CURRENT TREND

Primary prophylaxis of esophageal variceal bleeding in cirrhosis

Prévention primaire de la rupture de varices œsophagiennes au cours de la cirrhose

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Summary Variceal bleeding is a common and severe complication of liver cirrhosis. The risk of bleeding increases with the size of varices, red wheal marks and disease severity. Noninvasive tests are not accurate enough for the diagnosis of varices, so all patients with cirrhosis should be screened by endoscopy. Nonselective beta-blockers (propranolol, nadolol) are indicated for primary prophylaxis in patients with medium/large varices, and for those with small varices and red signs or advanced liver failure (Child C). In such patients, beta-blockers have been shown to reduce the risk of bleeding from 25 to 15%. There is no evidence to support using beta-blockers with nitrates or spironolactone. In patients with contraindication or intolerance to beta-blockers, endoscopic band ligations are indicated.

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Résumé L’hémorragie digestive par rupture de varices œsophagiennes est une complication fréquente et grave au cours de la cirrhose. Le risque d’hémorragie est d’autant plus important que les varices sont de grande taille, qu’il existe des signes rouges endoscopiques et que l’insuffisance hépatique est sévère. Aucune méthode non invasive n’est aujourd’hui suffisante pour le diagnostic de varices et tous les patients atteints de cirrhose doivent bénéficier d’une surveillance endoscopique. Les bétabloquants non cardiosélectifs (propranolol et nadolol) sont indiqués en prévention primaire chez les patients ayant des varices de stade II ou III et chez ceux ayant des varices de stade I avec signes rouges ou une insuffisance hépatique sévère (Child C). Chez ces malades, ils permettent de réduire le risque hémorragique de 25 à 15% à deux ans. L’intérêt de l’association des bétabloquants avec les dérivés nitrés ou la spironolactone n’est pas montré. En cas de contre-indication ou d’intolérance aux bétabloquants le traitement endoscopique par ligature élastique est recommandé.

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Variceal bleeding is one of the most common and severe complications of liver cirrhosis. Even with the best medical care currently available, mortality from variceal bleeding remains around 15–20% [1]. Moreover, variceal bleeding often leads to deterioration of liver function, and may trigger other complications of cirrhosis such as bacterial infections and hepatorenal syndrome. The high morbidity–mortality associated with variceal bleeding emphasizes the need of effective preventative therapy [1,2]. The present report reviews the established strategies for prevention of the first variceal bleeding.

Risk factors of first variceal bleeding

The probability of bleeding from esophageal varices is variable, but can be estimated according to clinical, endoscopic and hemodynamic parameters.

Clinical and endoscopic risk indicators

In patients with no varices on the initial endoscopy, the risk of bleeding is extremely low (1–2% at two years). The risk increases to 10% at two years for those with small varices, and to 30% for those with medium or large varices at diagnosis [2–4]. The risk of variceal bleeding also increases with the severity of liver dysfunction, according to the Child–Pugh classification, and the presence of red wheal marks in the varix wall [5]. The prognostic value of variceal size, the presence of red wheals and the Child–Pugh score have been combined in the North Italian Endoscopic Club (NIEC) index, which allows the classification of patients into different categories according to their predicted one-year bleeding risk (ranging from 6 to 76%) [5,6]. Although this index has been validated, its overall predictive accuracy is far from satisfactory, having only 74% sensitivity and 64% specificity in predicting the risk of variceal bleeding [6]. Moreover, among patients presenting with a first variceal bleeding episode, less than 50% would have been classified a priori as being high-risk patients by the NIEC index [7]. This suggests that decisions for prophylactic therapy based on components of the NIEC index would most likely result in no therapy for around half of the patients who would benefit from it.

