treated with a nonselective β -blocker as long as there are no contraindications to their use. The dose of the β -blocker should be adjusted to reduce the heart rate by 25%. Depending on the Child's class of the patients, between 5 and 14 patients need to be treated to prevent 1 episode of bleeding.¹⁸ If the patient bleeds while on β -blocker therapy, then banding of the varices should be instituted. Once the varices are eliminated the patient should remain on a β -blocker because variceal recurrence may be slowed.³¹ If there is a contraindication to the use of β -blockers then I feel esophageal variceal ligation is the preferred form of treatment. Combination therapy, β -blocker plus oral nitrate, does not appear to be warranted at this time

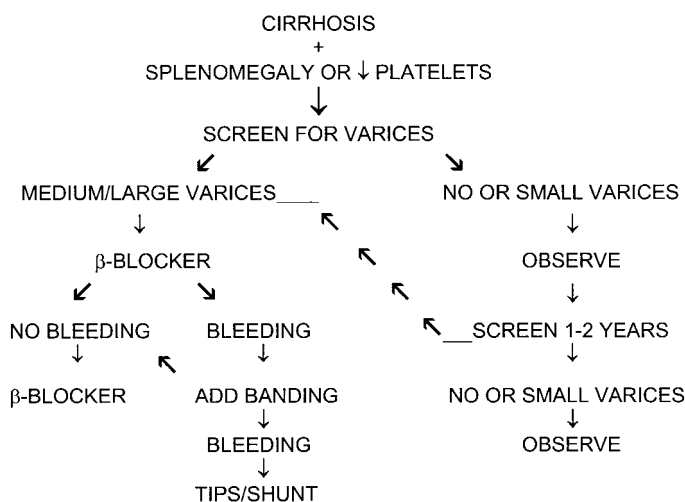


FIG. 1. Approach to primary prophylaxis of varices. For patients undergoing banding, β -blockers are continued following obliteration of the varices.

given the small decrease in risk of bleeding and the increase in side effects. The use of β -blockers in cirrhotic patients with no or small varices also is not warranted. There is no compelling evidence that the use of β -blockers prevents or slows the development of varices (there are ongoing studies of this issue). If patients are found to have no or small varices, then a repeat endoscopy in 1 to 2 years is appropriate. If the varices are again small or absent, then it is unclear whether and when further endoscopies are required.²⁴

Acute Bleeding

A complete review of treatment of the patient bleeding actively from varices is beyond the scope of this review. In 1980, the only drug widely used for the treatment of acutely bleeding varices was vasopressin.⁵ Subsequent studies showed that adding intravenous nitroglycerin caused a further decrease in portal pressure¹⁴ and decreased the side effects of vasopressin.^{3,4} Triglycyl-lysl-vasopressin (terlipressin) is a long-acting form of vasopressin that has fewer side effects. Terlipressin is an effective agent in controlling variceal bleeding.⁴ One study found that giving terlipressin with glyceryl trinitrate while the patient with bleeding varices was being transported to the hospital decreased bleeding and improved survival.²⁵ However, the control patients received no therapy for 12 hours (average time to endoscopy was about 17 hours), and it is unclear whether early therapy or no therapy was the critical determinant of which patients rebled during the first 12 hours. Perhaps the most important role for terlipressin is its reported positive effect on renal function in patients with the hepatorenal syndrome.²⁶ Terlipressin is an effective agent for treating complications of portal hypertension and is quite popular in Europe but unfortunately it is not available in the United States. The two agents that are now used most commonly in the actively bleeding patient in the United States are somatostatin and octreotide. Both lower portal pressure and decrease azygous blood flow (although the effects are rather transient) and have an efficacy in controlling bleeding that is similar to vasopressin and terlipressin.^{3,4,27} Both drugs have been used for several days in hospital while patients are undergoing sclerotherapy/banding and rebleeding rates are lower in the patients receiving combination therapy. However, there remains significant uncertainty as to the relative efficacy of these two drugs.²⁷ Their major advantage is a lack of serious side effects as compared with vasopressin. Sclerotherapy and esophageal variceal ligation are also effective in controlling bleeding.²⁸

Currently, patients with acute bleeding are treated with intravenous somatostatin or octreotide preceding endoscopy. During endoscopy, if actively bleeding varices are found or if there is evidence of recent variceal bleeding, either banding (preferred) or sclerotherapy is performed. If the bleeding cannot be controlled or rebleeding occurs, then a TIPS is performed. Emergency surgical shunts are associated with a high mortality⁴ and should not be performed except in patients with excellent liver function.

