THE SIXTH CARLOS E. RUBIO MEMORIAL LECTURE

Prevention and Treatment of Variceal Hemorrhage

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ABSTRACT. The medical treatment of portal hypertension has experienced a marked progress in the past decade due to the introduction of effective portal hypotensive therapy. This has been possible because of the better understanding of the pathophysiological mechanisms leading to portal hypertension. A major step forward was the introduction of ß-blockers for the prevention of bleeding and rebleeding from gastroesophageal varices. Effective therapy requires the reduction of the hepatic venous pressure gradient (HVPG) to 12 mmHg or below, or at least by 20% of baseline values. Unfortunately, this is only achieved in 1/3 to 1/2 of patients. Combination therapy, associating isosorbide-5-mononitrate and propranolol or nadolol administration enhances the reduction in portal pressure and increases the number of patients in whom HVPG decreases by more than 20% of baseline values and below 12 mmHg. Randomized clinical trials (RCT's) do support the concept that combination therapy is more effective than propranolol or nadolol alone, significantly better than sclerotherapy, and probably than endoscopic banding ligation. Therapy may be complemented by the association of spironolactone. The main inconvenience of pharmacological therapy is that there is no non-invasive method available to detect non-responders to treatment. Failures of drug therapy should be managed endoscopically. Failures of endoscopic treatment require 'rescue' by means of TIPS or shunt surgery. Patients with advanced liver failure should be considered for orthotopic liver transplantation, and put into a waiting list if eligible.

In the treatment of acute variceal bleeding pharmalogical therapy offers the unique advantage of allowing to provide specific therapy immediately after arrival to hospital, or even during transferral to hospital by ambulance, since it does not require sophisticated equipment and highly qualified medical staff. Vasopressin has been abandoned because of its toxicity, although this can be reduced by the combined administration of transdermal nitroglycerin. Terlipressin has longer effects and is more effective and safer than vasopressin alone or in combination with nitroglycerin. It has proved to be effective and to decrease mortality from bleeding in double-blind studies. RCT's have shown that this drug is as effective and safer than emergency sclerotherapy. Therapy should be maintained for five days to prevent early rebleeding. Somatostatin is probably as effective as terlipressin. Octreotide is probably useful after endoscopic therapy but can not be recommended as first line treatment. Endoscopic injection sclerotherapy and endoscopic banding ligation are very effective, but require well trained medical staff. There is an increasing trend for initiating therapy with a pharmacological agent, followed by semi-emergency endoscopic therapy as soon as a well trained endoscopist is available (within 12-24 hours), while maintaining drug therapy for 5 days. Failures of medical therapy may be treated by a second session of endoscopic treatment, but if this fails TIPS or emergency surgery should be done. In high-risk situations, such as bleeding from gastric varices or in patients with advanced liver failure, the decision for TIPS or surgery should be done earlier, after failure of the initial treatment.

Portal hypertension is a frequent clinical syndrome, defined by a pathological increase in the portal venous pressure. This makes the pressure gradient between the portal vein and the inferior vena cava (portal perfusion pressure of the liver or portal pressure gradient) to increase above normal values (1-5 mmHg). When the portal pressure gradient rises above 10-12 mmHg, complications of portal hypertension can arise. Therefore, this value represents the threshold for defining portal hypertension as clinically significant (1).

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The importance of this syndrome is defined by the frequency and seriousness of its complications: massive upper gastrointestinal bleeding from ruptured gastroesophageal varices and portal hypertensive gastropathy, ascites, hepatic encephalopathy, arterial hypoxemia, disorders in the metabolism from drugs or endogenous substances that are normally eliminated by the liver, bacteremia and hypersplenism (1). These complications represent the first cause of death and the main indication for liver transplantation in patients with cirrhosis.

Any process that interferes with the blood flow at any level within the portal venous system can cause portal hypertension. According to the anatomical location of these processes we distinguish portal hypertension of prehepatic, intrahepatic and posthepatic origin. The most frequent cause of portal hypertension is cirrhosis, either alcoholic or related to chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, which cause over 90% of portal hypertension cases in Europe and USA, followed by schistosomiasis, which has a high prevalence in Northern Africa and a large part of Latin America (1).

Natural history and magnitude of the problem. Cirrhosis is the fifth leading cause of death in the USA in individuals under the age of 65. The fact that the average age of these patients is 50 years emphasizes the great socioeconomic repercussion of this syndrome (1,2).

Over 90% of patients with cirrhosis develop portal hypertension. When the portal pressure gradient, usually evaluated by its equivalent, the hepatic venous pressure gradient (HVPG) increases above 10 mmHg, varices may appear. Varices are part of the collaterals that develop by the dilatation of pre-existing vascular channels connecting the portal and the systemic venous circulation. When cirrhosis is diagnosed, 50% of patients already have esophageal varices at the first endoscopy (2). Those who do not have varices are exposed to a considerable risk of developing them over time, at a rate rate of approximately 6-8% per year, so that 90% of patients who survive more than 10 years will have esophageal varices (2).

Once varices are present, they progressively increase in size under the influence of increased pressure and blood flow. When the HVPG is above 12 mmHg, the varices may rupture and bleed. If the portal pressure gradient is decreased below the threshold values, either by means of a portalsystemic shunt, pharmacological therapy or spontaneously, the varices will not bleed and progressively decrease in size until they finally disappear (1-3). The risk of bleeding from varices is quite high, of approximately 15% at 1 year, and increases if the patient has large varices with "red colour signs" (red whale marks, cherry-red spots, diffuse redness) and if the patient has any sign of clinical decompensation (Child-Pugh score B or C) (1,2,4).