Hemodynamic risk indicators

Cross-sectional and prospective studies have found that varices and ascites do not develop until the hepatic venous-pressure gradient (HVPG) increases to greater than or equal to 10 mmHg [4,8], and that the HVPG has to be at least 12 mmHg for variceal bleeding to occur [8–10]. Implicit in these findings is that preventing the HVPG from surpassing these values would prevent the development of these complications of portal hypertension. It is also a well-known development following drastic reductions in portal pressure through the use of surgical shunts or transjugular intrahepatic portosystemic shunt. Recent studies have further shown that if HVPG is reduced to below these thresholds by pharmacological treatments [11,12] or due to an improvement in liver disease [13], variceal bleeding can be completely prevented and the varices decreased in size. In fact, even if this target is not achieved, reducing the HVPG to greater than or equal to 20% from baseline is associated with a marked reduction in the risk of variceal bleeding [12,14–20].

Screening for esophageal varices

Noninvasive tests such as platelet count, the presence of splenomegaly, the ratio of both [21] or the data obtained from abdominal ultrasonography have all been suggested as useful for selecting patients who have a high risk of developing large esophageal varices. More recently, transient elastography has been proposed to be a sensitive noninvasive method to predict the presence of large varices [22,23], although it is less sensitive for varices of other sizes [24]. However, none of these tests, either alone or in combination, is accurate enough to completely exclude the presence of esophageal varices when noninvasive indicators are negative. This is important because, although the risk of bleeding in patients with small varices is lower than in those with moderate/large varices, almost 50% of all variceal bleedings occur in patients who originally had small varices. Thus, the current recommendation is that all patients with cirrhosis should be screened for the presence of esophageal varices at the time of initial diagnosis [25]. In patients without varices on the initial endoscopy, a follow-up evaluation should be performed after two to three years to detect the development of varices before they bleed. This interval should be shorter in patients who have an initial HVPG greater than 10 mmHg. Once they develop, varices may increase in size. Reported progression rates in prospective studies range from 5 to 20% per year, with a median rate of 12% [26]. Accordingly, in patients with small varices for whom no decision to initiate prophylactic treatment has been made, endoscopy should be repeated every one to two years to detect any progression to larger varices [2,3,27,28].

Patients eligible for primary prophylaxis

In clinical practice, patients with medium or large varices, as well as those who have small varices and advanced liver failure (Child–Pugh C) or red signs in the varix wall, are considered to be at considerable risk of bleeding and so should receive therapy to prevent variceal bleeding [28,29]. Patients with small varices and no other risk indicator can be treated pharmacologically if there are no contraindications.

Prevention of the development and progression in size of varices

The observation that it is possible to attenuate or delay the development of collaterals in experimental models of portal hypertension using nonselective beta-blockers [30,31] prompted studies to investigate whether these agents could prevent the development of esophageal varices in patients with cirrhosis. Unfortunately, this has not been confirmed in a recent study [32]. However, the study did find that a baseline HVPG less than 10 mmHg, or a decrease in HVPG greater than 10% of baseline or less than 10 mmHg, were the only independent predictors of being free of esophageal varices.
Table 1  Meta-analysis of randomized controlled trials comparing endoscopic band ligation (EBL) and nonselective beta-blockers for the prevention of first variceal bleeding shows that EBL significantly reduced the risk of first variceal bleeding in patients with medium and large esophageal varices compared with the drugs.

Meta-analyse des études contrôlées randomisées comparant la ligature endoscopique aux bétabloquants non sélectifs dans la prévention primaire de la rupture de varices œsophagiennes. Impact sur l’incidence du premier épisode hémorragique. Chez les patients ayant des varices de taille moyenne ou grande, la ligature réduit significativement le risque du premier épisode de rupture de varices œsophagiennes par rapport aux bétabloquants non sélectifs. EBL : ligature endoscopique, BB : bétabloquants ; n/N : nombre d’événements/nombre de malades ; RR : risque relatif ; CI : intervalle de confiance.