Secondary Prophylaxis

At least 12 controlled trials comparing β -blockers to inactive treatment in the prevention of recurrent bleeding from varices have been published. Based on a meta-analysis, the use of β -blockers was associated with a 21% decrease in the risk of bleeding, a 7% decrease in mortality, and a need to treat 5 patients to prevent 1 episode of bleeding.² The decrease in risk

of bleeding and mortality are significant.^{2,29} Treatment with β -blockers is as effective as treatment with sclerotherapy in the prevention of rebleeding with less severe side effects.^{2,4,28} The combination of β -blockers and nitrates also appears to be better than endoscopic therapy.³⁰

There is some uncertainty on whether or not to use β -blockers in patients undergoing sclerotherapy/banding. As β -blockers and sclerotherapy/banding attack the problem at different levels, it is tempting to believe that the combination would be better than either alone. When β -blockers have been used with or without sclerotherapy, the rebleeding rates are significantly higher in those who received β -blockers alone with no change in survival. Similarly, when sclerotherapy with or without β -blockers is studied there is a significant decrease in the rate of rebleeding in those who received combination therapy.^{2,4,28} Finally, the use of β -blockers plus sucralfate in patients undergoing banding reduces the rebleeding rate from 18% to 7%.³¹ The difficulty is that there is significant heterogeneity in the different studies making it difficult to reach firm conclusions. Combination therapy is not worse and probably better than monotherapy, especially if patients are undergoing sclerotherapy/banding as their primary form of therapy. It is less clear whether the small decrease in rebleeding rates achieved by adding sclerotherapy/banding to the treatment regimen of patients already receiving β -blockers as monotherapy is worth the significant increase in cost. Lastly, long-term (days to 6 months) octreotide administration has been used in combination with sclerotherapy in the prevention of rebleeding. Rebleeding tended to be lower in the octreotide-treated patients but no comparison with combination therapy with β -blockers was made.²⁷ The cost of octreotide makes this a poor alternative to β -blockers pending further studies.

The following recommendations are made for the prevention of rebleeding from esophageal varices in patients with cirrhosis (Fig. 2). β -blockers alone significantly reduce the risk of rebleeding from esophageal varices, improve survival, and should be prescribed for all patients who lack a contraindication to their use. Many experts feel β -blockers alone are adequate as initial therapy.² Not only do β -blockers reduce the risk of bleeding from esophageal varices but they also reduce bleeding from portal hypertensive gastropathy. However, many patients receive endoscopic therapy at the initial bleed and it is tempting to eradicate the varices endoscopically once the process has been begun. If the patient's physician chooses to use endoscopic therapy, then I recommend the

following approach be taken: First, banding is clearly superior to sclerotherapy and should be the procedure of choice.^{28,32} Second, when comparing sclerotherapy/banding to sclerotherapy/banding plus β -blockers, combination therapy is always associated with less rebleeding compared with monotherapy without an improvement in survival.^{2-4,28,31} For example, the average difference in the risk of rebleeding for sclerotherapy versus sclerotherapy plus β -blockers is 10% and for banding versus banding plus β -blockers is 11%.^{4,31} As there is a significant risk of dying associated with a variceal bleed and the side effects of β -blockers are generally mild, it would seem prudent to use combination therapy in these patients. In addition, the use of β -blockers will reduce the risk of bleeding from portal hypertensive gastropathy and may slow the redevelopment of varices.³¹ Therefore, I believe that patients undergoing variceal ligation should also be treated with a β -blocker. In addition, the β -blocker should be continued indefinitely, *i.e.*, even after the varices have been obliterated. Whether adding sucralfate or oral nitrates to the mix adds to the efficacy of the above two treatments remains unclear at this time. Finally, there is little information of the efficacy of β -blockers in the prevention of rebleeding from gastric varices. Although injection of gastric varices with Bucrylate is reported to be effective,²⁸ Bucrylate is not available in the United States and currently, if a patient bleeds from gastric varices, either a TIPS or surgical shunt should be performed.

