REVIEW ARTICLE

How we manage variceal hemorrhage in cirrhotic patients

Key practical messages from the British Guidelines

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KEY WORDS

endoscopic band ligation, nonselective β-blockers, portal hypertension, transjugular intrahepatic portosystemic shunt, varices

ABSTRACT

Variceal bleeding is a serious complication of portal hypertension with high morbidity and mortality. Advances in our understanding of screening and risk stratification along with evidence-based management strategies for acute variceal bleeding as well as primary and secondary prevention have improved overall outcomes in patients with portal hypertension. The guidelines recently published by the British Society of Gastroenterology (BSG) and Baveno 6 consensus have aimed to enhance the standard of care in the management of varices and their complications. This concise review focuses on the key practical messages for screening and management of varices and variceal bleeding in light of these guidelines. The review also takes into account important evidence published since the BSG guidelines and Baveno 6 consensus.

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Received: February 13, 2016.
Accepted: February 13, 2016.
Published online: March 21, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (3): 174-184
doi: 10.20452/pamw.3319

Introduction Variceal bleeding remains one of the major complications of chronic liver disease and portal hypertension and is associated with a mortality rate of 7% to 15%.[1] Prevention of bleeding or recurrent bleeding is critical in the management and prognosis of these patients, and recognition and treatment of patients at risk for variceal bleeding is therefore essential. There have been a multitude of studies published in recent times investigating whom to screen for varices, when they should be treated, and what the evidence is around prevention of bleeding and rebleeding and management of acute variceal bleeding. More recently, the British Society of Gastroenterology (BSG) and Baveno 6 consensus have updated their recommendations on the management of patients with gastroesophageal varices.[2,3] This review aims to briefly appraise the current evidence around prevention and management of both esophageal and gastric variceal bleeding and aims to give a concise overview and recommendations on the key management strategies in light of the recently published guidelines.

Risk factors for bleeding and diagnosis of gastroesophageal varices Longitudinal studies have shown that varices develop over time based on several factors including ongoing hepatic injury, degree of portosystemic shunting, and portal pressures. A database analysis using a competing risk model showed that the cumulative incidence of varices at 10 and 20 years was 44% and 53%, respectively.[1]

The risk of variceal hemorrhage is also influenced by the severity of liver disease and the presence of high-risk stigmata at endoscopy, such as red signs.[4] Gastroesophageal varices develop when the hepatic venous pressure gradient (HVPG) is higher than 10 mmHg, and the risk of rupture occurs when HVPG is higher than 12 mmHg.[5,6] Gastric varices can bleed despite lower portal pressure due to their larger diameter resulting in increased wall tension.[7] The risk of gastric variceal bleeding is between 20% and 50% during follow-up and is related to the pressure and flow within the varix, the size of the varix, and the wall thickness.[8]

Esophageal varices can be classified according to size[3]: 1) grade I, flatten on air insufflation; 2) grade II, do not flatten with air insufflation and are between grades I and II in size; 3) grade III, occupy the entire lumen. The introduction of transient elastography has allowed the early identification of patients with compensated chronic liver disease who are at risk of developing clinically significant portal hypertension, thus preventing

TABLE 1 Nonselective β-blockers used in portal hypertension

	Propanolol	Carvedilol	Nadalol
proposed mechanism of action	β_1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction via β_2 blockade	β_1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction via β_2 blockade additional intrinsic α1-adrenergic activity	β_1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction via β_2 blockade
side effects / cautions	hypotension, bradycardia, caution in peripheral vascular disease/asthma Consider discontinuation at time of spontaneous bacterial peritonitis, renal impairment, and hypotension (see text).		
indications	nonselective β-blockers in primary prevention of variceal hemorrhage nonselective β-blockers in combination with variceal band ligation for secondary prevention of variceal hemorrhage		
dose	40 mg twice daily if tolerated (maximum dose, 320 mg) or once HR <50–55 bpm	6.25 mg once daily to titrate to maintenance dose of 12.5 mg once daily if tolerated or once HR <50–55 bpm	40 mg once daily (maximum dose, 240 mg) or once HR <50–55 bpm

Abbreviations: HR, heart rate

the need for all patients with liver disease to undergo upper gastrointestinal endoscopy. Berzigotti et al[9] demonstrated that combined data on liver stiffness, spleen diameter, and platelet count in a statistical risk model can be used to identify patients with compensated cirrhosis most likely to have portal hypertension and esophageal varices. A meta-analysis of 18 studies on the diagnostic value of predicting portal hypertension highlighted that transient elastography could be used as a good screening tool for significant portal hypertension, but has only a moderate diagnostic utility for the prediction of esophageal varices or large esophageal varices.[10] Baveno 6 recommends that patients with compensated cirrhosis who have a liver stiffness of less than 20 kPa on transient elastography and with a platelet count exceeding 150 × 10^9/l have a very low risk of having varices requiring treatment and can avoid screening endoscopy and instead undergo annual transient elastography and measurement of platelet count.[2]

The prevalence of gastric varices (GVs) at index endoscopy in patients with portal hypertension is about 20%.[11] GVs are commonly seen in patients with portal hypertension secondary to portal or splenic vein obstruction.[11] GV bleeding accounts for 10% to 20% of all variceal bleeding, but the outcome is worse than with bleeding from the esophageal varices.[11,12] The Sarin classification is commonly used to classify GV, according to their location within the stomach.[11] Gastroesophageal varices (GOVs) are associated with the esophageal varices and are further subdivided into 2 groups. GOV1 are esophageal varices that extend 2 to 5 cm below the gastroesophageal junction along the lesser curve of the stomach. These are the most common type of GVs (75%) seen in cirrhotic patients.[11] GOV2 extend beyond the gastroesophageal junction into the fundus of the stomach and are the second common type of GV (21%). Isolated GVs (IGVs) occur independently of esophageal varices. These are also subdivided into IGV1, which are located in the fundus of the stomach (fundal varices), and IGV2, which refer to ectopic varices located elsewhere in the stomach.