Bleeding from varices is a very serious complication, with a mean mortality rate of around 30%, which calls for treatment under intensive care facilities, preferably in "Gastrointestinal Bleeding Units". Among the survivors, the risk of rebleeding is very high, of approximately 70% in two years. Rebleeding is specially frequent early after the index hemorrhage. Mortality from variceal rebleeding also averages 30% (2). Patients with greater portal pressure elevation and with more pronounced liver failure have a greater risk of dying and of experiencing early rebleeding. The mortality of variceal hemorrhage has probably been underestimated, since up to 20% of patients may die from massive hemorrhage before being admitted to the hospital (1,2).

Again, if portal pressure is reduced substantially (by more than 20% of its baseline value), the risk of rebleeding is dramatically reduced, and no rebleeding will occur if the HVPG is reduced below the 12 mmHg threshold (3,5).

Pathophysiological basis of therapy. Without any doubt, the best treatment for portal hypertension in cirrhosis is to cure the liver disease. The closest we can get to this aim, by now, is by means of orthotopic liver transplantation, which therefore should be considered in any patient with liver failure and complications from portal hypertension. Having said that, all other 'rational' treatments are aimed at achieving a sustained decrease in portal pressure and porto-collateral blood flow (1,2,4,5). As already mentioned, there is substantial evidence showing that the portal pressure response to treatment correlates with its efficacy in the prevention of bleeding and rebleeding: complete protection from the risk of bleeding requires the portal pressure gradient to be reduced to 12 mmHg or less (3). Even without reaching these figures, a decrease of the portal pressure gradient of more than 20% of baseline value is associated also with a marked reduction of the bleeding risk (5). Thus, in order to plan a rational treatment for portal hypertension it is mandatory to understand the mechanisms determining the increase in portal pressure.

The knowledge of the pathophysiology of portal hypertension and the mechanism of variceal bleeding have markedly improved over the last decade. Experimental studies have shown that the initial factor in the physiopathology of portal hypertension is the increase in vascular resistance to the portal blood flow. In cirrhosis this increase in resistance occurs at the hepatic microcirculation (sinusoidal portal hypertension). It is important to emphasize that, contrary to what was traditionally thought, increased hepatic vascular resistance in cirrhosis is not only a mechanical consequence of the hepatic architectural disorder caused by the liver disease,

but there is also a dynamic component, due to the active contraction of myofibroblasts, activated stellate cells and vascular smooth muscle cells of the intrahepatic veins. This dynamic component may be modified by endogenous factors and pharmacological agents. Thus, hepatic vascular resistance is increased by endothelin, alpha-adrenergic stimulus and angiotensin II, and is lessened by nitric oxide, prostacyclin and by many vasodilating drugs (organic nitrates, adrenolytics, and calcium channel blockers) (6). It is believed that in cirrhosis, the hepatic vascular resistance is further increased because of an imbalance between vasodilatory and vasoconstrictor stimuli, the former being insufficient to counteract the influence of the latter. This is important because it provides the rational basis for using vasodilators in the treatment of portal hypertension (6-8). Another way of overcoming the increased resistance through the cirrhotic liver is by means of portal-systemic shunt surgery and transjugular intrahepatic portalsystemic shunts (TIPS). These procedures are higly effective in decreasing portal pressure, but have the inconvenience that further decreasing the portal blood flow through the liver may enhance liver failure and facilitate hepatic encephalopathy. Experimentally, the increased hepatic resistance can also be overcome by means of a continuous pump placed in the portal vein, forcing portal blood through the liver, which has the potential of improving liver function (9). Unfortunately, much technological improvements are required for this to become a therapeutic option.

The second factor that contributes to the pathogenesis of portal hypertension is the increase in blood flow in the portal venous system, established through splanchnic arteriolar vasodilatation, which is caused by an excessive release of endogenous vasodilators (endothelial, neural and humoral). This increased portal blood inflow contributes to aggravate the increase in portal pressure and explains why portal hypertension persists despite the establishment of an extensive network of portosystemic collaterals, that may divert as much as 80% of the portal blood flow. The increased portal venous inflow can be corrected by means of splanchnic vasoconstrictors, which are the drugs that have more widely been used in the treatment of portal hypertension (1,2,8,10). Recently it has been shown that the portosystemic collaterals can actively contract in response to various stimuli like serotonin, vasopressin, α-adrenergic blockers, and nitric oxide antagonists (1,6). Splanchnic vasodilatation is accompanied by systemic vasodilation, representing the hyperkinetic circulatory syndrome associated with portal hypertension (1,6). Its manifestations include increased cardiac output, arterial hypotension and hypervolemia. The latter is necessary to maintain the hyperdynamic circulation, which provides a rationale for the use of low-sodium diet and spironolactone to attenuate the hyperkinetic syndrome and the portal pressure elevation in patients with cirrhosis (11).

Combination therapy attempts to enhance the reduction of portal pressure by associating vasoconstrictive drugs, which act by decreasing the portal blood inflow, and vasodilators, which lessen the intrahepatic and portocollateral vascular resistance (12). Spironolactone can also be associated with them.

Endoscopic treatments are directed at "erradicating" the varices by means of either injecting a variety of irritating substances into or around the varices to promote thrombosis and fibrosis, or ligating the varices using elastic bands. Gastric varices are much more difficult to treat endoscopically than esophageal varices (1). These treatments do not affect the portal hypertension, but try to prevent the formation of new varices by obliterating all the feeding vessels or by repeat endoscopic treatment when varices reappear (2). It is likely that the effectivity of endoscopic therapy can be enhanced if combined with an agent effectively lowering portal pressure. On the other hand, however, if a marked fall in portal pressure is achieved by means of drug therapy, there is probably no need of adding any endoscopic procedure.