FUTURE

The work during the last 2 decades has shown that it is possible, using oral medications, to lower portal pressure significantly and for long periods of time. In addition, the decrease in portal pressure is associated with a reduced risk of bleeding both in patients who have never bled and those who have bled at least once from varices. The therapies have also been shown to be cost effective. Unfortunately, the impact of treatment on survival has been less dramatic, but if patients who truly responded to therapy could be easily identified, then efficacy would be improved and survival probably enhanced. We need to continue to search for noninvasive methods to accurately measure portal pressure. Newer agents are also being developed. For example, carvedilol, is a nonselective β -blocker with anti- α 1-adrenergic activity. This new agent causes a greater decrease in portal pressure than does propranolol but also causes a greater decrease in systemic pressure.³³ Other pharmacologic agents that have been used include: clonidine, diuretics, verapamil, pentoxifyline, and

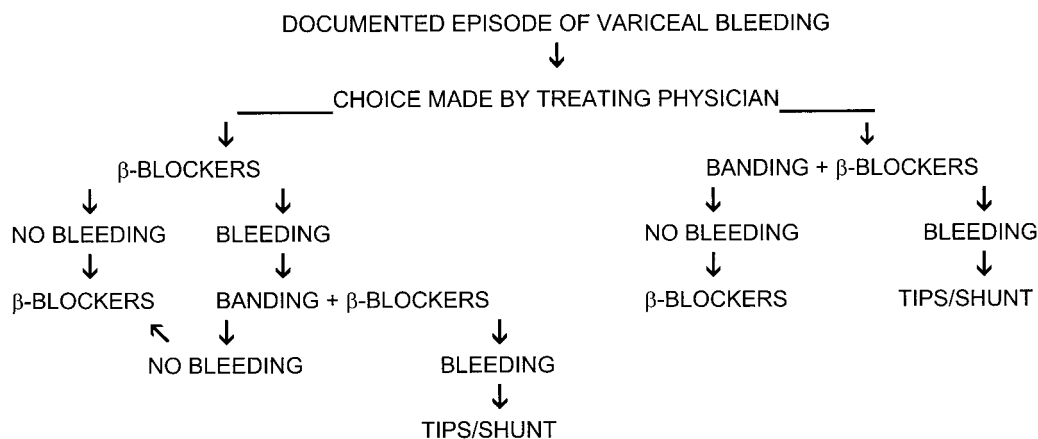


FIG. 2. Approach to secondary prophylaxis of varices. See Fig. 1.

metoclopramide to name a few.³ Whether these newer agents will prove to be more effective than currently available agents remains to be established.

The areas of investigation that are likely to lead to new paradigms for the pharmacologic treatment of portal hypertension are studies of agents such as endothelins. Endothelins are a group of compounds that are potent vasoconstrictors. They bind to 2 different types of receptors termed ET_A and ET_B. Binding of endothelins to ET_A receptors on vascular smooth muscle cells leads to vasoconstriction, whereas binding to ET_B receptors on endothelial cells leads to release of nitric oxide and vasorelaxation.³⁴ Levels of endothelin are increased in cirrhotic patients, especially those with ascites.³⁵ Infusion of endothelin into isolated perfused rat livers leads to an increase in portal pressure.³⁶ Hepatic stellate cells, on activation, become myofibroblasts, express ET_A and ET_B receptors and contract on exposure to endothelin 1.^{34,36} These and other data suggested that endothelins may increase portal pressure in liver disease by binding to hepatic stellate cells leading to their contraction and an increase in resistance within the liver microcirculation. In support of this idea are the findings that the acute administration of an ET_{A/B} antagonist leads to a fall in portal pressure in cirrhotic rats.³⁷ Chronic administration of an ET_{A/B} antagonist in an animal model, however, failed to lower portal pressure.³⁸ In addition, administration of an ET_A receptor antagonist to cirrhotic rats reduces collagen accumulation,³⁹ suggesting the effects of blockade of endothelin receptors may have more pronounced effects on fibrosis compared with vascular resistance. Studies in humans using these receptor antagonists are awaited.