Primary prevention of variceal bleeding Nonselective β-blockers (NSBBs) have been well established as the cornerstone of prevention of variceal bleeding in cirrhotic patients. By blocking β_1- and β_2-receptors, NSBBs reduce portal pressure by decreasing cardiac output and splanchnic blood flow, which results in splanchnic vasoconstriction due to the unopposed effect of α1-receptors.[13] The 3 NSBBs are propranolol, nadolol, and carvedilol (TABLE 1).

Preprimary prevention Prevention of the development of varices in patients with portal hypertension is known as preprimary prophylaxis. A recent meta-analysis of 6 studies did not support the use of NSBBs in cirrhotic patients with no and small varices, while highlighting that these heterogeneous studies had small cohorts with significant loss of follow-up.[14] Patients are also subject to side effects of NSBB (TABLE 1). At present, United Kingdom and international guidelines do not recommend NSBBs for preprimary prophylaxis.[2,3,14,15]

Primary prevention Small varices (Grade I) A meta-analysis of trials evaluating the effect of NSBBs in patients with small varices demonstrated that the incidence of first variceal hemorrhage was quite low at 7% over 2 years, and the reduction to 2% with NSBBs was not statistically significant.[15] There was also a significant increase in the number of adverse events from NSBBs. Hence, the use of NSBBs in all patients with small varices is not recommended, but potentially may be considered in patients with red signs overlying the varices on endoscopy.[3]

Medium-to-large varices (Grades II–III) Evidence for use of NSBBs in primary prevention of variceal bleeding in patients with medium-to-large esophageal varices is well established, with variceal band ligation (VBL) being an alternative method for primary prophylaxis. A meta-analysis

TABLE 2 Key messages for primary prevention

All patients with cirrhosis should undergo endoscopy, although liver stiffness (derived from transient elastrography) along with platelet count can be used to select patients with compensated cirrhosis who do not require endoscopic screening.
In patients without varices: • NSBBs are not recommended for prevention of the development of varices in patients with cirrhosis. • Repeat endoscopy at 2 to 3 yearly intervals depending on disease progression, for example, influenced clearance of viral hepatitis, active alcohol consumption.
In patients with grade I varices: • NSBBs should only be used if accompanied by red signs irrespective of the severity of liver disease. • If there are no red signs, then these patients should undergo annual surveillance endoscopy.
In patients with grade II–III varices: • NSBBs with propranolol, carvedilol, or nadolol should be used as first-line treatment. • VBL should be reserved for patients with contraindications to or intolerance of NSBBs. Patient's preference should also be considered.
In patients with gastric varices: • NSBBs can be considered in GOV1 and large GOV2. • Cyanoacrylate is only recommended in clinical trials.
The dose of NSBBs should be titrated to the maximum tolerated dose.
Consideration should be given to discontinuing NSBBs (and commencing VBL) at time of spontaneous bacterial peritonitis, hypotension, and acute renal impairment. After treatment of precipitant, NSBBs can be recommenced with very close monitoring of hemodynamic parameters.
Surveillance endoscopy is not recommended if the patient is commenced on an NSBB.
Combination therapy (drug and endoscopic therapy), sclerotherapy, transjugular intrahepatic portosystemic shunt or shunt surgery, and isosorbide mononitrate are not recommended for primary prevention.

Abbreviations: GOV, gastroesophageal varices; NSBB, nonselective β-blockers; VBL, variceal band ligation

published in 2003 of 11 trials that included 1189 patients evaluating NSBBs vs nonactive treatment or placebo in the prevention of the first variceal hemorrhage demonstrated that β-blockers significantly reduced the risk of the first variceal bleeding in patients with medium- or large--sized varices (30% in controls vs 14% in patients treated with β-blockers) with a number needed to treat of 10 patients to prevent 1 bleeding episode.[16] Mortality was also shown to be significantly lower and cost effectiveness was higher in the β-blocker-treated group in other studies.[16,17] The efficacy of NSBBs in the prevention of bleeding is independent of the cause and severity of cirrhosis, ascites, and size of varices, and the risk of variceal hemorrhage returned to baseline when β-blockade was discontinued.[18]

With its efficacy in primary prevention established, trials have subsequently focused on comparing NSBBs with other therapies, including endoscopic therapy. Sclerotherapy has been substituted by VBL as endoscopic intervention of choice and has no added benefit over NSBBs in primary prevention.[19] A recent Cochrane meta-analysis of 19 randomized controlled trials (RCTs) with 1504 patients, comparing VBL with NSBBs for primary prevention, showed no significant difference in mortality (overall and bleeding-related) between the 2 groups.[20] NSBBs were shown to be significantly less effective in comparison with VBL in preventing index variceal bleeding (13% VBL vs 19% NSBBs; risk ratio [RR], 0.66; 95% confidence interval [CI], 0.45–0.96); however, this significance was lost when the analysis only included trials with randomization or full papers. Treatment with NSBBs was associated with adverse events including lethargy, dizziness, hypotension, impotence, and peripheral edema, whereas VBL was associated with clinically significant bleeding and chest pain. Carvedilol has the potential to have a better side effect profile compared with propranolol, with only 10% of patients experiencing significant problems.[21] However, the evidence of combined treatment strategies (ie, NSBB and VBL) for primary prevention is conflicting.[22-24] A recent RCT revealed that VBL alone and VBL + NSBB therapy were equally effective in primary prophylaxis, although the risk of variceal recurrence was lower in the combination group than VBL alone.[25]

