Treatment of portal hypertension in the light of the Baveno VI Consensus Conference

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Abstract

Background: Portal hypertension is the haemodynamic abnormality associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy and bleeding from gastro-oesophageal varices. Pharmacological and endoscopic treatment of portal hypertension has played an increasing clinical role in the past 30 years. Despite the progress achieved over the last decades, the 6-week mortality associated with variceal bleeding is still in the order of 10–20%. In the setting of acute variceal bleeding, drug and endoscopic therapy should be considered the initial treatment of choice and can be administered as soon as possible. Management of treatment of portal hypertension and variceal hemorrhage is based on the clinical stage of portal hypertension. Prevention of first variceal hemorrhage depends on the size of varices. In patients with small varices and high risk of bleeding, non-selective β-blockers are recommended, while patients with medium/large varices can be treated with either β-blockers or oesophageal band ligation. Standard of care for acute variceal hemorrhage consists of vasoactive drugs, endoscopic band ligation and antibiotics prophylaxis. Patients who had failed this therapy should be considered for transjugular intrahepatic portosystemic shunt or shunt surgery. Prevention of recurrent variceal hemorrhage consists of the combination of β-blockers ± isosorbide 5-mononitrate and endoscopic band ligation. Patients with recurrent variceal hemorrhage are in a category of "further decompensation" of cirrhosis and, as such, should be evaluated for liver transplantation.

Conclusions: In the last decades significant advances in the field of portal hypertension have improved the clinical care and survival of patients with cirrhosis and portal hypertension. Further research is necessary to explore new pharmacological options that would allow to get a positive hemodynamic response in most patients.

Key words: portal hypertension, liver cirrhosis, variceal hemorrhage, treatment.

History consensus conferences dedicated to the treatment of portal hypertension

The management of portal hypertension is linked with so-called "Baveno consensus" that serves as an important basis for developing guidelines and clinical protocols in this area. Baveno is a small town in northern Italy situated on the west Shore of Maggiore Lake. It became the epicenter of consensus workshops dedicated to portal hypertension, which aim is to reach a common denominator about definitions and the most important events associated with portal hypertension and variceal bleeding. The first workshop dedicated to Baveno consensus was held in April 1990 [1], in which were evaluated significant progress in terms of diagnosis and management of eso-gastric varices and variceal bleeding, including the administration of vasoactive drugs and the use of endoscopic sclerotherapy. Additionally, were defined certain features and complications of portal hypertension including the varices sizes, the bleeding and its recurrences, the recommendations about diagnosis methods and were traced new directions for future clinical studies. Therapeutic recommendations included the following: β-blockers for primary prophylaxis of bleeding from large varices, endoscopic sclerotherapy and vasoactive drugs for acute variceal bleeding, and to prevent recurrent bleeding – endoscopic sclerotherapy, β-blockers or surgical shunt.

The Baveno II workshop was held in April 1995 [2]. Were revised definitions of the most important clinical syndromes in portal hypertension and new definitions were proposed. After analyzing several randomized controlled trials, nonselective β-blockers were recommended as the elective treatment for primary prevention of variceal bleeding, while isosorbide-5 mononitrate has been recommended in patients who were intolerant or had contraindications to β-blockers. Endoscopic sclerotherapy was not recommended for the prevention of the first episode of bleeding. While the treatment of acute bleeding was based on endoscopic therapy, on terlipressin administration (which was considered one of the most effective vasoactive agents) and somatostatin analogues. TIPS has been recommended in case of failure of endoscopic and pharmacological treatment. The recommendations related to the prevention of recurrent bleeding include the administration of β-blockers or endoscopic variceal ligation, which it has shown to be more effective and safer than sclerotherapy [3]. TIPS and surgical shunt followed to be used only for patients with frequent repeated episodes of variceal bleeding.