<table>
<thead>
<tr>
<th>Study</th>
<th>better EBL n/N</th>
<th>better B-blockers n/N</th>
<th>RR (random) 95% CI</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 1998</td>
<td>1/26</td>
<td>2/28</td>
<td>0.54 [0.05, 5.59]</td>
<td></td>
</tr>
<tr>
<td>De 1999</td>
<td>2/15</td>
<td>1/15</td>
<td>2.00 [0.20, 19.78]</td>
<td></td>
</tr>
<tr>
<td>Sarin 1999</td>
<td>4/45</td>
<td>12/44</td>
<td>0.33 [0.11, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Song 2000</td>
<td>6/31</td>
<td>7/30</td>
<td>0.83 [0.32, 2.18]</td>
<td></td>
</tr>
<tr>
<td>de la Mora 2000</td>
<td>1/12</td>
<td>2/12</td>
<td>0.50 [0.05, 4.81]</td>
<td></td>
</tr>
<tr>
<td>Gheorge 2002</td>
<td>3/25</td>
<td>13/28</td>
<td>0.26 [0.08, 0.60]</td>
<td></td>
</tr>
<tr>
<td>Lui 2002</td>
<td>4/44</td>
<td>9/66</td>
<td>0.67 [0.22, 2.03]</td>
<td></td>
</tr>
<tr>
<td>Lo 2004</td>
<td>6/50</td>
<td>13/50</td>
<td>0.46 [0.19, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Schepeke 2004</td>
<td>19/75</td>
<td>22/77</td>
<td>0.89 [0.52, 1.50]</td>
<td></td>
</tr>
<tr>
<td>Drastich 2005</td>
<td>2/40</td>
<td>3/33</td>
<td>0.55 [0.10, 3.10]</td>
<td></td>
</tr>
<tr>
<td>Juthaba 2005</td>
<td>0/31</td>
<td>5/31</td>
<td>0.09 [0.01, 1.58]</td>
<td></td>
</tr>
<tr>
<td>Pelipouli 2005</td>
<td>2/30</td>
<td>9/30</td>
<td>0.22 [0.05, 0.94]</td>
<td></td>
</tr>
<tr>
<td>Thuluvath 2005</td>
<td>2/16</td>
<td>1/15</td>
<td>1.88 [0.19, 18.60]</td>
<td></td>
</tr>
<tr>
<td>Abdelfattah 2006</td>
<td>4/51</td>
<td>13/52</td>
<td>0.33 [0.11, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Lay 2006</td>
<td>11/50</td>
<td>12/50</td>
<td>0.92 [0.45, 1.88]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 541/561

<table>
<thead>
<tr>
<th>Event</th>
<th>0.01</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>favours EBL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>favours BB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BB: beta-blockers; n/N: number of events/number of patients in the treatment arm; RR: relative risk; CI: confidence interval.

Although this occurred more frequently with beta-blockers than with a placebo, overall the study was negative, so beta-blockers cannot be recommended for the prevention of the development of esophageal varices in patients with cirrhosis.

Two controlled studies have evaluated the role of non-selective beta-blockers in preventing the increase in size of small varices. Cales et al. [33] showed no benefit with long-acting propranolol versus placebo in preventing the development of large varices in 206 cirrhotic patients who either had no or small varices. This study has been criticized because, although the risk of developing large varices in the propranolol group was greater than in the placebo group (31% versus 14%), this was not matched by an increased risk of bleeding. This unexpected finding may be due to an undetected bias, perhaps in part attributable to the large proportion (one-third) of patients lost to follow-up. In contrast, in the study by Merkel et al. [34], including 161 cirrhotic patients with small varices, there was a significantly lower rate of variceal size increase in patients receiving nadolol compared with a placebo. In addition, the bleeding risk at the end of follow-up was significantly lower in the nadolol group (12%) compared with the placebo group (22%). Based on these data, the last Baveno consensus conference concluded that: “Prophylactic treatment with nonselective beta-blockers could be considered in patients with small esophageal varices with the primary aim to reduce variceal growth. However, further studies are required before this suggestion can be accepted as a formal recommendation”.