The use of NSBBs in advanced cirrhosis and its association with a higher mortality in patients with spontaneous bacterial peritonitis has recently caused controversy; however, the evidence is conflicting.[26-28] The higher mortality is likely to reflect the effect on impairment of cardiovascular reserve by the NSBB in the event of sepsis. The BSG advise that NSBB are discontinued at the time of spontaneous bacterial peritonitis, renal impairment, and hypotension, and Baveno 6 makes similar recommendations.[2,3]

Gastric varices A prospective RCT compared the efficacy of a cyanoacrylate (CA) injection and NSBBs in primary prevention of bleeding from large (>10 mm) GOV2 and GOV1 in 89 patients.[29] Over a 26-month follow-up period, bleeding occurred in 38%, 10%, and 53% of patients in the NSBB, CA, and no-treatment groups, respectively. Mortality was lower in the CA group (7%) than in those given no treatment (26%) but was similar to that in the NSBB group (17%). Variceal size and liver dysfunction evaluated by the Model for End-Stage Liver Disease score were factors associated with a high risk of bleeding. In another retrospective study, 27 patients with high risk of bleeding from GV (large or fundal or Child's C cirrhosis) had a CA injection as prophylaxis.[30] It demonstrated that CA may be an effective prophylactic treatment for higher-risk GV.

However, the above studies were small and many clinicians have concerns about the safety of CA injection in the context of primary prophylaxis. Therefore, larger studies are needed before a formal recommendation in primary prophylaxis for GV can be made.

Other therapies At present there is no role of nitrates and transjugular intrahepatic portosystemic stent shunt (TIPSS) in primary prophylaxis.[2,3] The role of surgery such as portocaval shunts is limited by increased risk of encephalopathy and

