Esophageal bleeding disorders

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Purpose of review
Management of esophageal bleeding disorder remains a challenging problem. This review focuses on studies published in previous 12 months that provided further understanding on the appropriate treatment of various esophageal bleeding disorders. Other uncommon causes of esophageal bleeding will also be discussed in this review.

Recent findings
With the advances in endoscopic and pharmacological treatments, mortality of variceal hemorrhage has been substantially reduced. Apart from its major role in initial treatment of variceal bleeding, mounting evidence shows that band ligation is a safe alternative to β-blocker for primary prophylaxis and may even be used as an adjunct to the transjugular intrahepatic portosystemic stent shunt to obviate the need of long-term surveillance. While vasoactive agents remain the most important pharmacological treatment of esophageal variceal bleeding, antibiotic prophylaxis is also increasingly recognized to play a role in prevention of variceal rebleeding. The benefit of β-blocker has now been extended to halt the progression of esophageal varices and combination of β-blocker and band ligation remains the most cost-effective treatment strategy for secondary prophylaxis of variceal bleeding. Other new treatments such as endoloop and recombination factor VII have produced promising results. The clinical courses of variceal bleeding in patients with hepatocellular carcinoma and acute necrotizing esophagitis are now better defined.

Summary
There are significant advances in the treatment of esophageal variceal bleeding and further understanding on the management and clinical courses of various esophageal bleeding disorders.

Keywords
esophageal varices, hemorrhage, Mallory–Weiss syndrome

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Introduction

Esophageal varices and Mallory–Weiss syndrome are the two major esophageal bleeding disorders. Despite significant advances in endoscopic and medical treatment in recent years, management of these esophageal bleeding disorders remains a challenging problem. This review focuses on studies published in the previous 12 months that provide further understanding of the appropriate treatment for various esophageal bleeding disorders.

Esophageal varices

There has been a substantial reduction in the rebleeding and mortality rate of variceal hemorrhage with advances in endoscopic therapy and vasoactive agents, and increased application of antibiotic prophylaxis and portasystemic shunts. In a study involving 725 patients with variceal bleeding, the overall short-term mortality after index bleeding was only 12.9% [1]. In another retrospective analysis involving 231 patients, the in-hospital, 6-week, and overall mortality rates were reported to be only 14.2%, 17.5%, and 33.5%, respectively [2]. The time trend of mortality of esophageal variceal bleeding was clearly shown in a retrospective review, which analyzed the in-hospital mortality rates of variceal hemorrhage from 1980 to 2000 [3]. The in-hospital mortality rate significantly decreased from 42.6% in 1980 to 14.5% in 2000. Mortality rates dropped from 9% (Child–Pugh A) and 46% (Child–Pugh B) to 0%. Furthermore, there was also a substantial reduction in mortality from 70% to 32% in Child–Pugh C patients. This improved survival was associated with a decrease of rebleeding (from 47% in 1980 to 13% in 2000) and bacterial infection rates (from 38% to 14%). Endoscopic therapy and antibiotic prophylaxis were independent predictors of survival in this study.

Endoscopic therapy of acute variceal hemorrhage

Band ligation has replaced sclerotherapy as the first line endoscopic treatment of esophageal varices because of its superior safety profile and efficacy. In recent years, endoscopic clipping and endoloop are emerging endoscopic

treatment modalities for variceal hemorrhage. A prospective randomized study involving 40 patients with esophageal variceal hemorrhage compared the efficacy of endoscopic clipping and variceal ligation [4]. It was found that initial hemostasis was achieved in all patients who received endoscopic clipping, but two patients in the band ligation group had failure in hemostasis. Endoscopic clipping achieved significantly higher variceal eradication rate (89% versus 76%) and fewer treatment sessions (three versus four) than band ligation. Endoloop ligation is a newly developed technique that has certain technical advantages over band application: a better field of vision, tighter ligation, and good results with junctional varices. Endoloop was compared with band ligation in a randomized trial of 50 patients with acute esophageal variceal bleeding [5]. Although the 6-month rebleeding rate tended to be lower in the endoloop group (12%) as compared with band ligation group (28%), this difference was not statistically significant. Furthermore, there was no significant difference in the variceal eradication rate, the number of treatment sessions required for variceal eradication, and the rate of variceal recurrence. The therapeutic benefit of endoloop needs further evaluation in a study with a larger sample size.