Scenarios of treatment. The treatment of portal hypertension includes several scenarios, with different prognostic and therapeutic implications. These include the treatment of the acute bleeding episode (a major medical emergency requiring the combined effort of hepato-gastroenterologists, endoscopists and surgeons), the elective treatment (prevention of rebleeding in patients who have survived a bleeding episode from esophageal or gastric varices) and the so called primary prophylaxis (prevention of the first variceal hemorrhage in patients who have never bled). The principal difference between them is that the risk of death and rebleeding is much higher in patients seen during active bleeding or shortly after than in those who have never bled (death rates of 30% *vs.* <5%; bleeding rates at one year of 70% in the first group *vs.* 15-20% in patients treated as primary prophylaxis) (2,13). This makes hazardous the use of invasive therapies or treatments with risk of causing serious complications (endoscopic treatments, TIPS, and surgery) in primary prophylaxis, since the risk of bleeding is not superior to the complications associated with these treatments. Therefore, for now, the prophylaxis of bleeding from esophageal varices should be done exclusively with drug therapy (2,4,13-15). An additional scenario that may come into practice is the 'pre-primary' prophylaxis, or treatment of compensated patients earlier in order to prevent the development of varices and of ascites by maintaining the

portal pressure below the threshold values for the appearance of these complications (1,2).

Prevention of Variceal Hemorrhage: Primary and Secondary Prophylaxis

Beta-blockers in the treatment of portal hypertension.

Hemodynamic effects. Propranolol and nadolol are the ß-blockers most commonly used in the treatment of portal hypertension (10). These are non-cardioselective ß-blockers that reduce portal pressure through a reduction in portal and collateral blood flow (1,2). This is due in part to a reduction in the cardiac output caused by the blockade of $ß_1$adrenoreceptors in the heart and in part to the splanchnic vasoconstriction caused by the blockade of the vasodilatory $ß_2$adrenoreceptors of the splanchnic circulation. This explains why atenolol and other selective ß-blockers (with no effect on the $ß_2$receptors) have a less pronounced portal pressure reducing effect (1,8).

The effect of propranolol on HVPG is moderate (mean reduction: 12-16%) (3,5). Propranolol also causes a marked reduction of the gastroesophageal collateral blood flow (estimated by the measurement of azygos blood flow) and of the esophageal variceal pressure (1,12). As indicated, adequate protection from the risk of bleeding requires the portal pressure gradient to be reduced to 12 mmHg or less (3,5), or by more than 20% from its baseline value (5). This is achieved in about one third to one half of the patients treated with propranolol. The response is better in compensated patients, without previous episodes of variceal bleeding. Therefore, ß-blockers as monotherapy have a greater potential in primary prophylaxis than in the prevention of rebleeding (2).

Dosage. The dose of propranolol should be individualized. The drug is administered at the maximal tolerated dose. Progressive doses are administered beginning at 20 mg/12 h, increasing or decreasing the dose every 3-4 days, until the heart rate is reduced by around 25%, provided that it does not go below 55 bpm or the systolic arterial pressure does not go below 90 mmHg, to avoid excessive fatigue and symptoms of low cardiac output (10). The average dose of propranolol administered is usually 80 mg/day (40 mg bid). We do not recommend giving more than 320 mg/day. If using nadolol, the total dose is half that of propranolol, administered in one daily dose.

Monitoring the response to treatment. As indicated, an effective treatment requires the reduction of the portal pressure gradient by more than 20% of the baseline value and preferably to 12 mmHg or below (1,5). This can only be verified through hepatic vein catheterization. Though this is an invasive technique, it is fast and easy to perform. It is inexpensive and risk-free (we have not had any lethal complication in over 6,000 patients studied in our laboratory) (l). Unfortunately, none of the non-invasive methods proposed (Doppler ultrasonography, plethysmography, measurement of catecholamine levels, etc.) are sufficiently precise to predict the portal pressure response. Endoscopic measurement of variceal pressure does allow to assess the response to treatment, but this method cannot be considered non-invasive and it has difficulties and limitations. Clinically, however, we know that the probability of achieving a satisfactory response is greater (nearly 45%) in compensated patients without a history of bleeding and ascites. The inconvenience of an insufficient portal pressure response can be overcome in part by using combination therapy, which attains a higher percentage of satisfactory responses (12).

Contraindications and side effects. Propranolol is contraindicated in patients with asthma, chronic pulmonary obstructive disease, aortic stenosis, A-V block, intermittent claudication and psychosis. Sinus bradycardia and insulin-dependent diabetes mellitus are relative contraindications, although the index of adverse effects during long-term therapy is about 15% (2, 10, 13, 14). The most frequent ones are dyspnea on exertion, bronchospasm, insomnia, fatigue, impotence and apathy. These side effects are frequently controlled by decreasing the dose of propranolol.

Expected Results

Primary prophylaxis. Treatment with propranolol or nadolol decreases by 50% the risk of the first variceal hemorrhage in patients with varices who have never bled before (2,10, 13,14). Also, the risk of death due to variceal bleeding is significantly reduced (Table 1). Since many of these patients will exhibit a satisfactory response to treatment and the risk of first bleeding is relatively low, it is not cost-effective to measure the HVPG response to treatment in this situation (1,2). All patients with cirrhosis found to have esophageal varices are potential candidates for prophylactic treatment. Treatment is mandatory if the varices are large and if there is moderate to severe liver failure (Child-Pugh grades B and C) (2, 13,14). The beneficial effect of propranolol is limited to the period of administration, so that once treatment is initiated, it should be maintained indefinitely. It has been suggested that the discontinuation of treatment can be followed by a 'rebound' increase in portal pressure, so it is prudent to advise that under no concept should the therapy be abruptly interrupted.

Prevention of rebleeding. Pharmacological treatment with propranolol or nadolol significantly reduces the risk

Table 1. Nonsurgical Treatments for Prevention of First Bleeding. Summary of results of controlled clinical studies (RCT's) and their meta-analysis.