Treatments for the prevention of the first bleeding

Pharmacological therapy

A total of 12 trials has assessed nonselective beta-adrenergic blockers for the prevention of first bleeding. Meta-analysis of these studies shows that continued propranolol or nadolol therapy reduces the risk of a first variceal bleeding episode from approximately 25% with nonactive treatment to 15% with beta-adrenergic blockers, over a median follow-up of two years [35]. Mortality was not significantly reduced (from 27 to 23%). The benefit of therapy extends to patients with medium or large varices, with or without ascites, or with good or poor liver function [35,36]. Once initiated, therapy with beta-adrenergic blockers should be maintained indefinitely, as the bleeding risk reverts to baseline if treatment is withdrawn [37].

Propranolol and nadolol are the two most widely used nonselective beta-blockers [35]. Nadolol is easier to administer because it has a longer half-life, thereby allowing once-a-day dosing. In addition, its low lipid solubility means that it does not cross the blood—brain barrier and, for this reason, may have a lower likelihood of causing central side-effects [38].

Beta-adrenergic blockers are titrated in stepwise increases until the maximum tolerated dose is reached—around 160 mg bid for propranolol and 240 mg/day for
nadolol. Propranolol is commonly initiated at a dose of 40 mg bid, while nadolol is usually begun at a dose of 40 mg/day. The most common side-effects are light-headedness, fatigue, shortness of breath, impotence and sleep disorders. Although these are usually not severe, they may require a dose-reduction or result in noncompliance. Around 10—15% of side-effects result in treatment discontinuation [39]. In addition, approximately 15% of patients have contraindications to the use of beta-blockers [40]. Absolute contraindications include congestive heart failure, asthma, severe chronic obstructive pulmonary disease, second- or third-degree heart block, severe aortic stenosis and peripheral vascular disease. Insulin-dependent diabetes and sinus bradycardia are relative contraindications.

The role of nonselective beta-blockers in the prevention of first bleeding in patients with cirrhosis and gastric or esophageal varices has not been properly evaluated, as is the case for noncirrhotic (including prehepatic) portal hypertension. However, because the effect of nonselective beta-blockers in decreasing portal pressure has also been well established in noncirrhotic portal hypertension, it is assumed that they are likely to be useful in cirrhetic patients with varices as well.

The addition of isosorbide mononitrate enhances the portal pressure reduction achieved with beta-adrenergic blockers [41,42]. However, it is not clear whether or not this translates into greater clinical efficacy. A clinical trial comparing nadolol with nadolol plus isosorbide mononitrate demonstrated a significantly lower rate of first bleeding in the combination group, but no improvement in survival rate [43,44]. However, a larger randomized double-blind study failed to confirm the advantage of the combination treatment. Furthermore, more side-effects were observed with the combination [39]. Therefore, the combination of isosorbide mononitrate with nonselective beta-blockers is not recommended as a standard therapy for the primary prophylaxis of variceal bleeding [25]. The same limitations apply to the combination of propranolol or nadolol with other vasodilators. Spironolactone and a low-sodium diet have been shown to reduce portal pressure in patients with compensated cirrhosis by diminishing the increased plasma volume and splanchnic blood flow [45]. However, nadolol plus spironolactone has not been shown to improve the clinical efficacy of nadolol alone as primary prophylaxis [46]. Isosorbide mononitrate on its own does not prevent variceal bleeding [40] and may increase morbidity, especially in patients with advanced cirrhosis and ascites [47].

In conclusion, nonselective beta-blockers are the only pharmacological treatment with proven efficacy for primary prophylaxis of esophageal variceal bleeding. They are also among the safest and cheapest drugs in Europe. However, around 20—30% of cirrhotic patients with medium/large esophageal varices may either have contraindications for nonselective beta-blockers or simply cannot tolerate these drugs, and the degree of protection afforded (about 40% reduction in relative risk) is far from ideal, which has stimulated the search for alternatives.