Pharmacological therapy of acute variceal hemorrhage

Pharmacological therapy remains an important component in the management of acute variceal hemorrhage. Terlipressin is a new vasopressin analogue with good cardiovascular safety and it has an additional advantage of easy administration by intravenous injection. The efficacy and safety of terlipressin was evaluated in a systemic review of 20 randomized trials involving 1609 patients, which compared terlipressin with placebo, balloon tamponade, endoscopic treatment, octreotide, somatostatin, or vasopressin [6]. Terlipressin has been shown to reduce mortality (relative risk 0.66), the failure of hemostasis (relative risk 0.63), and the number of emergency procedures required for uncontrolled bleeding or rebleeding (relative risk 0.72). When used as an adjuvant to endoscopic sclerotherapy, terlipressin was also the only pharmacological agent that appeared to reduce mortality (relative risk 0.74, 95% CI 0.53–1.04). Apart from a vasoactive agent, the correction of coagulopathy with a recombinant coagulation factor is a novel pharmacological treatment for acute variceal hemorrhage, especially in patients who do not respond to conventional vasoactive agents. The hemostatic efficacy of activated recombinant factor VII in bleeding esophageal varices was evaluated in an open-label study [7•]. A single intravenous dose of recombinant factor VII was given in eight patients who experienced severe esophageal variceal hemorrhage unresponsive to pharmacologic therapy, endoscopic therapy, or balloon tamponade. Hemostasis was achieved in all patients after recombinant activated factor VII therapy. The encouraging results of this study confirm the need

of a randomized controlled trial to confirm the role of recombinant factor VII as a rescue therapy of refractory variceal bleeding particularly if a transjugular intrahepatic portosystemic stent shunt (TIPSS) is not feasible.

It has been thought that bacterial infection may adversely affect the hemostasis of patients with variceal bleeding. The role of antibiotic prophylaxis in preventing rebleeding is unclear. In a retrospective study, 221 cases of variceal bleeding without sign of infection at the time of admission were evaluated [8]. Systemic antibiotic prophylaxis was administered to 126 patients; the overall incidence of new onset infections (19.8% versus 34.7%; $P < 0.01$) and of early rebleeding (17.5% versus 32.6%; $P < 0.01$) was significantly reduced. There was a strong correlation of rebleeding with new onset infection ($P < 0.001$) and lack of prophylactic antibiotic treatment ($P < 0.05$). Antibiotic prophylaxis was particularly useful in patients with high-risk factors of infection such as Child–Pugh C cirrhosis, ventilatory assistance, and balloon tamponade. This finding was further supported by another randomized controlled trial. One hundred twenty patients with acute variceal bleeding, but without evidence of bacterial infection were randomized prior to endoscopic treatment to receive prophylactic antibiotics (ofloxacin 200 mg IV q12 h for 2 days followed by oral ofloxacin 200 mg q12h for 5 days) or receive antibiotics only when infection became evident [9••]. It was noted that antibiotic prophylaxis significantly decreased infections (2/59 versus 16/61; $P < .002$), early rebleeding rate within 7 days (4/12 versus 21/27, $P = .0221$) and blood transfusion (1.4 versus 2.8 units, $P < .05$). Moreover, bacterial infection was identified as an independent predictor of rebleeding. There was no survival benefit from the use of antibiotic prophylaxis.

Role of hepatic venous pressure gradient measurement in acute variceal bleeding

Two studies underscore the usefulness of hepatic venous pressure gradient (HVPG) measurement in acute esophageal variceal bleeding. The importance of HVPG as a predictor of treatment failure was reported in a study of 116 cirrhotic patients with acute variceal bleeding [10]. These patients underwent HVPG measurement within 24 hours after sclerotherapy. Fifty-two patients with HVPG ≥ 20 mm/Hg were defined as high-risk patients and were randomly assigned to receive a transjugular intrahepatic portosystemic shunt (TIPS) within the first 24 hours or no TIPS. It was found that the non-TIPS group had significantly more treatment failures (50% versus 12%), transfusional requirements (3.7 versus 2.2), need for intensive care (16% versus 3%), and worse actuarial probability of survival. Early TIPS placement reduced treatment failure (12%); in-hospital and 1-year mortality were 11% and 31%, respectively. This study concluded that increased portal pressure estimated by early HVPG measurement is a main determinant of treatment failure and survival in variceal

bleeding, and early TIPS placement may be beneficial in hemodynamically high-risk patients. In another study, the use of HVPG lends further support to the superior efficacy of endoscopic band ligation as compared with sclerotherapy [11]. Fifty cirrhotic patients with bleeding esophageal varices were treated either with sclerotherapy (n = 25) or band ligation (n = 25), HVPG measurements were performed before and immediately after endoscopic treatment and every 24 h for a 5-day period. Both endoscopic treatment modalities led to a significant increase in portal pressure immediately after treatment as compared with pretreatment. However, HVPG returned to baseline values within 48 hours after band ligation, while patients received sclerotherapy had persistently high HVPG during the 5-day period, and it was associated with a significantly higher rebleeding rate than band ligation.