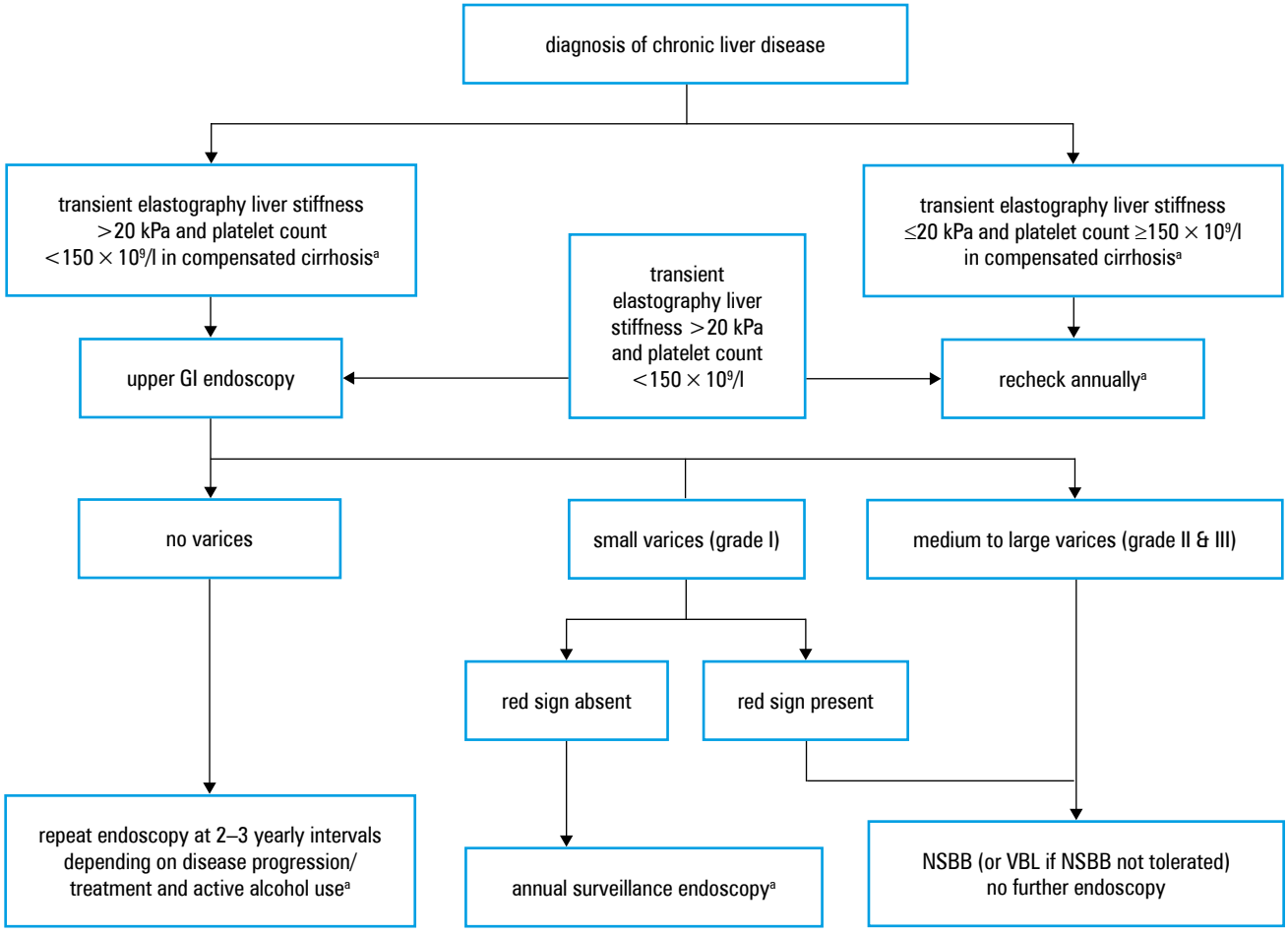

FIGURE 1 Recommended variceal surveillance and primary prevention pathway
a endoscopy should be offered at any time of decompensation
Abbreviations: GI, gastrointestinal; others, see TABLE 2

mortality despite better efficacy in the prevention of bleeding.[19]

The key recommendations for screening of varices and primary prophylaxis are summarized in TABLE 2 and FIGURE 1.

Acute variceal hemorrhage (FIGURE 2) Acute variceal hemorrhage (AVH) remains a devastating complication of portal hypertension. Despite improvements in survival, the 6-week mortality still reaches 20%,[31] with inpatient mortality of 15%.[32] Much of the improvement in recent years relates not just to advances in endoscopy, interventional radiology and drug therapy but also to better intensive unit care. This is evidenced in a recent retrospective series showing improved survival at 2 time points separated by 10 years, despite the patients having greater comorbidities.[33]

A number of variables have been shown to predict mortality and rebleeding following AVH. These include the Model for End-stage Liver Disease (MELD) >19, HVPG >20 mmHg within 48 hours, and clinical parameters such as active bleeding at endoscopy.[34-37] These can be helpful in stratifying patients most likely to benefit from further interventions such as prompt TIPSS to improve outcomes.[38]

Initial management Initial resuscitation must aim to correct hypovolemia and ensure adequate tissue perfusion and oxygenation. Although good intravenous access is mandatory, there is no absolute requirement for central venous access. Inadequate resuscitation can have adverse consequences and should aim for a systolic blood pressure of 100 mmHg and, if possible, venous saturations above 70%.[3] Particular care should be exercised in patients who are older and with more comorbidities who are at high risk of mortality. Patients must be managed with close monitoring of vital signs. An ultrasound scan after immediate management is important to assess portal vein patency.

There is good evidence from a large RCT for restrictive transfusion with the aim of maintaining the hemoglobin level at 7 to 8 g/dl.[39] Although there was no clear survival benefit in the subgroup of patients with cirrhosis and variceal bleeding, there were significantly fewer treatment failures and need for salvage TIPSS. There was also lower HVPG with restrictive transfusion. The BSG guidelines would recommend restrictive transfusion provided patients are hemodynamically stable.[3] The role of platelet transfusion and correction of clotting abnormalities is unproven. However, some practical advice is given below.

Patients should be managed in a high-dependency setting with early involvement of an anesthetist in those actively bleeding at risk of aspiration. Invasive ventilation and airway protection are essential prior to endoscopic therapy in actively bleeding patients.[3]