The Baveno III Conference was held in April 2000 [4], where it was introduced the concept of portal hypertension with significant clinical manifestations, which is determined if hepatic venous pressure gradient (HVPG) ≥ 10 mmHg. The presence of varices, variceal bleeding or ascites indicates the portal hypertension with significant clinical manifestations. Nonselective β-blockers were kept in elective treatment for preventing the first episode of bleeding from large/medium varices, while the endoscopic variceal ligation was considered necessary for an additional evaluation. Were defined the targets of β-blockers therapy (25% reduction in heart rate from baseline or establishing a heart rate of 55 beats/min). It was not proposed the using of isosorbide-5 mononitrate as an alternative treatment, which was previously recommended [5]. For the acute bleeding treatment, immediate administration of vasoactive medications and the continuation over 5 days together with endoscopic therapy (endoscopic variceal ligation or sclero-

therapy) were considered as the standard. Also, were proposed some additional measures: antibiotic use to prevent bacterial infection [6] and the lactulose for the treatment of hepatic encephalopathy. About the prevention of repeated bleeding, β-blockers were considered first-line therapy [7], in parallel with endoscopic variceal ligation, and TIPS was reserved in the case of treatment failure. Also, were clearly defined the complications of portal hypertension and were proposed targets for further research.

The Baveno IV Conference was held in April 2005 [8], there were revised some key criteria (inability to control bleeding, the failure of secondary prevention). For primary prevention, β-blockers were kept as an elective treatment, but endoscopic ligation was placed as an excellent alternative for patients with large and medium varices and contraindications or intolerance to β-blockers [9, 10]. Isosorbide 5-mononitrate, was not recommended either in monotherapy, or even in a combination of pharmacological therapies [11]. Primary prevention of small varices can be considered only if they are at high risk for hemorrhage ("red signs" or Child-Pugh Class C) [12]. The recommendations for acute variceal bleeding were kept the same as in the Baveno III Consensus. Along with vasoactive drugs administration for at least 5 days, it was recommended the use of tamponade with balloon and only in massive bleeding as a temporary bridge until the establishment of defenitive treatment. The endoscopic variceal ligation was declared superior to sclerotherapy and was considered the elective endoscopic procedure for acute bleeding control [10, 13]. It is recommended that secondary prophylaxis should be initiated by the 6th day after variceal hemorrhage, which must include a combination of endoscopic ligation and nonselective β-blockers [14, 15]. As in previous consensuses, TIPS and surgical shunts were reserved for patients with secondary prevention failure.

The Baveno V Conference of May 2010 revised the definitions relating to the failure of variceal bleeding control and secondary prophylaxis [16]. Primary prophylaxis recommendations for small varices were the same as in the previous consensuses. There was no significant change in the recommendations for primary prevention of medium and large varices (β-blockers or endoscopic variceal ligation). The choice of therapy was dictated by local resources, the experience of specialists and patient preference [17]. The recommendations for treatment of acute variceal bleeding were unchanged, except a recommendation, which involves the use of TIPS in the early period (in 72 hours) in patients with increased risk of pharmacological or endoscopic treatment failure [18]. For preventing recurrent bleeding was proposed the combination therapy of β-blockers and endoscopic variceal ligation.

The Baveno VI Consensus Conference took place in April 2015. Below are outlined the basic principles of modern management of portal hypertension.

Standard modern treatment of portal hypertension in adults

The therapy of esophageal varices and variceal bleeding in adult patients with cirrhosis should be differentiated according to clinical stages of the natural history of portal hypertension which were divided into 4 stages:

1. Patients with cirrhosis and portal hypertension, which has not yet developed varices and the therapy purpose is to prevent the formation of varices (pre-primary prophylaxis).

2. Patients with esogastric varices which are not bleeding and the therapy purpose is to prevent their rupture (primary prevention).

3. Patients with acute variceal hemorrhage for which the objective of treatment is to stop the bleeding and prevent its recurrence in the early period.

4. Patients who had survived an acute variceal bleeding and the goal of therapy is to prevent recurrence of bleeding in the late period (secondary prevention).

The prevention of the esogastric varices formation (pre-primary prophylaxis)

Each new patient diagnosed with cirrhosis requires the effectuation of upper gastrointestinal endoscopy for the identification of varices presence and their degree. Large, multicenter, randomized and controlled trials found no difference between placebo and β-blockers in preventing the formation of varices in patients who have not developed esogastric varices [19]. Therefore, no specific treatment for portal hypertension is recommended in these patients. The main focus at this stage is to treat the underlying cause of cirrhosis, which will reduce portal hypertension and therefore will prevent the development of clinical complications.