Secondary prophylaxis

No consensus has yet been reached on the most effective strategy for secondary prophylaxis of esophageal variceal hemorrhage. Nonselective β-blocker, with or without isosorbide mononitrate, has been extensively used as the first line medical therapy for secondary prophylaxis. Other commonly used treatment modalities include band ligation and a combination of band ligation with medical therapy. The transjugular intrahepatic portasystemic shunt has been consistently shown to be superior for the prevention of variceal hemorrhage, but it should only be used as rescue therapy for a failure of medical and endoscopic therapies because of the lack of survival benefit and significant risk of aggravating hepatic encephalopathy [12]. The cost-effectiveness of these treatment modalities was recently evaluated [13]. A Markov model was developed for the following five strategies: observation alone, medical therapy, endoscopic band ligation, endoscopic band ligation plus medical therapy, and transjugular intrahepatic portosystemic shunt. The effect of adherence on these strategies was also considered. It was found that combination therapy with band ligation plus medical therapy had the highest incremental cost-effectiveness ratios for quality-adjusted life-years (QALYs) gained in a 3-year period, meaning that it was more effective and less expensive than the others. Endoscopic band ligation was the second most cost-effective strategy. TIPS was the most optimal strategy only if adherence rates for all other strategies were less than 12%. This study concluded that combination therapy is the most cost-effective modality of treatment, whereas TIPS should be reserved only for patients with very poor adherence.

The need of invasive portographic follow-up is one of the reasons that limit the use of a transjugular intrahepatic portosystemic stent shunt (TIPSS). It has recently been postulated that combining endoscopic band ligation and TIPSS may obviate the need for long-term TIPSS surveillance. In a randomized controlled trial, 79 patients who required TIPSS for the prevention of esophageal variceal rebleeding were randomized to either TIPSS alone followed by long-term TIPSS angiographic surveillance, or combination treatment of band ligation plus TIPSS, with TIPSS surveillance only continued for up to one year [14•]. There was a tendency to higher variceal rebleeding in combination treatment without long-term TIPSS surveillance but it did not reach statistical significance (8% versus 15%; relative hazard 0.58; 95% confidence interval 0.15–2.33). There was also no difference in hepatic encephalopathy and mortality between the two strategies. Therefore, combining band ligation with TIPSS may replace long-term TIPSS surveillance without jeopardizing the efficacy.

Primary prophylaxis

Medical therapy with non-selective β-blocker (propranolol, nadolol) remains the most widely accepted and the most cost-effective strategy for primary prophylaxis of variceal hemorrhage [15,16]. However, 30% of patients develop intolerance to propranolol requiring discontinuation of therapy. Furthermore, a significant proportion of patients are 'non-responders'. Although combination of propranolol and isosorbide mononitrate achieved greater reduction in portal pressure than propranolol alone, combination medical therapy has not been shown to give additional benefit on prevention of first variceal hemorrhage or improvement in survival [17]. Endoscopic band ligation begins to have a competitive edge over medical therapy in primary prevention. The efficacy and safety of band ligation as compared with β-blocker for primary prevention of variceal bleeding was addressed again in another randomized trial involving 100 patients with high-risk esophageal varices [18••]. In the ligation group, variceal obliteration was achieved in 82%. In the nadolol group, a mean daily dose of nadolol administered was 60 mg. Esophageal variceal bleeding occurred in 10% of patients in the ligation group and 18% in the nadolol group in 22-month follow-up period. There was no statistical significant difference in incidence of bleeding, complication, and survival. In contrast to previous trials, this study failed to show any advantage of band ligation despite a comparable safety profile with medical therapy. In another recent study, 152 cirrhotic patients with two or more esophageal varices (diameter >5 mm) without prior bleeding were randomized to band ligation or propranolol [19]. Over a mean follow-up of 34 months, neither bleeding incidence nor mortality differed significantly between the two groups. Variceal bleeding occurred in 25% and 29% in the band ligation and propranolol groups, respectively. There was also no difference in mortality. Although current evidence does not support superiority of band ligation, it is an effective alternative for patients who cannot tolerate β-blocker.

Apart from primary prophylaxis against bleeding, β-blocker has also been shown to be effective in delaying growth of

small varices. One hundred sixty-one patients with cirrhosis and small esophageal varices without previous bleeding were randomized to nadolol or placebo [20•] and they underwent yearly endoscopic surveillance. The principal endpoint was occurrence of large esophageal varices (F2 or F3 according to the classification of Beppu et al.). Over a mean follow-up period of 36 months, 9 patients in the nadolol group and 29 in the placebo group had progression to large esophageal varices. There was a substantial risk reduction in progression of esophageal varices (odds ratio, 4.0; 95% confidence interval, 1.95–8.4). This study suggests that β-blocker prophylaxis should be started early when small esophageal varices are present.