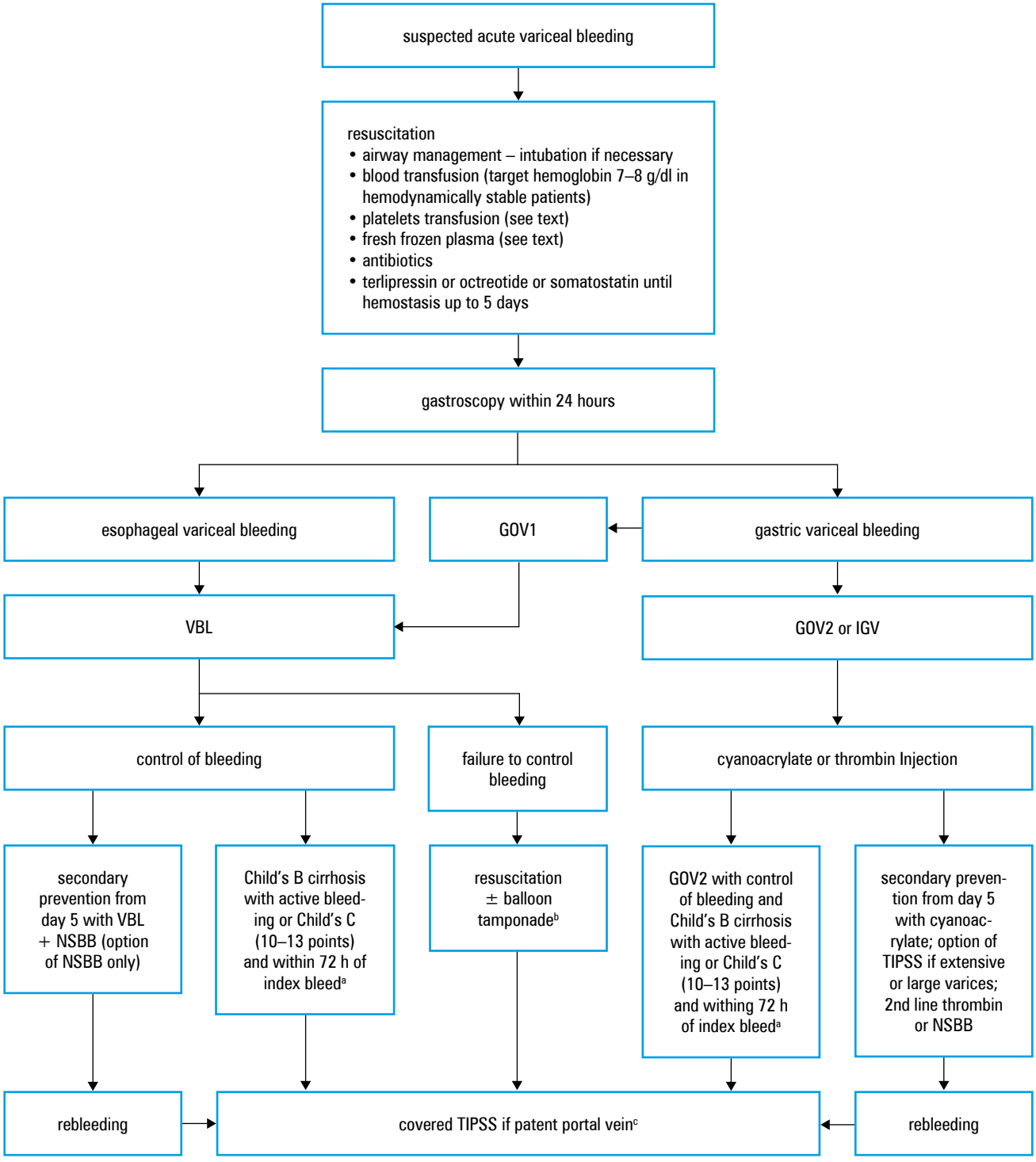

FIGURE 2 Algorithm for the management of acute variceal hemorrhage

a as an option if local resources available or refer to specialist center

b removable esophageal stents can be considered in esophageal variceal bleeding and if local resources are available

c option of shunt surgery in well-compensated patients or where TIPSS not feasible. B-RTO may also be considered (see text). In sinistrial portal hypertension options of splenectomy or splenic artery embolization depending on resources.

Abbreviations: B-RTO, balloon-occluded retrograde transvenous obliteration; IGV, isolated gastric varices; TIPSS, transjugular intrahepatic portosystemic shunt; others, see TABLE 2 and FIGURE 1

Drug therapy (TABLE 3) Drug therapy is crucial to improve outcomes and should be administered as soon as variceal bleeding is suspected even before endoscopy.

Broad-spectrum antibiotics compared with placebo resulted in a 21% reduction in mortality, 47% reduction in rebleeding, and 57% reduction in bacterial infections in a recent meta-analysis.[40] Local antibiotic polices should be observed, although there are reports of quinolone resistance when cephalosporins may be a better choice.[41] The duration should be up to 5 days. A recent observational study reported on a low risk of bacterial infections in patients with Child's A disease who

TABLE 3 Vasoactive drugs used in portal hypertension

Drug	Dose	Adverse events
terlipressin	2 mg IV immediately, then 1–2 mg every 4–6 hours until hemostasis achieved, or for 3 to 5 days	Caution should be exercises in ischemic heart disease, peripheral vascular disease, epilepsy. Can cause hyponatremia. Other side effects include abdominal pain and diarrhea.
octreotide	50 mcg bolus IV initially, followed by 50 mcg/h IV infusion until hemostasis achieved or for 3 to 5 days	vomiting and diarrhea
somatostatin	250 mg bolus IV initially, followed by 250 mg/h IV infusion for 3 to 5 days	abdominal pain and diarrhea

may have less benefit from prophylactic antibiotics.[42] This requires confirmation in controlled studies.

Vasoactive agents are highly effective in preventing rebleeding. The main agents are summarized in TABLE 2. Terlipressin compared with placebo reduces failure to control bleeding and survival by 34%.[43] There is evidence from a recent meta-analysis that terlipressin, somatostatin, and octreotide have equal efficacy.[44] Caution is required due to the risk of ischemic side effects and hyponatremia.[45] Regular clinical examination and monitoring of electrolytes is essential, with prompt discontinuation of terlipressin, if required, and commencement of alternative drugs. Vasoactive agents are best used in combination with endoscopic therapy and continued until there is hemostasis for up to 5 days, although 2 days are likely to be sufficient.[46]

Endoscopic therapies Endoscopy should be performed as soon as possible after satisfactory resuscitation. The role of early endoscopy has been studied in uncontrolled studies suggesting a benefit.[47] Current guidelines recommend endoscopy within 24 hours or as soon as possible in unstable patients.[3]

VBL is the first-line endoscopic therapy. There is good evidence to support the superiority of VBL over sclerotherapy with a 53% reduction in rebleeding and 33% reduction in mortality.[48] Complications such as esophageal ulceration are also less common with VBL.