### Endoscopic therapy

The introduction of endoscopic band ligation (EBL), and the demonstration that its use is more effective and associated with fewer side-effects than endoscopic injection

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**Table 2** Meta-analysis of randomized controlled trials comparing endoscopic band ligation (EBL) and nonselective beta-blockers in the prevention of first variceal bleeding shows no significant differences in mortality between the two.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>EBL n/N</th>
<th>Beta-blockers n/N</th>
<th>OR (fixed) 95% CI</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 1998</td>
<td>3/26</td>
<td>3/28</td>
<td>1.09 [0.26, 5.94]</td>
<td></td>
</tr>
<tr>
<td>Sarin 1999</td>
<td>5/45</td>
<td>5/44</td>
<td>0.98 [0.26, 3.63]</td>
<td></td>
</tr>
<tr>
<td>Song 2000</td>
<td>5/31</td>
<td>8/30</td>
<td>0.53 [0.15, 1.85]</td>
<td></td>
</tr>
<tr>
<td>de la Mora 2000</td>
<td>0/12</td>
<td>1/12</td>
<td>0.31 [0.01, 8.31]</td>
<td></td>
</tr>
<tr>
<td>Gheorge 2002</td>
<td>1/25</td>
<td>5/28</td>
<td>0.19 [0.02, 1.77]</td>
<td></td>
</tr>
<tr>
<td>Lu 2002</td>
<td>11/44</td>
<td>18/66</td>
<td>0.89 [0.37, 2.12]</td>
<td></td>
</tr>
<tr>
<td>Lo 2004</td>
<td>12/50</td>
<td>11/50</td>
<td>1.12 [0.44, 2.84]</td>
<td></td>
</tr>
<tr>
<td>Schepke 2004</td>
<td>34/75</td>
<td>33/77</td>
<td>1.11 [0.58, 2.10]</td>
<td></td>
</tr>
<tr>
<td>Drahtsch 2005</td>
<td>2/40</td>
<td>1/33</td>
<td>1.68 [0.15, 19.44]</td>
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</tr>
<tr>
<td>Juthaba 2005</td>
<td>0/31</td>
<td>4/31</td>
<td>0.10 [0.01, 1.88]</td>
<td></td>
</tr>
<tr>
<td>Thuluvath 2005</td>
<td>6/16</td>
<td>3/15</td>
<td>2.40 [0.47, 12.13]</td>
<td></td>
</tr>
<tr>
<td>Abdellatifah 2006</td>
<td>4/51</td>
<td>5/52</td>
<td>0.60 [0.26, 1.37]</td>
<td></td>
</tr>
<tr>
<td>Lay 2006</td>
<td>5/50</td>
<td>4/50</td>
<td>1.28 [0.32, 5.07]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>496</td>
<td>516</td>
<td>0.91 [0.65, 1.27]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 7.70, df = 12 (P = 0.81), I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
Table 3  Side-effects of endoscopic band ligation (EBL) compared with nonselective beta-blockers (BB) as the primary prophylaxis for esophageal variceal bleeding.

<table>
<thead>
<tr>
<th>Study</th>
<th>EBL</th>
<th>Beta-blockers a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EBL-related deaths (n)</td>
<td>Severe side-effects (n/N)</td>
</tr>
<tr>
<td>De et al., 1999</td>
<td>0/15</td>
<td>0</td>
</tr>
<tr>
<td>Sarin et al., 1999</td>
<td>2/45</td>
<td>Ulcer-related bleeding</td>
</tr>
<tr>
<td>Lui et al., 2002</td>
<td>2/44</td>
<td>Ulcer-related bleeding, Overtube perforation</td>
</tr>
<tr>
<td>Lo et al., 2004</td>
<td>0/50</td>
<td>0</td>
</tr>
<tr>
<td>Schepke et al., 2004</td>
<td>5/75</td>
<td>Ulcer-related bleeding</td>
</tr>
<tr>
<td>Jutabha et al., 2005</td>
<td>1/31</td>
<td>Melena post-EBL</td>
</tr>
<tr>
<td>Thuluvath et al., 2005</td>
<td>1/16</td>
<td>EBL-related bleeding</td>
</tr>
<tr>
<td>Psilopoulos et al., 2005</td>
<td>0/30</td>
<td>0</td>
</tr>
<tr>
<td>Lay et al., 2006</td>
<td>0/50</td>
<td>0</td>
</tr>
</tbody>
</table>

a No beta-blocker-related fatalities.
b Four further patients were not compliant.
c Seven further patients were not compliant.
d Four patients were not compliant; n/N: number of patients with complication/total number of patients.