RCT	Number of patients	Bleeding rate (%)			Death rate (%)		
		% Bleeding		Odds ratio	Control	Treated	Odds ratio
		Control	Treatment	(95 % CI)			(95 % CI)
Sclerotherapy compared with nonactive treatment							
Paquet	71	61	9	0.10 (0.04-0.27)	39	6	0.15 (0.05-0.46)
Witzel et al	109	57	9	0.12 (0.05-0.26)	55	21	0.25 (0.11-0.53)
Koch et al	60	33	30	0.86 (0.29-2.53)	33	37	1.16 (0.40-3.31)
Kobe et al	63	73	30	0.19 (0.07-0.50)	58	47	0.65 (0.24-1.73)
Wordehoff et al	49	63	20	0.18 (0.06-0.55)	67	56	0.64 (0.21-2.00)
Santangelo et al	95	15	35	2.77 (1.10-6.97)	24	24	1.03 (0.40-2.63)
Sauerbruch et al	113	43	32	0.63 (0.29-1.33)	45	28	0.49 (0.23-1.05)
Piai et al	140	42	14	0.25 (0.12-0.52)	38	23	0.49 (0.24-1.00)
Potzi et al	82	34	29	0.80 (0.32-2.02)	46	24	0.39 (0.16-0.95)
Russo et al	41	15	0	0.12 (0.01-1.18)	10	0	0.12 (0.00-2.03)
Adreani et al	83	32	21	0.59 (0.23-1.57)	44	43	0.96 (0.40-2.27)
Triger et al	68	40	39	0.97 (0.37-2.56)	60	61	1.02 (0.39-2.69)
Gregory et al	281	17	22	1.36 (0.76-2.45)	17	32	2.19 (1.28-3.77)
NIEC	106	37	36	0.96 (0.44-2.11)	47	35	0.60 (0.28-1.29)
PROVA	145	18	18	1.00 (0.43-2.33)	19	25	1.38 (0.63-3.01)
Saggioro et al	29	75	23	0.13 (0.03-0.57)	25	15	0.57 (0.10-3.35)
Fleig et al	49	18	14	0.77 (0.17-3.52)	29	29	1.00 (0.29-3.45)
Strauss et al	37	0	22	9.42 (1.21-72.9)	32	39	1.36 (0.36-5.18)
Planas et al	46	8	27	3.63 (0.80-16.4)	21	23	1.11 (0.28-4.46)
POR (95% CI)				0.58 (0.47-0.72)§			0.76 (0.62-0.94)§
-blockers compared with nonactive treatment							
Pascal et al	227	27	17	0.57 (0.30-1.06)	36	22	0.49 (0.29-0.88)
Ideo et al	79	22	3	0.23 (0.07-0.81)	18	10	0.53 (0.15-1.85)
Lebrec et al	106	19	13	0.66 (0.23-1.85)	19	19	1.00 (0.38-2.63)
IMPP	174	35	21	0.51 (0.26-0.99)	31	43	1.67 (0.91-3.08)
Adreani et al	84	32	5	0.16 (0.05-0.49)	44		
Conn et al	102	22	4	0.21 (0.06-0.66)	22	16	0.68 (0.25-1.84)
PROVA	140	18	18	0.99 (0.42-2.35)	19	10	0.49 (0.20-1.26)
Strauss et al	36	25	20	0.76 (0.16-3.59)	44	35	0.67 (0.19-2.64)
Colman et al	48	8	35	4.90 (1.23-19.5)	28	26	0.91 (0.26-3.21)
POR (95% CI)				0.54 (0.39-0.74)			0.75 (0.57-1.06)

In this table and in the following, results are presented as odd ratios and the confidence itervals (CI) are 95%. The meta-analysis is expressed by Pooled Odds Ratio (POR) and its 95% CI. The result is statistically significant when the 95% CI does not include unit (1.00). Modified from reference #6.

of rebleeding and this is associated with a prolongation of survival (2). Studies comparing propranolol versus endoscopic sclerotherapy show that sclerotherapy is more effective in the prevention of variceal rebleeding, but it is also accompanied by a greater incidence of gastric hemorrhage (Table 2). The complications of treatment are more frequent and severe in patients treated with endoscopic injection sclerotherapy than in those receiving ß-blockers (2). Probably because of this, the survival is identical in patients treated with sclerotherapy or with propranolol.

At variance with primary prophylaxis, patients treated

Table 2. Nonsurgical Treatments for Prevention of Rebleeding. Summary of results of controlled clinical studies (RCT's) and their meta-analyses