Endoscopic therapy should be used in combination with vasoactive agents as mentioned above, and there is evidence to support reduced treatment failures and rebleeding, although survival was not affected.[49]

Failure of endoscopic therapies Balloon tamponade is very effective where endoscopic therapy is ineffective, but is associated with a 50% rebleeding rate on deflation of the balloon.[50] Adverse events can be severe with mucosal injury or even necrosis and aspiration risk in up to 20% of patients. Endoscopic placement may reduce complications. Esophageal balloon inflation is only required in exceptional cases. Balloon tamponade facilitates stabilization of a patient and must only be considered as a bridge to definitive therapies such as TIPSS or surgery. There has been recent interest in removable esophageal stents, which are placed with radiological guidance or at endoscopy. A recent randomized trail suggested a benefit over balloon tamponade with reduced bleeding and trend towards lower adverse events, transfusion requirement, and need for salvage therapy.[51] However, it was small, with only 28 patients, and survival benefit was not seen. Removable esophageal stents can be left in place for up to 14 days. A recent systematic review showed that stent migration can be an issue in up to 36% of cases[52]; however, the expertise for inserting stents may not be available in many centers.

Transjugular intrahepatic portosystemic shunt TIPSS allows for immediate decompression of the portal system, with over 90% success in controlling variceal bleeding.[53] It can be used as salvage therapy when other measures in patients fail, but mortality can be high with risk of decompensation and hepatic encephalopathy.

Stratification of patients most likely to benefit was initially explored in an RCT utilizing HVPG measurements within 24 hours of admission with AVB. Patient with HVPG of 20 mmHg or higher were randomized to TIPSS using uncovered stents or standard of care with endoscopic therapy and antibiotics.[54] Bleeding and survival were both better with TIPSS and comparable to patients with HVPG of less than 20 mmHg. However, endoscopic therapy was sclerotherapy and not all patients received a vasoactive medication. HVPG measurements are only available in larger centers.

A further RCT addressed these shortcomings. Patients were randomized to polytetrafluoroethylene (PTFE)-covered TIPSS within 72 hours of admission or standard of care (VBL, antibiotics, and vasoactive drugs) if they were Child's B with active bleeding or Child's C (Child's score ≤13).[38] There was a significant benefit of early TIPSS with survival of 86% versus 61% and treatment failure of 3% vs 50%, with no difference in encephalopathy over a 12-month period. However, a recent meta-analysis of 2 RCTs and 2 observational studies of early TIPSS was marred by significant heterogeneity in survival analysis.[55] Further RCTs are therefore recommended.

Surgery As a result of advances in interventional radiology, in particular PFTE-covered TIPSS, surgery plays a limited role in the management of acute variceal bleeding. Shunt surgery may have a role where TIPSS is not feasible, such as in portal vein thrombosis.[3]

Gastric varices The initial management of GV bleeding is similar to that of OV bleeding with regards to resuscitation and pharmacological therapies. GOV1 are treated as OV with endoscopic band ligation. Endoscopic therapy with tissue

TABLE 4 Key messages for management of acute variceal bleeding

Resuscitation should aim for optimal airway management including intubation if needed.
A restrictive blood transfusion to maintain hemoglobin levels of 7 to 8 g/dl in hemodynamically stable patients is suggested.
Platelet transfusion in active bleeding with platelet count of less than 50×10^9/l is suggested
Fresh frozen plasma where fibrinogen is <1 g/l or INR >1.5 is suggested.
Pharmacological therapy with vasoconstrictors (terlipressin, octreotide, or somatostatin) until hemostasis or up to 5 days and antibiotics as soon as possible following suspected variceal hemorrhage is recommended.
Gastroscopy should be performed as soon as possible in unstable patients, and within 24 hours in all other patients.
If there is evidence of variceal bleeding, the recommended first-line endoscopic therapies are as follows: • VBL of esophageal varices or gastric varices (GOV1). • cyanoacrylate or thrombin injection of gastric varices (GOV2 or IGV) • PTFE-covered TIPSS can also be considered if there are extensive gastric varices.
If bleeding is controlled: • Commence secondary prophylaxis with NSBB and continue banding program until variceal eradication. • For GOV2 and IGV continue endoscopic therapy with cyanoacrylate or thrombin.
In the case of failure to control bleeding, consider: • Balloon tamponade (for esophageal, GOV- and IGV1-type varices) or removable esophageal stents (for esophageal varices only) as temporary measure. • PTFE-covered TIPSS insertion or surgical therapies as definitive therapies. • In GV bleeding, B-RTO can be considered if PTFE-covered TIPSS is not feasible, depending on local resources. • In GV bleeding from sinistral portal hypertension, splenectomy or splenic artery embolization are the options.
Consider early PTFE-covered TIPSS if Child's B cirrhosis with active bleeding from esophageal varices or gastric varices (GOV1 or GOV2), or Child's C cirrhosis (Child's score ≤13 or less) within 72 hours of initial bleed.

Abbreviations: INR, international normalized ratio; PTFE, polytetrafluoroethylene; others, see TABLE 2 and FIGURE 2

adhesives, mainly CA, is the therapy of choice for bleeding IGV1 and GOV2.[2,3,56] A recent systematic review showed that the rate of rebleeding was lower with CA compared with band ligation (prevention of rebleeding, RR, 0.60; 95% CI, 0.41–0.88), with no difference in control of acute bleeding or mortality.[57] Distant emboli (pulmonary, cerebral, and splenic) are seen in 0.7% to 3% of patients, and complication-related mortality was 0.5%.[56,58,59] Endoscopic ultrasonography (EUS)-guided therapy of GV is emerging as a promising approach in selected patients. A report on 30 patients showed 100% acute hemostasis with EUS-guided therapy for fundal GV (IGV1 and GOV2) with CA and fibered coils over standard endoscopic injection with CA alone.[60] In recent uncontrolled studies, human thrombin was found to be safe and effective in the treatment of acute GV bleeding, with hemostasis rates of 70% to 100%, although rebleeding rates ranged from 7% to 50%.[60-64]