sclerotherapy, has prompted its use in the prevention of first variceal bleeding [48,49]. Fifteen trials have compared EBL with beta-adrenergic blockers as the first-line option for primary prophylaxis of variceal bleeding [50–62]. A meta-analysis of these trials shows an advantage of EBL over beta-adrenergic blockers in preventing a first bleeding, but with no difference in mortality (Tables 1 and 2). However, most of these trials were underpowered (10 involved fewer than 90 patients), of low quality, reported only as abstracts and had short follow-ups. This has led to considerable controversy as to whether or not beta-blockers should remain the first-line treatment option to prevent first variceal bleeding. The relative impact of both treatments in terms of adverse effects was analyzed by Khuroo et al. in a systematic review of nine of the 15 randomized controlled trials [63]. An updated meta-analysis confirmed that adverse events requiring treatment discontinuation were significantly more frequent in patients treated with nonselective beta-blockers than in those treated with EBL (Table 3). However, the type and severity of the side-effects were different. Most of the side-effects with beta-blockers (hypotension, tiredness, breathlessness, poor memory, insomnia) were subjective, easily managed by adjusting the dose or discontinuing the drug, did not require hospitalization and led to no fatalities. In contrast, the side-effects with EBL included 10 bleeding episodes and one esophageal perforation. In most cases, these complications required hospitalization and blood transfusions, and two patients died. Furthermore, because of the short duration of follow-up in most studies, the long-term safety and benefits of prophylactic EBL remain uncertain.

Indeed, a recent study has questioned the efficacy of EBL as the primary prophylaxis in cirrhotic patients with contraindications or intolerance to beta-blockers [64].
Primary prophylaxis of esophageal variceal bleeding in cirrhosis

Figure 1 The current recommendations for primary prophylaxis in cases of portal hypertensive bleeding. EBL, endoscopic band ligation.

Récemment, la long-term safety and efficacy of prophylactic nonselective beta-adrenergic blockers has been well established [37,65]. Nevertheless, bleeding episodes after discontinuing beta-blockers because of side-effects have also been considered an argument against its use as the first prophylaxis. However, as shown in Table 3, bleeding usually occurred months after beta-blockers were withdrawn, suggesting that if EBL were used in patients with intolerance or contraindications to beta-blockers, some of these bleeding episodes might have been prevented.

Evaluation of the cost-benefits of EBL versus beta-blockers for primary prophylaxis has been done using the Markov model. However, depending on the use of different assumptions of the incidence of variceal bleeding, mortality or other portal hypertensive complications leads to different conclusions [66–68]. Until further large-scale studies are available, the recommendation made at the 2005 Baveno consensus conference is that nonselective beta-blockers should be considered the first-choice treatment to prevent first variceal bleeding, while EBL should be offered to patients with medium/large varices and contraindications or intolerance to beta-blockers.

Combined endoscopic and pharmacological therapy

Recently, a study has examined the possible role of combining beta-blockers and EBL. The combination of both procedures appears to offer no greater benefit in terms of prevention of first bleeding when compared with EBL alone, and was associated with more side-effects [69]. More studies are required to assess the true potential of such a combination therapy.

Conclusion

The evidence from prophylactic trials indicates that endoscopic screening for varices should be a routine clinical practice in patients with cirrhosis. If varices are found, prophylactic treatment to prevent the first variceal bleeding episode should be given to those who have one or more risk factors for variceal bleeding (large varices, presence of red wheals and advanced liver dysfunction) (Fig. 1).

Nonselective beta-blockers remain the recommended first-line therapeutic choice. Nitrates alone should not be prescribed, and there is insufficient evidence to recommend the combination of beta-blockers with either nitrates or spironolactone. Endoscopic band ligation is recommended for patients who cannot tolerate or have contraindications to beta-blockers.

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References


Primary prophylaxis of esophageal variceal bleeding in cirrhosis

539