Hepatocellular carcinoma and variceal bleeding

Variceal bleeding is an important presentation of hepatocellular carcinoma (HCC). However, the disease course and outcome of variceal bleeding in these patients is unclear. In a retrospective series, 78 HCC patients who presented with variceal bleeding were analyzed [21]. It was noted that HCC patients with variceal bleeding had more severe cirrhosis, smaller tumor size but more frequent portal vein thrombosis. They had significantly shorter life expectancy (median survival: 3.5 months versus 7.5 months in non-bleeders). Although this group of patients generally had poor prognosis, those patients who received treatment with transarterial chemoembolization had much better survival rates (odds ratio 17.16, 95% CI: 2.81–104.91).

Mallory–Weiss syndrome

Mallory–Weiss syndrome, which refers to laceration of the gastroesophageal junction, account for 5% to 15% of upper gastrointestinal bleeding. The bleeding stops spontaneously in 90% of patients and they can be managed conservatively. Endoscopic therapy is required when there are risk factors such as bleeding diathesis, evidence of active bleeding such as hematemesis and hemodynamic instability, or presence of stigmata of recurrent bleeding such as visible vessel, adherent clot. Endoscopic injection of adrenaline or saline has been the treatment of choice for Mallory–Weiss tear. In recent years, endoscopic clipping and band ligation are emerging as alternative modalities of treatment. Endoscopic clipping has been shown to have a comparable success rate of initial hemostasis [22] and even lower rebleeding rate as compared with adrenaline injection. Endoscopic clipping may be the preferred treatment for deeper extension of Mallory–Weiss tear with an esophageal perforation. The use of band ligation was compared with endoscopic epinephrine injection in a small-scale study of 34 patients with actively bleeding Mallory–Weiss syndrome [23]. Primary hemostasis was achieved in all 17 patients in the band ligation group and in 16 of 17 patients (94.1%) in the epinephrine injection group. There was no recurrence of bleeding or major complication in either group.

Other esophageal bleeding disorders

Corrosive injury is one of the rare causes of bleeding in the esophagus. The optimal management and evaluation of severity of this condition is far from satisfactory. A recent study explored the use of endoscopic ultrasound (EUS) for prediction of complications related to corrosive injury [24]. Sixteen patients underwent upper endoscopy and concurrent EUS within 24 hours after ingestion of a caustic agent. The severity of injury in the different segments of the esophagus and stomach was graded by endoscopy and by EUS. The development of complications during hospitalization and 3-month follow-up were recorded. The accuracy of prediction of bleeding or stricture was 100% with endoscopy compared with 75% for bleeding and 100% for stricture with EUS. Although EUS was proven safe in this study, there was no additional benefit in prediction of early or late complications. Another rare esophageal bleeding disorder that is increasingly recognized is necrotizing esophagitis. Its incidence has not yet been established, and its multifactorial etiology remains unknown. A retrospective analysis of the clinical course in 29 patients with acute necrotizing esophagitis was published [25]. Eighty-three percent of the patients had comorbid conditions. In all cases, acute necrotizing esophagitis became evident with upper gastrointestinal bleeding, with hemodynamic instability in more than 70% of cases. The lesions predominantly affected the lower two-thirds of the esophagus (59%). Although the esophagitis in resolved in all patients, 10 patients died of other coexisting illnesses. This series shows that prognosis of necrotizing esophagitis depends more patient's age and comorbid illnesses instead of the esophagitis. Dieulafoy's lesion, an arterial malformation in the submucosal layer, is another rare esophageal bleeding disorder. The optimal treatment of Dieulafoy's lesion in esophagus is unknown. Recently, there are reports of successful treatment with endoscopic injection of N-butyl-2-cyanoacrylate [26] and Sengstaken–Blakemore tube [27].

Conclusion

With the advances in endoscopic and pharmacological therapies, mortality from variceal hemorrhage has been substantially reduced. Antibiotic prophylaxis is increasingly recognized to have a role in the prevention of variceal rebleeding. New treatments such as endoloop and recombination factor VII have produced promising results. Apart from its major role in the initial treatment of variceal bleeding, mounting evidence shows that band ligation is a safe alternative to β-blocker for primary prophylaxis and may even be used as an adjunct to TIPSS to obviate the need of long-term surveillance. The benefit of β-blocker has now been extended to halt the progression of esophageal varices and a combination of β-blocker and band ligation remains the most cost-effective treatment strategy for secondary prophylaxis of variceal bleeding.

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