Balloon tamponade is used where there is failure to control bleeding. A single study demonstrated that the Linton–Nachlas tube was more effective in achieving hemostasis in fundal variceal bleeding than the Sengstaken–Blakemore tube due to the large volume of its gastric balloon.[65]

TIPSS is the treatment of choice in patients with bleeding GVs after failure to control initial hemorrhage.[66,67] Early TIPSS using covered stents as previously mentioned also has a role in GOV1 and GOV2.[2,38] TIPSS may also be considered in patients with extensive GV in the presence of a patent portal vein.[3]

Balloon-occluded retrograde transvenous obliteration (B-RTO) was introduced in Japan as a treatment method aiming to directly obliterate GV in patients with gastrorenal or gastrocaval shunts. A balloon catheter is introduced into these shunts via the femoral or internal jugular vein and inflated to block blood flow. Veins draining GVs are then embolized with microcoils and a sclerosant is injected to obliterate the varices. Hemostasis after a successful B-RTO is comparable to TIPSS and CA.[68,69] Procedure-related complications have been described in 4% of patients.[70] B-RTO obliterates a spontaneous portosystemic shunt and therefore can aggravate preexisting esophageal varices and ascites.[71,72] B-RTO may have a role in GV bleeding with appropriate shunts where TIPSS is contraindicated; however, there is limited expertise in Europe.

Surgery in experienced centers can lead to good results. It is mainly confined to splenectomy or splenic artery embolization in patients with sinistral portal hypertension secondary to splenic vein thrombosis in low-risk patients.[73,74] A portosystemic shunt can be an effective treatment for bleeding varices in patients with portal vein thrombosis and preserved liver function.[75] The key recommendations for management of acute variceal bleeding are summarized in TABLE 4 and FIGURE 2.

Secondary prevention (FIGURE 2) Studies have shown that variceal bleeding recurs in 60% of patients at 1 year with 6-week mortality of 20% for every rebleeding episode and 1-year mortality of 40%.[2,15] This highlights the importance of secondary prevention, and NSBBs have been used extensively for the prevention of rebleeding and have been shown to decrease the rate of rebleeding from varices (42% vs 63% in control arms) in several meta-analyses.[76] In addition, NSBBs have been shown to significantly decrease bleeding--related and overall mortality from 27% to 20%.[77] Studies that have compared carvedilol with a combination of nadalol or isosorbide mononitrate did not show any significant difference in the rate of recurrence of variceal bleed.[78] Although one study showed a reduced risk of rebleeding when isosorbide mononitrate was combined with propranolol without survival benefit, a meta-analysis of a total of 27 RCTs did not show any benefit of isosorbide mononitrate when used alone or in combination with NSBBs in the prevention of bleeding or rebleeding.[79] There has also been some early evidence to suggest the role of adjunctive use of simvastatin for secondary prevention in Child's A and B cirrhosis; however, this requires further evaluation before recommendations can be made.[80]

TABLE 5 Key messages for secondary prevention of variceal bleeding

NSBB (propranolol or nadolol as first line, carvedilol as alternative) and VBL combination therapy are recommended in all patients for secondary prevention of esophageal variceal bleeding or GOV1.
Monotherapy with VBL or NSBB may be considered depending on patient preference or clinician's judgment.
The dose of NSBB should be titrated to the maximum tolerated dose.
Caution is advised in selected patients with spontaneous bacterial peritonitis, acute renal impairment, and hypotension as mentioned before.
VBL for esophageal varices or GOV1 should be performed at 2 to 4 weekly intervals till eradication; however, there is no need for further endoscopy if the patient is on NSBB alone. Following eradication, repeat endoscopy at 3 months and then every 6 months is recommended. Recurrent varices should be treated with VBL and continued until eradication.
For GOV2 and IGV continue endoscopic therapy with cyanoacrylate or thrombin. The optimal time interval between treatments and follow-up are not clear. NSBBs should be considered depending on patient preference or clinician's judgment.
PTFE-covered TIPSS is recommended where there is failure of endoscopic and drug therapies.
In patients who have Child's A or Child's B cirrhosis, shunt surgery has a role where TIPSS is not feasible and depends on local availability.

Abbreviations: see **TABLE 2** and **FIGURE 2**

Endoscopic therapies VBL has replaced sclerotherapy in secondary prevention owing to improved outcomes and fewer complications. A recent systematic review confirmed that the addition of NSBB to VBL improves the efficacy of VBL alone in preventing rebleeding with no effect on overall mortality.[81] However, the combination of VBL and drug therapy versus drug therapy alone did not show any differences in rebleeding or mortality. A multicenter RCT comparing carvedilol with VBL for secondary prevention of esophageal variceal bleeding demonstrated no significant difference in rebleeding rates between the 2 groups (37.5% vs 29%; P = 0.72); however, there was a strong trend towards patients in the carvedilol group to have lower 1-year mortality rates.[82]

Transjugular intrahepatic portosystemic shunt Bare TIPSS compared with endoscopic therapy reduced variceal rebleeding by nearly 70%, but was associated with an over 2-fold increase in hepatic encephalopathy with no difference in survival in a meta-analysis.[83] A recent RCT of 8-mm diameter PTFE-covered TIPSS versus medical therapy with propranolol and isosorbide mononitrate using HVPG guidance showed reduced rebleeding rates with TIPSS (7% vs 26%).[84] However, encephalopathy and adverse events were increased with TIPSS, and there was no difference in survival. Early TIPSS has been covered in the previous section.