The prevention of the first variceal bleeding (primary prevention)

The first variceal hemorrhage occurs with an annual rate about 15%, although currently mortality after a variceal bleeding is lower than in the last two decades, however, remains significant (7% – 15%) [20 – 22] and it is associated with significant morbidity and high costs for treatment. The prevention of the first episode of bleeding, therefore, is an important part of the portal hypertension treatment. The size of varices, "red signs" on varices (endoscopic view) and severity of liver disease (Child-Pugh C class) identifies patients with the highest risk of variceal hemorrhage [12]. Therefore, at this stage, patients must be differentiated depending on the risk of bleeding:

- high-risk patients (those with medium/large varices or those with small varices, but with "red signs" or evolutionary stage Child-Pugh C).
- low-risk patients (those with small varices without "red signs" or which appear in patient with Child-Pugh A or B class).

Several studies had demonstrated that for patients with medium/large varices, the nonselective β-blockers (propranolol, nadolol) are as effective as endoscopic variceal ligation in the prevention of first variceal bleeding [23, 24], but the author's recommendations are based on using the therapy according to existing local resources, the specialist experience in this area and patient preference.

For patients with increased risk of bleeding and a low degree of varices the principal therapeutic options is nonselective β-blockers administration, and the application of endoscopic variceal ligation is difficult.

For patients with low risk of hemorrhage and small varices there is limited evidence demonstrating that their growth can be slowed by using nonselective β-blockers [25]. Therefore, the use of nonselective β-blockers in this case is considered optional and should be discussed with the patient.

For primary prevention the starting dose of propranolol administration is 20 mg orally 2 times a day. Dosage adjustment is made every 2–3 days until the target dose is reached, which decreases the heart beats by 25% from the initial, but must not fall below 50 – 55 beats/minutes. The maximum dose does not exceed 320 mg. At each ambulatory visit it is necessary to adjust the dose of β-blocker. In the absence of contraindications the treatment is indefinite. Nadolol is administered in a 40 mg dose in a single dose and the maximum dose should not exceed 160 mg. Dose adjustments are performed as in the case of propranolol administration. Endoscopic variceal ligation is performed every 2 – 4 weeks until the final variceal obliteration. The repeating of endoscopy is made over 1 – 3 months after obliteration and later over every 6 – 12 months.

For secondary prophylaxis, the management of nonselective β-blockers administration and endoscopic procedures is the same as in primary prevention. Isosorbide-5-mononitrate may be associated with non-selective β-blockers initially in a dose of 10 mg orally at night, and then 10 mg orally twice a day with a maximum dose of 20 mg twice a day. Systolic blood pressure should not fall below 95 mmHg. The duration of therapy with isosorbide-5-mononitrate is also indefinite.

Nonselective β-blockers decrease portal pressure by reducing portal blood flow. Their mechanism of action involves the decreasing of cardiac output by blocking β_1 receptors, but splanchnic vasoconstriction is achieved by blocking β_2 receptors. The latter is the most important effect of nonselective β-blockers in portal hypotensive therapy (unlike the selective β-blockers). Nonselective β-blockers advantages include low cost and simplicity of administration. Because nonselective β-blockers decrease the degree of portal hypertension, their use may also reduce other complications of cirrhosis, such as bleeding from eso-gastric varices and portal-hypertensive gastropathy, ascites and spontaneous bacterial peritonitis [26, 27]. It was found that, in fact, a significant reduction in portal pressure was associated with the improvement of survival in patients with liver cirrhosis [28]. In addition, in the opinion of some authors, once the patient administers nonselective β-blockers it is not necessary to repeat endoscopy.

Endoscopic variceal ligation has some advantages: during the procedure can be examined the whole upper digestive tract mucosa, has relatively few contraindications and a lower incidence of side effects compared to nonselective β-blockers [9].

The main disadvantage of nonselective β-blockers is that approximately 15% of patients may have absolute or relative contraindications to the therapy administration and the other 15% require dose reduction or discontinuation of therapy due to frequent side effects (eg, fatigue, weakness, bronchospasm) that disappear after stopping these medicines [17].

Endoscopic variceal ligation risks include those related to endoscopic procedures and sedation (bleeding, aspiration, perforation and reaction to medications), along with the risk of bleeding from ulcers induced by the ligation. In fact, although the number of side effects is higher in nonselective β-blockers administration than after endoscopic variceal ligation [9], the severity of side effects is higher in performing the latter. Fatal side effects after using the non-selective β-blockers have been not reported, but have been reported deaths resulting from endoscopy procedures (e.g., bleeding from ulcers induced by varices ligation) [9, 10].