		Rebleeding rate (%)		Death Rate (%)		
RCT	Number of patients	Control Treated	Odds Ratio (95%CI)	Control	Treated	Odds Ratio (95%CI)
-blockers compared with nonactive treatment						
Burroughs et al	48	59 54	0.81 (0.26-2.51)	23	5	0.62 (0.14-2.63)
Lebrec et al	74 64	21	0.17(0.07-0.44)	22	8	0.32 (0.09-1.16)
Villeneuve et al	79	81 76	0.75 (0.25-2.18)	38	45	1.35 (0.55-3.29)
Quenier et al	99 64	57	0.72 (0.32-1.62)	21	23	1.16 (0.45-2.99)
Gatta et al	24 67	25	0.20 (0.04-0.96)	25	8	0.31 (0.03-2.59)
Colombo et al*	62	47 25	0.39 (0.14-1.10)	23	12	0.48 (0.13-1.75)
Colombo et al	62	47 31	0.52 (0.19-1.45)	23	9	0.36 (0.09-1.38)
Sheen et al	36 55	28	0.32 (0.08-1.21)	11	0	0.12 (0.01-2.12)
Garden et al	81 84	53	0.23 (0.09-0.60)	44	37	0.74 (0.30-1.79)
Rossi et al	54 63	48	0.55 (0.19-1.60)	33	26	0.70 (0.22-2.24)
Cerbelaud et al	84	78 40	0.21 (0.08-0.49)	NR	NR	
Colman et al	52 50	35	0.54 (0.18-1.60)	4	4	1.00 (0.06-16.4)
POR (95%)			0.40 (0.30-0.54)			0.70 (0.48-1.02)
Sclerotherapy compared with nonactive treatment						
Terblanche et al	75	55 57	1.06(0.42-2.62)	63	62	0.95 (0.37-2.42)
EVASP	187	54 48	0.79 (0.44-1.40)	78	64	0.52 (0.28-0.99)
Westaby et al	116	82 55	0.29 (0.13-0.64)	53	32	0.42 (0.20-0.88)
Soderlund et al	107	66 56	0.66 (0.30-1.44)	70	56	0.55 (0.25-1.20)
Korula et al	120	84 49	0.21 (0.10-0.45	33	33	1.00 (0.46-2.13)
Rossi et al	53 63	50	0.60(0.20-1.75)	33	23	0.61 (0.19-1.99)
Burroughs et al	204	60 56	0.85 (0.48-1.48)	54	47	0.76 (0.44-1.31)
Gregory	153	63 55	0.70 (0.43-1.65)	56	63	1.32 (0.80-2.17)
POR (95%)			0.62 (0.49-0.79)			0.77 (0.61-0.98)
Sclerotherapy compared with -blockers						
Alexandrino et al	65	73 55	0.44 (0.16-1.22)	32	29	0.85 (0.30-2.44)
Dollet et al	55 41	64	2.52 (0.88-7.21)	41	53	1.65 (0.58-4.73)
Westaby et al	108	56 50	0.79 (0.37-1.68)	42	37	0.82 (0.38-1.76)
Rossi et al	53 48	50	1.07 (0.37-3.12)	26	23	0.86 (0.24-2.97)
Martin et al	76 53	55	0.36 (0.16-0.83)	23	31	1.44 (0.52-3.93)
Dasarathy et al	91 67	42	0.36 (0.16-0.83)	41	22	1.04 (0.45-2.38)
Fleig et al	105	52 47	0.82 (0.38-1.77)	32	36	1.21 (0.54-2.70)
Liu et al	118	57 33	0.38 *0.18-0.80)	39	28	0.60(0.28-1.29)
Terés et al	116	64 45	0.47 (0.23-0.97)	40	36	0.86 (0.41-1.82)
POR (95% CI)			0.66 (0.50-0.88)			0.96 (0.71-1.28)
Endoscopic ligation compared with sclerotherapy						
Stiegmann et al	129	48 36	0.62 (0.31-1.24)	45	28	0.49 (0.24-1.00)
Lame et al	77	44 26	0.47 (0.19-1.19)	15	10	0.65 (0.17-2.45)
Gimson et al	103	53 30	0.38 (0.17-0.84)	NR	NR	
POR (95% CI)			0.49 (0.31-0.78)			0.53 (0.28-0.99)

*Propranolol
Atenolol
Trial published as an abstract

with ß-blockers after an episode of variceal bleeding usually exhibit a less pronounced reduction in HVPG. A satisfactory response (>20% HVPG reduction) is achieved in less than one third of the patients (5). Since the bleeding risk in non-responders is much higher than in responders (50% *vs.* 6%), patients treated electively should have repeat HVPG measurements to assess the portal pressure response (1,5).

Vasodilators in the Treatment of Portal Hypertension

Isosorbide-5-mononitrate (ISMN) reduces the hepatic vascular resistance and HVPG in patients with cirrhosis. A recent randomized controlled trial (RCT) has shown ISMN to be as effective as propranolol in the prevention of first bleeding, but unlike propranolol, it did not improve survival in primary prophylaxis (16). ISMN may represent an alternative in patients with contra-indications to ß-blockers, but no RCT has examined this issue so far (2). ISMN is used at increased doses, starting by 20 mg at bedtime and increased up to 20-40 mg bid. At the beginning of treatment cephalea and orthostatic hypotension could be a problem, but usually subside after 3-4 days. The greater concern with the use of ISMN -as with other vasodilators- is its potential to adversely influence renal function and sodium retention (8).

Clonidine and prazosin also reduce HVPG in patients with cirrhosis. The magnitude of the portal pressure reduction on long-term administration of these agents is greater than with ISMN, but the unwanted arterial hypotension is also greater. Prazosin has been shown to induce sodium retention and ascites in some patients. Thus, although these agents may represent another alternative to ß-blockers, its safety should be confirmed in carefully performed RCT's (7).

Combination Therapy

Hemodynamic studies have shown that the portal hypotensive effect of propranolol or nadolol is significantly enhanced by associating ISMN to the blocker treatment (12). After adjusting the dose of ß-blockers, ISMN is initiated, starting with 20 mg at bed time/day and increasing progressively until reaching the maintenance dose (20-40 mg twice a day). RCT's have demonstrated that this therapeutic combination has a greater clinical efficacy than the isolated administration of ß-blockers in the prophylaxis of the first bleeding, and that it is superior to sclerotherapy in the prevention of rebleeding (2). Combination therapy is as effective as invasive treatments, and probably more than endoscopic banding ligation (2). Therapy may be complemented by the administration of spironolactone (11).

Another possible therapeutic combination is the association of propranolol or nadolol with prazosin (7). This pharmacological association has a more pronounced effect on HVPG than propranolol plus ISMN but has not yet been evaluated in controlled therapeutic studies. The association of prazosin plus propranolol has less marked effects on renal function and systemic hemodynamics than prazosin alone, but it is not as well tolerated as the association of propranolol plus ISMN.

Endoscopic Therapy

In patients with contraindications, side-effects or previous failure of pharmacological therapy, alternative treatments should be used. The best alternatives are represented by endoscopic treatments (2).

Sclerotherapy. This technique consists of an intra or perivariceal injection of a variety of sclerosing substances (5% ethanolamine, 1-2% polydocanol, ethanol, sodium morrhuate) that provoke thrombosis of the varices and a fibrous reaction that tends to eliminate them. Sclerotherapy is usually done under sedation at weekly intervals. Approximately 4 to 5 sessions are necessary for the eradication of varices, which is achieved in nearly 70% of patients. Frequent endoscopic controls should be done, as varices reappear in the majority of patients after stopping the treatment, with new sclerotherapy sessions being necessary. Sclerotherapy can cause serious complications (dysphagia, bleeding from esophageal ulcers, esophageal stenosis and perforation, sepsis, portal thrombosis, pleural effusions, etc.). These complications are lethal in 3% of cases (2,14).