There also is intense interest in the role nitric oxide plays in portal hypertension as well as the hyperdynamic circulation. The reader is referred to excellent reviews on this subject.^{40,41} Nitric oxide overproduction appears to contribute to the development of the hyperdynamic circulation. This conclusion is based on the findings in humans that, in exhaled air, levels of nitric oxide are increased in cirrhotic patients before but not after liver transplantation. The exhaled levels of nitric oxide correlate with cardiac index.^{42,43} Patients with cirrhosis have increased plasma concentrations of nitric oxide as well, and the splanchnic bed appears to be the principle source of the nitric oxide.⁴¹ Finally, in animals, blockade of nitric oxide synthesis ameliorates the hyperdynamic state.^{40,41}

In contrast to the belief that the nitric oxide is overproduced in the splanchnic bed and systemically contributes to the hyperdynamic circulation, in the portal system it is believed there is an underproduction of nitric oxide, which makes the portal hypertension worse.⁴⁰ The release of nitric oxide is reduced from the endothelial cells of cirrhotic animals, especially in the face of increased levels of endothelin 1.^{40,44} If this relative nitric oxide deficiency could be corrected, then there should be a decrease in portal pressure. Recently, nitric oxide synthase was overexpressed in normal and cirrhotic rat livers. Overexpression of nitric oxide synthase was associated with an increase in nitric oxide levels and a decrease in intrahepatic resistance and portal pressure in cirrhotic animals.⁴⁵ It is unclear whether gene therapy will be a practical approach for the treatment of portal hypertension in humans; however, this work does suggest that targeted increases in nitric oxide levels in the portal circulation could be used to lower portal pressure. If drugs, such as nitrates, can be developed that increase nitric oxide levels in the portal

system without spillover into the systemic circulation, then new therapies will be possible.

In conclusion, pharmacologic therapy of portal hypertension has come of age. In contrast to 20 years ago when we believed that prophylactic therapy of varices was not possible, we now have excellent therapies that reduce the risk of the initial bleed from varices. We also know which patients are most likely to benefit from pharmacologic therapy. Unfortunately, we lack a noninvasive method for measuring portal pressure, which if available, would allow for better management of our patients. For example, if a patient was started on a β -blocker and failed to respond, then oral nitrates could be added. We also have to resolve whether pharmacologic therapy is better than endoscopic banding of varices in patients who have never bleed from their varices. The pharmacologic treatment of acutely bleeding varices has also improved. We now control bleeding with drugs that have fewer side effects than vasopressin. In addition, the effectiveness of endoscopic therapy and use of TIPS in the refractory patient has made the management of these sick patients much more effective. The situation for the prevention of rebleeding from varices is even better. Pharmacologic therapy has clearly reduced the incidence of rebleeding from varices and improved survival as well. We still remain uncertain as to the primary role of endoscopic versus pharmacologic therapy, but further studies are sure to resolve this issue. We do need further trials on which is better, TIPS or shunts, for the management of patients who fail pharmacologic and endoscopic therapy yet still have good hepatic function. Finally, with the research that is ongoing as to how portal vascular resistance is controlled, there is no doubt new drugs will be developed that will lower portal pressure. The future for the pharmacologic treatment of portal hypertension has never been brighter.