It is certain that the ideal portal hypotensive therapy has not been established. There are medical centers where is preferred endoscopic variceal ligation, while in other centers prefer to start with nonselective β-blockers, and then, if necessary, the use of endoscopic variceal ligation.

Carvedilol is a nonselective β-blocker, possessing additional vasodilating effect through anti-α_1-adrenergic activity. There is evidence that carvedilol administration in portal hypotensive purpose is more effective than endoscopic variceal ligation in preventing first variceal bleeding [29]. Although the use of carvedilol is considered a promising alternative, it is necessary to perform further research before it can be widely recommended.

The management of acute variceal hemorrhage

Acute variceal hemorrhage is a major medical emergency requiring intensive care. First, the basic treatment is directed to achieve hemodynamic stability. Blood transfusion is done to raise hemoglobin levels between 70 – 80 g/l [30], because the return of excessive blood volume can increase portal pressure [31, 32]. The survival is higher in patients with variceal hemorrhage submitted to restrictive transfusion policy. Restrictive transfusions significantly reduce mortality, particularly in Child-Pugh A and B cirrohosis [33].

It is necessary to correct coagulation disorders, although, currently, there are no clear recommendations on the management of coagulopathy and thrombocytopenia [34, 35].

Antibiotic prophylaxis is an integral part of therapy for patients with liver cirrhosis and upper gastrointestinal bleeding since the admission. Antibiotic prophylaxis is provided by quinolones and/or ceftriaxone in i/v administration [6, 36]. The risk of bacterial infections and mortality is reduced in patients Child-Pugh A, but are necessary prospective studies that can demonstrate that antibiotico-prophylaxis may be excluded from this group of patients.

Vasoactive medication needs to be started as soon as possible, even before diagnostic endoscopy. Endoscopy also is made as soon as possible and not later than 12 hours after addressing. If the bleeding source is identified, the elective procedure is endoscopic variceal ligation, but sclerotherapy is an option when ligation is technically difficult. TIPS is recommended in patients failing standard therapy (a combination of endoscopic and pharmacological treatment).

However, TIPS has a high mortality. The predictive factors of standard therapy failure are Child-Pugh C class, HVPG > 20 mmHg, and active bleeding on endoscopy [37]. Using the TIPS in the early period (approximately 48 hours of onset) in patients with increased risk of failure to standard therapy, significantly reduces mortality [18]. It occurs in patients with evolutionary stage Child-Pugh C (score 10 – 13 points) or evolutionary stage Child-Pugh B with active bleeding (at the moment of diagnostic endoscopy) and represents <20% of patients with variceal bleeding. In these patients it is recommended to consider the possibility of TIPS effectuation. The rest of the patients need to continue the standard therapy with vasoactive drugs for 2 – 5 days continually, depending on the bleeding control and the severity of liver disease. Vasoactive drugs may be discontinued once the patient had no bleeding for at least 24 hours. The tamponade with balloon is used only as a temporary measure (balloons are inflated for 12 hours or less) to control bleeding, while is planned the definitive treatment (TIPS or endoscopic therapy). A new esophageal stent was proposed last year that can replace the tamponade with ballon [38].

Although there are pros and cons for each of these first-line therapies, current recommendations are for the combination of pharmacological and endoscopic methods to effectively control acute hemorrhage.

Vasoactive agents improve the control of variceal bleeding when are combined with endoscopic therapy in comparison with application of endoscopic therapy exclusively [39]. However, there is a significant difference between various vasoactive agents on controlling bleeding and early rebleeding. Vasopressin is a powerful vasoconstrictor, but because it is associated with more side effects [40] it is not considered as vasoactive drug for first-line. Its use is limited because of many side effects associated with splanchnic vasoconstriction (for example, intestinal ischemia) and systemic vasoconstriction (e.g., hypertension, myocardial ischemia). However, in case of using vasopressin, it must be taken with nitroglycerin.Terlipressin is an analogue of vassopresin and represents a pharmacological agent which demonstrated in comparative studies the improvement of survival in patients with variceal hemorrhage [40]. It possess splanchnic vasoconstrictor effect. The active metabolite of terlipressin, lysine-vasopressin, is released gradually over several hours thus reducing typical side effects of vasopressin. Terlipressin is administered 2 mg i/v in bolus, and 2 mg every 4 hours during a bleeding episode. For the prevention of rebleeding the maintenance doses are 1 mg/4 hours i/v bolus up to 5 days.