Endoscopic banding ligation of varices. This has been introduced as a technical improvement over injection sclerotherapy, since it is less prone to complications such as esophageal perforation, infections and esophageal stenosis. Moreover, its efficacy is slightly superior than that of sclerotherapy. Although it may be difficult during active bleeding, it has progressively replaced sclerotherapy for elective treatment. As sclerotherapy, banding ligation is not adequate for gastric varices. Banding ligation sessions are usually performed every 2 weeks. Three sessions with 5-7 bands each are usually required for the initial eradication of varices (2). However, as with any procedure depending on the skill of who performs it, the reported results with banding ligation probably overestimate its efficacy when used in the community. Indeed, the efficacy of endoscopic banding ligation in recent trials comparing it with TIPS or combined drug therapy is less than that reported in the initial trials versus

injection sclerotherapy. There is still debate on whether injection sclerotherapy may be useful after a few sessions of banding ligation to delay the reappearance of varices.

It is unclear if these treatments might be used in primary prophylaxis, where ß-blockers are the only accepted treatment (4). RCT's on the prophylactic use of endoscopic injection sclerotherapy produced divergent results, some trials even showing a worse outcome in the treated patients than in controls. This may not apply to endoscopic banding ligation, but this should be proved in adequate RCT's vs. ß-blockers (2,4). Endoscopic banding ligation may be an option in patients with grade III varices who have contraindications or can not tolerate ß-blockers.

When patients are treated to prevent rebleeding, banding ligation is the recommended alternative treatment. It's use should be considered not only for failures or contraindications to ß-blockers, but also when the portal pressure response to maximal pharmacological therapy is insufficient (5).

Surgery and TIPS

Endoscopic techniques are less effective than shunt surgery, but they do not increase the risk of encephalopathy, so that generally surgery is only used as a 'rescue' therapy for failures of medical and endoscopic treatments. At present, TIPS has substituted surgery in many situations, especially in emergency treatment in patients with advanced hepatic failure, who are potential candidates for orthotopic liver transplantation (2,4).

The major limitation of TIPS is its elevated cost and the very high incidence of TIPS dysfunction due to stenosis or occlusion of the shunt through excessive proliferation of the neointima that covers the stent (1,4). Dysfunction requires reintervention, with angioplasty or placement of new endoprotheses in over 50% of cases. In the same way, TIPS causes encephalopathy in nearly 30% of cases, especially in patients who are older than 60 and who maintain a marked reduction of portal pressure after the procedure.

Treatment of the Acute Bleeding Episode

Variceal bleeding is one of the most dramatic complications in gastroenterology, and it should be treated under intensive care facilities using a multidisciplinary team approach, integrating hepatologists, endoscopists and surgeons in the so called Gastrointestinal Bleeding Units (1).

Treatment involves several steps, including the initial resuscitation and replacement of the blood volume loss, diagnosis of the source of bleeding through emergency endoscopy (during the first 6 hours), prevention of complications (hepatic encephalopathy, bronchial aspiration, systemic infections, renal failure) and the specific treatment of the bleeding lesion (2,4). As a rule, blood volume replacement is done using packed red cells and plasma substitutes, to maintain a hematocrit of 25-30%, a systolic blood pressure >80 mmHg, a pulse rate <100 bpm and a central venous pressure >2 cmH,O. Overtransfusion should be avoided since it can precipitate rebleeding (1). Prevention of bronchial aspiration and hepatic encephalopathy is done by close monitonng, continuous nasogastric aspiration, and administration of lactulose. Orotracheal intubation may be needed in patients with impaired conciousness. It is essential to prevent systemic infections and spontaneous bacterial peritonitis by means of giving prophylactic antibiotics, such as norfloxacin or amoxycillin-clavulamic acid (4). Specific therapy of variceal hemorrhage is based on medical treatments, using either vasoactive drugs, endoscopic therapies, or both. Surgery and TIPS are most commonly used as rescue treatments for failures of medical therapy.

Pharmacological Therapy

The more important, and unique, advantage of pharmacological therapy is that it does not require specialised personnel or sophisticated equipment, so that it can be used at any center, and therapy can be started much earlier than when using endoscopic therapy: at the arrival of patients to the emergency room or even before admission, during transferral to hospital by medical or paramedical teams (1,2,4).

Several drugs have been used in the pharmacological treatment of variceal bleeding (Table 3). In a chronological order these include vasopressin, vasopressin associated with nitroglycerin, terlipressin, somatostatin and somatostatin analogs (2). All these require parenteral administration.

Vasopressin has almost been abandoned because it is less effective and more dangerous than other therapeutic options. The toxicity of vasopressin can be reduced by the combined administration of vasopressin plus transdermal nitroglycerin. This drug combination is more effective in decreasing HVPG than vasopressin alone, and RCT's have shown that it is also superior in controlling variceal hemorrhage. This is still the recommended drug therapy in countries were other drugs are not available.

Terlipressin (triglycil-lisine-vasopressin or glypressin) is a synthetic analogue of vasopressin with prolonged biological effects, which allow it to be administered intravenously in doses of 2 mg every 4 hours. It's major advantage over vasopressin is that it is more effective and

better tolerated, rarely causing severe side effects (2). It also lacks the fibrinolytic effect of vasopressin, which may explain in part its greater efficacy in controlling variceal bleeding (2,4).