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REFERENCES

1. Lebec D, Nouel O, Corbic M, Benhamou J-P. Propranolol—a medical treatment for portal hypertension? *Lancet* 1980;2:180-182.
2. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999;19:475-505.
3. Luketic VA, Sanyal AJ. Esophageal varices. I. Clinical presentation, medical therapy and endoscopic therapy. *Gastroenterol Clin North Am* 2000;29:337-326.
4. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *HEPATOLOGY* 1995;22:332-353.
5. Benhamou J-P, Lebec D. Drug therapy of portal hypertension due to cirrhosis. *Semin Liver Dis* 1982;2:227-232.
6. Reynolds T. Portal hypertension, In: Schiff L, Schiff ER, eds. *Diseases of the Liver*. 5th ed., Philadelphia: Lippincott 1982;393-431.
7. Conn HO. Cirrhosis, In: Schiff L, Schiff ER, eds. *Diseases of the Liver*. 5th ed., Philadelphia: Lippincott 1982;847-977.
8. Boyer TD. Portal hypertension and its complications, In: Zakim D, Boyer TD, eds. *Hepatology: A Textbook of Liver Diseases*. 1st ed., Philadelphia: Saunders 1982;464-499.
9. Conn HO, Lindenmuth WW, May CJ, Ramsby GR. Prophylactic portacaval anastomosis. A tale of two studies. *Medicine* 1972;51:27-40.
10. Terblanche J, Bornman PC, Jonker MAT, Kirsch RE, Saunders SJ. Injection sclerotherapy of esophageal varices. *Semin Liver Dis* 1982;2:233-241.
11. Terblanche J, Northover JMA, Bornmann P, Kahn D, Silber W, Barbezat GO, Sellars S, et al. A prospective controlled trial of sclerotherapy. I. The long-term management of patients after oesophageal variceal bleeding. *Surg Gynecol Obst* 1979;148:323-333.