Surgery In view of the advances in TIPSS, shunt surgery has a limited role in patients with Child's A or B cirrhosis and where there is adequate expertise. Liver transplantation should be considered in advanced liver disease.[3]

Gastric varices Various studies have reported rebleeding rates after an acute GV bleeding episode treated with tissue adhesives (mainly CA) from 7% to 65%.[57] Most of the large studies have reported rates below 15%. Therefore, after the index hemostasis with tissue adhesives, repeated endoscopic sessions are performed on a 2- to 4-week basis until GV are obliterated. In most studies, obliteration was achieved with 2 to 4 injections.

CA has been shown to be superior to both endoscopic sclerotherapy and VBL for secondary prophylaxis. An RCT involving 64 patients who bled from GV (54 GOV2 and 10 IGV1) compared repeated endoscopic CA (n = 33) with propranolol (n = 34) for secondary prophylaxis.[85] The probability of GV rebleeding rate in the CA group was significantly lower than in the propranolol group (15% vs 55%, P = 0.004), and the mortality rate was also lower (3% vs 25%, P = 0.026) during a median follow-up of 26 months. The rate of complications in the CA group was 3%.

A recent study investigated the efficacy of additional NSBBs to repeated endoscopic GV obliteration in the secondary prevention of GV bleeding.[86] A total of 95 patients, who bled from GV (GOV2, n = 77; IGV1, n = 18) and were successfully treated with CA, were assigned to receive treatment with NSBB plus repeated CA (every 3 to 4 weeks until the varices were obliterated, n = 47) or repeated CA injections alone (n = 48). After a mean follow-up of 19 months, the overall rebleeding (22 vs 26 patients, P = 0 .336) and survival rates (22 vs 20, P = 0.936) were not different between the 2 groups. Moreover, 1-year rebleeding free survival was also similar (77% vs 76.5%).

An RCT on 72 patients showed a significantly lower rate of GV rebleeding with TIPSS as compared with CA (11% vs 38%).[87] Encephalopathy was more common in patients treated with TIPSS (26% vs 3%). However, overall complication and survival rates were similar in both groups.

In a small study, 15 patients with acute GV bleeding were randomized to receive TIPSS (n = 7) or B-RTO (n = 8). No significant differences were observed in rebleeding, hepatic encephalopathy, or survival.[68] Some other studies concluded that B-RTO might be better than TIPSS[88] or CA glue[69] in the prevention of GV bleeding. Nonetheless, these studies had small sample sizes and because in most patients treatment was administered as primary prophylaxis for high-risk GV and the efficacy of the comparative groups (either TIPSS or endoscopic glue therapy) was poorer than expected, definitive conclusions cannot be drawn. Surgery may also have a role in selected patients as previously described.

United Kingdom guidelines recommend that NSBB and VBL combination therapy should be considered in all cirrhotic patients for secondary prevention of esophageal variceal bleeding; however, monotherapy may be an alternative based on patient preference or clinical judgement.[10] The dose of NSBB should be titrated to the maximum tolerated dose. VBL should be performed at 2 to 4 weekly intervals until eradication of varices; however, there is no need for further endoscopy

if the patient is on NSBB alone. Similar recommendations are made in the Baveno 6 and American Association for the Study of Liver Disease guidelines.[2,15] The key recommendations for secondary prevention of variceal bleeding are summarized in **TABLE 5**.

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ARTYKUŁ POGLĄDOWY

Jak leczymy krwawienie żylakowe u chorych z marskością wątroby

Praktyczne wskazówki z wytycznych brytyjskich (2015)

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SŁOWA KLUCZOWE

endoskopowe podwiązywanie żylaków, nadciśnienie wrotne, nieselektywne β-blokery, przezszyjne wewnątrzwątrobowe zespolenie wrotno-układowe, żylaki

STRESZCZENIE

Krwawienie z żylaków przełyku lub żołądka jest poważnym powikłaniem nadciśnienia wrotnego, związanym z dużą chorobowością i śmiertelnością. Postępy w badaniach przesiewowych i stratyfikacji ryzyka, jak też oparte na danych naukowych strategie postępowania w ostrym krwawieniu żylakowym oraz w prewencji pierwotnej i wtórnej doprowadziły do poprawy ogólnego rokowania u chorych z nadciśnieniem wrotnym. Ostatnio opublikowane wytyczne British Society of Gastroenterology (BSG) oraz konsensus Baveno 6 powstały z myślą o podniesieniu standardu leczenia żylaków przełyku i żołądka oraz ich powikłań. W tym krótkim przeglądzie przedstawiono najważniejsze wskazówki praktyczne dotyczących badań przesiewowych i leczenia żylaków oraz krwawienia żylakowego. Uwzględniono też ważne dane opublikowane po wytycznych BSG i konsensusie Baveno 6.

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Praca wpłynęła: 13.02.2016.
Przyjęta do druku: 13.02.2016.
Publikacja *online*: 21.03.2016.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2016; 126 (3): 174-184
doi: 10.20452/pamw.3319
Tłumaczył lek. Łukasz Strzeszyński