Placebo-controlled studies have proven the efficacy of terlipressin in the treatment of acute bleeding from ruptured esophagogastric varices and, probably more important, its unique capacity to reduce the mortality associated with variceal bleeding (2). Comparative studies have also demonstrated that terlipressin is more effective than vasopressin alone or associated with nitroglycerin, and that it causes less adverse effects (Table 3). The more common adverse effects are arterial hypertension and bradycardia, but these require withdrawal of therapy very rarely. The 80% rate of efficacy of terlipressin is very uniform accross studies. Once hemostasis is attained (which is defined by accomplishing a 24-hour period without signs of hemorrhage) terlipressin can be administered for 5 days in smaller doses (1 mg/4 hours) to prevent early rebleeding. In a recent international study, terlipressin was found to be as effective as emergency injection sclerotherapy in controlling the bleeding and in preventing variceal rebleeding, with a lower rate of complications. Terlipressin has also been shown to be effective in portal hypertensive gastropathy and in the prevention of early variceal rebleeding after sclerotherapy (2).

Terlipressin has been used with success in the treatment of bleeding cirrhotic patients while they were travelling to the hospital from their homes by ambulance (17). In this situation, a recent double blind study showed its efficacy in arresting the bleeding and increasing 6-week survival in treated patients. This underlines the unique advantage of pharmacological treatments, not requiring specialized personnel or sophisticated equipment, and allowing immediate administration (2,4)

Somatostatin is a natural hormone which at pharmacological doses decreases portal blood flow and portal pressure, without significant systemic side effects. Its effectivity reducing HVPG is much greater following bolus injections than after continuous infusions, but the latter are required due to the very transient effect of bolus injections (3-5 minutes). Clinically, somatostatin is used as a continuous intravenous infusion at doses of 250-500 µg/hour after a bolus of 250µg, which can be repeated up to three times in the first hours if the bleeding is not controlled. Although placebo-controlled studies have not been conclusive, comparison with other forms of treatment strongly suggests that somatostatin (at the indicated doses) is effective and safe in bleeding gastroesophageal varices. After achieving hemostasis, somatostatin perfusion can be maintained for 5 days to prevent early rebleeding (1,2). Somatostatin has been shown to be as effective as terlipressin in double-blind controlled trials, and as effective as endoscopic injection sclerotherapy in other studies.

Octreotide is a synthetic analogue of somatostatin that has been shown to be effective in reducing the complications of variceal bleeding after emergency sclerotherapy. However, it's efficacy as first-line treatment for variceal bleeding has not been established, so its use should be restricted to controlled trials (2).

Endoscopic Therapy

Endoscopic treatments have the advantage of allowing specific therapy at the time of diagnosis. This is only true when the diagnostic endoscopy is performed by a fully trained endoscopist, otherwise it usually results in unsatisfactory endoscopic treatment (either insufficient or excessive). Most endoscopists prefer to perform these techniques on a 'clean' esophagus, and during working hours. Because of that, endoscopic treatments are usually preceded by other therapies, most commonly by pharmacological treatment (2).

Unfortunately, endoscopic treatment is not 100% effective. Its efficacy in achieving hemostasis (defined as attaining a 24 hour bleeding-free period) is over 80%. However, due to very early rebleeding in some patients, at day 5 its effectivity declines to 70%. Although failures of endoscopic treatment may be managed by a second session of endotherapy, no more than two sessions should be allowed before making a decision for TIPS or surgery.

Endoscopic injection sclerotherapy. It is a very effective emergency treatment for acute variceal bleeding (1,2,4). Until recently, it was considered the gold-standard for acute variceal hemorrhage. This has been challenged by recent studies showing comparable efficacy using drugs (terlipressin or somatostatin) and by the advent of endoscopic banding ligation (2). Other limitations of sclerotherapy are that it requires a well trained endoscopist available on a 24 hours a day basis, which is costly and not possible in every center,and that it is of little effectivity in gastric varices (except perhaps if the injection is done using bucrylate). Moreover, the complications of sclerotherapy are more frequent when done as an emergency during acute bleeding than in elective conditions (2).

Endoscopic elastic band ligation. It is less prone to complications than injection sclerotherapy. However, in acute bleeding its advantage over injection sclerotherapy has not been clearly established. Banding ligation has the same limitations of availability, cost and difficulty in gastric varices as sclerotherapy. In most centers, treatment

Table 3. RCT's of Drug Therapy for Acute Variceal Bleeding. Summary of results of controlled clinical studies (RCT's) and their meta-analyses.