Somatostatin inhibits the vasodilatory substances, such as glucagon, causing splanchnic vasoconstriction and the decrease of portal blood flow. Initially, is administered 250 pg i/v in bolus followed by continuous infusion from 250 pg to 500 pg/hour up to 5 days.

Octreotide is a somatostatin analogue and has the same mechanism of action as somatostatin, but a longer duration of action. Initially, is administered 50 μg i/v in bolus, then each 50 μg/hour in continuous infusion up to 5 days.

Vapreotide is also an analogue of somatostatin with the same mechanism of action but with a higher metabolic stability. Initially it is administered 50 μg i/v in bolus, then each 50 μg/hour in continuous infusion up to 5 days. The main side effects of somatostatin analogues (octreotide and vapreotide) are sinus bradycardia, hypertension, arrhythmias and abdominal pain.

In practice, the choice of a pharmacological agent is based usually on availability and cost.

So, the preferable treatment of acute variceal hemorrhage is combined: vasoactive drugs administered before the effectuation of endoscopy and emergency endoscopic therapy. Pharmacological elective therapy is represented by terlipressin (lower mortality in placebo-controlled trials) or somatostatin and octreotide (fewer side effects). The elective endoscopic therapy is endoscopic variceal ligation.

Recommendations can vary according to the severity of liver disease. In patients who are in evolutionary stage of cirrhosis Child-Pugh C (or Child-Pugh B with active bleeding), the risk of standard therapy failure (vasoactive drugs plus endoscopic variceal ligation) is large and therefore it is appropriate to pass to "rescue" therapy (i.e., TIPS) before we get a failure of standard therapy. Patients in Child-Pugh A class, the mortality after standard treatment is around zero [20, 22], and these patients may respond to vasoactive treatment in monotherapy, although this requires further researches.

The prevention of variceal hemorrhage recurrence (secondary prevention)

The risk of rebleeding in patients who have suffered a variceal bleeding is high (average rate of rebleeding is 60%), with a mortality of up to 33%. The prevention of rebleeding is therefore an essential part of the management in patients with variceal bleeding. Patients in the acute episode of bleeding who benefited from TIPS, do not require a specific hypotensive therapy or endoscopic surgery on varices, but should be cautious for transplant. TIPS's permeability should be checked by Doppler ultrasonography every 6 months. For most patients (who have not been effectuated TIPS during an acute episode of bleeding), the secondary prophylaxis with nonselective β-blockers should be started as soon as possible, but after intravenous vasoactive drug administration is discontinued. Nonselective β-blockers significantly reduce the risk of recurrent bleeding [7]. Although, according to several studies, the addition of isosorbide 5-mononitrate with nonselective β-blockers has a greater effect on reducing portal pressure [41], in clinical trials the combination of these groups is not different from monotherapy with nonselective β-blockers in terms of rate rebleeding or death, but has a higher rate of side effects [42].

The sclerotherapy decreases the rate of bleeding and the mortality, but is associated with serious complications (eg., esophageal stricture, bleeding from ulcer). Sclerotherapy has been replaced with endoscopic variceal ligation because the ligature showed significantly better results in comparison with sclerotherapy about rebleeding, mortality and side effects. Several studies have compared pharmacological treatment

(nonselective β-blockers in addition with isosorbide 5-mononitrate) versus variceal endoscopic ligation and found that there are no significant differences in the occurrence of recurrent haemorrhage, but long-term administration of pharmacological treatment has a beneficial effect on patient survival [43]. It was found that the combination of pharmacological treatment (nonselective β-blockers in monotherapy or nonselective β-blockers + isosorbide 5-mononitrate) plus endoscopic variceal ligation is associated with lower rates of rebleeding than pharmacological or endoscopic monotherapy [44, 45] and it is an elective option.

If patients have and recurrent variceal hemorrhage despite of combined pharmacological and endoscopic treatment, is indicated the application of TIPS with polytetrafluoroethylene-covered stents [46] or, if necessary, surgical shunts [47].