12. Clark AW, MacDougall BRD, Westaby D, Mitchell KJ, Silk DBA, Strunin L, Dawson JL, et al. Prospective controlled trial of injection sclerotherapy in patients with cirrhosis and recent variceal haemorrhage. *Lancet* 1980;2:552-554.
13. Galambos JT, Warren WD, Rudman D. Selective and total shunts in the treatment of bleeding varices: a randomized controlled trial. *N Engl J Med* 1976;295:1089-1095.
14. Groszmann R, Kravetz D, Bosch J, Glickman M, Briux J, Bredfeldt J, Conn HO, et al. Nitroglycerin improves the hemodynamic response to vasopressin in portal hypertension. *HEPATOLOGY* 1982;2:757-762.
15. Lebrech D, Poynard T, Hillon P, Benhamou J-P. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. A controlled study. *N Engl J Med* 1981;305:1371-1374.
16. Hillon P, Lebrech D, Munoz C, Jungers M, Goldfarb G, Benhamou J-P. Comparison of the effects of a cardioselective and a nonselective β -blocker on portal hypertension in patients with cirrhosis. *HEPATOLOGY* 1982;2:528-531.
17. Burroughs AK, McCormick PA. Long-term pharmacologic therapy of portal hypertension. *Surg Clin North Am* 1990;70:319-339.
18. Teran JC, Imperiale TF, Mullen KD, Tavill AS, McCullough AJ. Primary prophylaxis of variceal bleeding in cirrhosis: a cost effectiveness analysis. *Gastroenterology* 1997;112:473-482.
19. Garcia-Pagan JC, Feu F, Bosch J, Rodes J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis. A randomized controlled study. *Ann Intern Med* 1991;114:869-873.
20. Merkel C, Marin R, Sacerdoti D, Donada C, Cavallarin G, Torboli P, Amodio P, et al. Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *HEPATOLOGY* 2000;31:324-329.
21. Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988-993.
22. de Franchis R. Updating consensus in portal hypertension: report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol* 2000;33:846-852.
23. Chalasani N, Imperiale TF, Ismail A, Sood G, Carey M, Wilcox CM, Madichetty H, et al. Predictors of large esophageal varices in patients with cirrhosis. *Am J Gastroenterol* 1999;94:3285-3291.
24. Boyer TD. Natural history of portal hypertension. *Clin Liver Dis* 1997;1:31-44.
25. Levacher S, Letoumelin P, Pateron D, Blaise M, Lapandry C, Pourriat J-L. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. 1995;346:865-868.
26. Arroyo V. New treatments for hepatorenal syndrome. *Liver Transpl* 2000;6:287-289.
27. Hadengue A. Somatostatin or octreotide in acute variceal bleeding. *Digestion* 1999;60(suppl 2):31-41.
28. deFranchis R, Primignani M. Endoscopic treatments for portal hypertension. *Semin Liver Dis* 1999;19:439-455.
29. Bernard B, Lebrech D, Mathurin P, Opolon P, Poynard T. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *HEPATOLOGY* 1997;25:63-70.
30. Villanueva C, Balanzo J, Novella MT, Soriano G, Sainz S, Torras X, Cusso X, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal bleeding. *N Engl J Med* 1996;334:1624-1629.
31. Lo G-H, Lai K-H, Cheng J-S, Chen M-H, Huang H-C, Hsu P-I, Lin C-K. Endoscopic variceal ligation plus nadolol and sucralofate compared with ligation alone for the prevention of variceal bleeding: a prospective, randomized trial. *HEPATOLOGY* 2000;32:461-465.
32. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. *Ann Intern Med* 1995;123:280-287.
33. Banares R, Moitinho E, Piqueras B, Casado M, Garica-Pagan JC, de Diego A, Bosch J. Carvedilol, a new nonselective β -blocker with intrinsic alpha-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. *HEPATOLOGY* 1999;30:79-83.
34. Rockey DC. The cellular pathogenesis of portal hypertension: stellate cell contractility, endothelin, and nitric oxide. *HEPATOLOGY* 1997;25:2-5.
35. Asbert M, Gines A, Gines P, Jimenez W, Claria J, Salo J, Arroyo V, et al. Circulating levels of endothelin in cirrhosis. *Gastroenterology* 1993;104:1485-1491.
36. Pinzani M, Gentilini P. Biology of hepatic stellate cells and their possible relevance in the pathogenesis of portal hypertension in cirrhosis. *Semin Liver Dis* 1999;19:397-410.
37. Rockey DC, Weisinger RA. Endothelin-induced contractility of stellate cells from normal and cirrhotic rat liver: implications for regulation of portal pressure and resistance. *HEPATOLOGY* 1996;24:233-240.
38. Poo J-L, Jimenez W, Munoz RM, Bosch-Marce M, Bordas N, Morales-Ruiz M, Perez M, et al. Chronic blockade of endothelin receptors in cirrhotic rats: hepatic and hemodynamic effects. *Gastroenterology* 1999;116:161-167.
39. Cho J-J, Hoher B, Herbst H, Jia J-D, Ruehl M, Hahn EG, Riecken EO, Shuppan D. An oral endothelin-A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis. *Gastroenterology* 2000;118:1169-1178.
40. Wiest R, Groszmann R. Nitric oxide and portal hypertension: its role in the regulation of intrahepatic and splanchnic vascular resistance. *Semin Liver Dis* 1999;19:411-426.
41. Martin P-Y, Gines P, Schrier R. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. *N Engl J Med* 1998;339:533-541.
42. Matsumoto A, Ogura K, Hirata Y, Kakoki M, Watanabe F, Takenaka K, Shiratori Y, et al. Increased nitric oxide in the exhaled air of patients with decompensated liver cirrhosis. *Ann Intern Med* 1995;123:110-113.
43. Rolla G, Brussino L, Colagrande P, Scappaticci E, Morello M, Bergerone S, Ottobrelli A, et al. Exhaled nitric oxide and impaired oxygenation in cirrhotic patients before and after liver transplantation. *Ann Intern Med* 1998;129:375-378.
44. Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial cell dysfunction in portal hypertension. *Gastroenterology* 1998;114:344-351.
45. Yu Q, Shao R, Qian HS, George SE, Rockey DC. Gene transfer of the neuronal NO synthase isoform to cirrhotic rat liver ameliorates portal hypertension. *J Clin Invest* 2000;105:741-748.