	Failure to control Bleeding (%)				Death Rate (%)		
RCT	Number of Patients	Control	Treated (95% CI)	Odds Ratio	(95% CI)	Control	Treated Odds Ratio
Vasopressin plus nitroglycerin compared with vasopressin							
Tsai et al	39	79	55	0.35 (0.94-1.30)	58	55	0.89 (0.25-3.11)
Gimson et al	72	56	3f2	0.38 (0.15-0.95)	26	24	0.86 (0.29-2.49)
Bosch et al	65	46	27	0.45 (0.16-1.22)	29	30	1.07 (0.37-3.10)
POR (95% CI)				0.31 (0.15-0.61)			0.32 (0.15-0.70)
Glypressin compared with placebo							
Walker et al	50	48	20	0.29(0.09-0.93	32	12	0.32 (0.08-1.20)
Freeman et al	31	62	40	0.42 (0-.10-1.67)	25	20	0.76 (0.14-397)
Soderlund et al	60	45	16	0.26 (0.09-0.78)	38	10	0.21 (0.06-0.69)
POR (95% CI)				0.31 (0.15-0.61)			1.48 (0.85-2.57)
Glypressin compared with vasopressin							
Freeman et al 21	91		30	0.08 (0.01-0.47)	27	20	0.68 (0.09-4.86)
De Saint et al	16	17	20	1.23 (0.10-15.1)	33	30	0.86 (0.10-7.16)
Lee et al	45	67	81	2.04 (0.55-7.56)	33	48	1.79 (0.55-5.83)
Chiu et al	54	46	50	1.15 (0.39-3.31)	36	46	0.52 (1.52-4.48)
D'Amico et al 111	24		9	0.34 (0.12-0.93)	16	25	1.68 (.67-4.19)
POR (95% CI)				0.64 (0.36-1.14)			1.48 (085-2.57)
Glypressin compared with balloon tamponade							
Colin et al	54	12	12	1.00 (0.18-5.41)	22	15	0.62 (0.16-2.41)
Fort et al	47	21	22	1.05 (2.65-4.20)	8	13	1.62 (0.26-10.2)
POR (95% CI)				1.03 (0.35-3.00)			0.87 (0.29-2.59)
Glypressin compared with somatostain							
Silvain et al	87	43	54	1.50 (0.65-3.46)	22	27	1.31(0.49-3.50)
Walker et al	50	32	20	0.54 (0.15-1.89)	24	16	0.61 (0.15-2.41)
VBSG	161	16	20	1.30 (0.58-2.91)	17	20	1.19 (0.54-2.63)
POR 95 % CI)				1.18 (0.70-1.99			1.10 (0.63-1.93)
Somatostatin compared with placebo							
Valenzuela et al	84	25	44	2.24 (0.91-5.18)	28	31	1.18 (0.46-3.01)
Burroughs et al	120	59	36	0.39 (0.18-0.81)	11	15	1.28 (0.45-3.65)
Avgerinos et al	205	55	35	0.65 (0.01-1.27)	19	9	1.48 (0.81-2.43)
Somatostatin compared with vasopressin							
Kravetz et al	61	42	47	1.21 (0.44-3.29)	45	47	1.06 (0.39-2.88)
Jenkins et al	22	67	30	0.24 (0.05-1.27)	33	20	0.53 (0.08-3.32)
Pagarani et al	49	68	33	0.26 (0.09-0.78)	40	25	0.51 (0.16-1.67)
Cardona et al	38	44	60	1.83 (0.52-6.46)	17	30	2.05 (0.47-8.99)
Hsia et al	46	63	45	0.51 (0.16-1.61)	62	63	1.05 (0.32-3.43)
Saari et al	54	48	35	0.53 (0.18-1.58)	36	34	0.92 (0.23-2.83)
Rodr guez-Moreno	31	37	60	0.42 (0.10-1.67)	19	20	1.08 (0.19-6.24)
Hwang et al *	48	54	37	0.52 (0.17-1.59)	50	46	0.85 (0.28-2.60)
POR (95% CI)				0.68 (0.45-1.04)			0.92 (0.59-1.43)

* Octreotide compared with vasopressin.
Most patients also received sclerotherapy.

is usually initiated with drug therapy, followed by semi-emergency endoscopic treatment (within 12-24 hours) using injection sclerotherapy, banding ligation or a combination of both (2,4).

References

1. Bosch J, (Ed). Portal Hypertension. Baillière's Clinical Gastroenterology, 1997;11 (N.2).
2. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995;22:332-354.
3. Groszmann RJ, Bosch J, Grace N, Conn HO, García-Tsao G, Navasa M, Fischer R, Bermann M, Rofe S, Patrick M, Rodés J. Hemodynamic events in a prospective randomized trial of propranolol vs. placebo in the prevention of the first variceal hemorrhage. Gastroenterology 1990;99:1401-1407.
4. De Franchis R. (Ed). Portal Hypertension II: Proceedings of the Second Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies. Oxford. (UK): Blackwell Science; 1996.
5. Feu F, García-Pagán JC, Bosch J, Luca A, Terés J, Escorsell A, Rodés J. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346:1056-59.
6. Groszmann RJ. The pathophysiological basis of therapy in portal hypertension and ascites: an overview. In: Arroyo V, Bosch J, Bruguera M, Rodés J, editors. Therapy in liver diseases: the pathophysiological basis of therapy. Barcelona, Paris, Milano: Masson; 1997.p.13-20.
7. Albillos A, Lledó JL, Rossi I, Pérez-Páramo M, Tabuenca MJ, Bañares R, Iborra J, Garrido A, Escartín P, Bosch J. Continuous prazosin administration in cirrhotic patients: effects on portal hemodynamics and on liver and renal function. Gastroenterology 1995;109:1257-1265.
8. Groszmann RJ. Beta-adrenergic blockers and nitrovasodilators for the treatment of portal hypertension: the good, the bad and the ugly. Gastroenterology 1997;113:1794-1797.
9. Cardoso JE, Meteini ME, Calmus Y, Vaubourdelle M, Houssin D. Portal pumping: a new perspective for treatment of variceal hemorrhage and liver failure in end-stage cirrhosis? J Hepatol 1994; 19:375-380.
10. Lebrec D, Poynard T, Bernuau J, et al. A randomized controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. A final report. Hepatology 1984; 4:355-58.
11. García-Pagán JC, Salmerón JM, Feu F, Luca A, Ginés P, Pizcueta P, Clana J, Piera C, Arroyo V, Bosch J, Rodés J. Effects of low sodium diet and spironolactone on portal pressure in patients with compensated cirrhosis. Hepatology 1994;19:1095-1099.
12. García-Pagán JC, Feu F, Bosch J, Rodés 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.
13. Poynard T, Calès P, Pasta L et al. Beta-adrenergic antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices: an analysis of data and prognostic factors in 589 patients from four randomised clinical trials. N Engl J Med 1991,324:1532-1538.
14. Pagliaro L, D'Amico G, Sörensen TIA, et al. Prevention of first bleeding in cirrhosis. A metaanalysis of randomized trials of nonsurgical treatment. Ann Inter Med 1992;117:59-70.
15. Grace ND. Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. Am J Gastroenterol 1997;92: 1081-1091.
16. Angelico M, Carli L, Piat C, Gentile S, Capocaccia L. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long term survival in cirrhosis. Gastroenterology 1997;113:1632-1639.
17. Levacher S, Letoumelin P, Pateron D, Blaise M, Lapandry C, Pourriat JL. Early administration of terlipressin plus glyceril trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. Lancet 1995;346:865-868.