Pharmacologic agents give protection against rebleeding both in the period up to the first variceal bleeding and in the period of recurrence prevention, with or without the effectuation of endoscopic variceal ligation. It is considered useful to give nonselective β-blockers in monotherapy or in combination with isosorbide 5-mononitrate. The choice of treatment tactics depends on patient tolerability. Patients who are not candidates for endoscopic variceal ligation should administrate the combined drug therapy (nonselective β-blockers + isosorbide 5-mononitrate).

The lowest rates of variceal bleeding recurrences (about 10%) are observed in people who have a positive hemodynamic response to pharmacological treatment, defined as a decrease in HVPG under 12 mmHg or a decrease of more than 20% from baseline of HVPG [28, 48]. It is reasonable to guide pharmacological therapy according to hemodynamic response and, therefore, patients who achieve a positive hemodynamic response do not require endoscopic therapy. Patients who are intolerant or have contraindications to pharmacological therapy should receive endoscopic variceal ligation in monotherapy.

Some researchers have observed that the administration of non-selective β-blockers in patients with refractory ascites is associated with a lower survival than patients without refractory ascites [49]. However, it is noted that patients with refractory ascites have a higher prevalence of varices and, particularly, those with an increased risk of bleeding, which leads to a higher mortality. So now, even these patients may benefit from treatment with nonselective β-blockers [7, 50] and therefore nonselective β-blockers are not contraindicated in patients with refractory ascites. It is necessary to note that combined treatment with nonselective β-blockers and isosorbide 5-mononitrate has a higher incidence of superimposed side effects caused by isosorbide 5-mononitrate association, usually manifested by headaches and dizziness. As mentioned above, the lowest rate of rebleeding is in patients with a positive hemodynamic response. On the other hand, while HVPG guiding therapy seems to be rational, a small study showed that HVPG guiding therapy results are not different from combined endoscopic and pharmacological treatment [51]. Although HVPG determination is standardized and it is performed widely in large clinical centers, HVPG guiding therapy has not yet been introduced in the guidelines recommendations[52].

As mentioned above, endoscopic variceal ligation is associated with bleeding from ulcer induced by this procedure. Treatment with proton pump inhibitors after variceal ligation significantly reduces the size of these ulcers and, ultimately, decreases the risk of bleeding [53].

The current standard treatment of portal hypertension in children

The most common causes of portal hypertension in children are biliary atresia and portal vein thrombosis. The data about prevalence of esophageal varices in children with portal hypertension are very limited and till now there have been no randomized controlled trials that would compare different methods of treatment for primary and secondary prevention [54].

About primary prevention, currently there are no clear treatment recommendations [55, 56]. Gathering of experts at the annual meeting of the American Association for Study of Liver Disease concluded that before getting the results of a randomized study in children, the pediatric research should focus on approach to the natural history and diagnosis of varices, the predictive factors of variceal bleeding, optimal therapy with β-blockers and endoscopic variceal ligation and alternative methods of treatment to assess therapeutic efficacy in children [57]. The management of acute variceal bleeding in children is based on the use of vasoactive agents, antibiotic prophylaxis and endoscopic variceal ligation. In children with portal vein thrombosis, the meso-rex by-pass seems to be the best option for secondary prophylaxis [55, 56, 58].

Conclusions

The elective treatment for the prevention of variceal hemorrhage is a combination of pharmacologic therapy (nonselective β-blockers ± isosorbide 5-mononitrate) and endoscopic variceal ligation. The assessment of bleeding risk is difficult, but the most important predictor of recurrent bleeding is evolutionary stage of cirrhosis Child-Pugh. The patients with Child-Pugh A class cirrhosis need to apply a single method of treatment, while patients with advanced liver disease require a combined therapy. Patients who have failed this therapy should be considered for TIPS placement, or surgical shunt. Patients with recurrent variceal bleeding are in a state of "continuous decompensation" of liver cirrhosis and, as such, should be evaluated for liver transplantation.

In the last two decades significant advances in the management of portal hypertension have improved the survival of patients with liver cirrhosis and portal hypertension. Were developed treatment strategies and well-established therapeutic options for each clinical stage and were identified different subpopulations of patients who require differentiated management.

It is evident the necessity to perform new research directed towards identifying new pharmacological options that would

allow to get a positive hemodynamic response in most patients and thus would give up on the necessity to determine HVPG and may even give up on endoscopic therapy.

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