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Abstract

Gastroesophageal variceal hemorrhage is the most important clinical event that results from portal hypertension. It is a life-threatening condition that demands rapid and efficient treatment. The first step in bleeding control is hemodynamic stabilization and pharmacological treatment, which includes administration of vasoactive drugs and short-term antibiotic prophylaxis. After initial hemodynamic stabilization, endoscopic therapy should be performed. The first choice of endoscopic treatment for esophageal bleeding is endoscopic variceal ligation (EVL), or endoscopic injection sclerotherapy (EIS) if EVL cannot be performed. Several rescue therapies, such as application of balloon tamponade, a self-expandable metal stent (SEMS), or a transjugular intrahepatic portosystemic shunt (TIPS), are available in cases of resistant variceal bleeding that cannot be controlled with endoscopic therapies.

Gastric varices have a lower incidence than esophageal varices, but bleeding from gastric varices is associated with higher mortality and morbidity rates. The first-line treatment, as with esophageal variceal bleeding, is stabilization of the patient. After that, control of bleeding can be attempted. Optimal management of gastric variceal bleeding is not yet standardized due to diverse underlying pathologies and the lack of large, randomized controlled trials. Among endoscopic techniques, endoscopic variceal obturation (EVO) has been acknowledged as reliable. Among rescue therapies, balloon-occluded retrograde transvenous obliteration (B-RTO) of gastric varices and TIPS are the most common techniques. (Acta gastroenterol. belg., **2018**, 81, **305-316**).

Keywords : Balloon tamponade, endoscopic injection sclerotherapy, endoscopic variceal ligation, endoscopic variceal obturation, variceal bleeding.

Abbreviations : B-RTO, Balloon-occluded retrograde trans-venous obliteration ; EVL, Endoscopic variceal ligation ; EIS, Endoscopic injection sclerotherapy ; EVO, Endoscopic variceal obturation ; ET, Endoscopic treatment ; GVL, Gastric variceal ligation ; GVS, Gastric variceal sclerotherapy ; GOV1, Type 1 gastroesophageal varices ; GOV2, Type 2 gastroesophageal varices ; IGV1, Type 1 isolated gastric varices ; IGV2, Type 2 isolated gastric varices ; SEMS, Self-expandable metal stent ; TIPS, Transjugular intrahepatic portosystemic shunt ; NSBB, Non-selective beta-blocker ; HVPG – Hepatic venous pressure gradient ; ISMN – Isosorbide mononitrate.

Esophageal varices and their management

General overview

According to the UK guidelines on the management of variceal haemorrhage in cirrhotic patients (1), esophageal variceal hemorrhage represents bleeding from esophageal varices at the time of endoscopy or the presence of large esophageal varices with blood in the stomach and no other recognizable cause of bleeding (1). Variceal hemorrhage is a life-threatening condition and the most important clinical event that results from portal hypertension (2,3).

The most common cause of portal hypertension in the Western world is cirrhosis, the end stage of any chronic liver disease. Cirrhosis accounts for 90% of cases of portal hypertension (2). Although portal hypertension is defined as a portal pressure gradient of above 5 mmHg, a gradient above 10 mmHg is clinically significant and responsible for different clinical manifestations (4). One of the major manifestations of portal hypertension is the development of collateral circulation, which allows blood flow from the portal to the systemic circulation (4). Among those collaterals, gastroesophageal varices are clinically the most important due to the risk of their rupture, which results in variceal hemorrhage (4).

At the time of diagnosis of cirrhosis, around 50% of patients already have gastroesophageal varices. The exact rate of varices depends on the stage of liver disease at the time of diagnosis. Approximately 42% of patients who are classified as Child-Pugh class A have gastroesophageal varices, compared with 72% of patients who are classified as Child-Pugh class B/C (5). In patients without varices, the expected incidence of newly developed varices exceeds 5% per year (2,6-8). The most useful predictor for variceal bleeding is the size of the varix. The risk of bleeding in patients with small varices is approximately 5% per year, but in those with medium or large varices, the risk goes up to 15% per year at the time of diagnosis (9). The most important factors that can stimulate variceal rupture and, consequently, hemorrhage are pressure within the varix, variceal size, tension on the variceal wall, and severity of the liver disease (1). As mentioned before, variceal hemorrhage is a medical emergency, with a mortality rate that can exceed 30% within 4 to 6 weeks after the bleeding episode, depending

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Submission date : 25/08/2016
Acceptance date : 10/12/2017

by flexible scopes (9). EIS consists of the injection of a sclerosing agent into the variceal lumen or the area surrounding the varix in order to induce vessel thrombosis and inflammation of the vascular wall, which induces fibrosis and consequent variceal obliteration (9). For the intravariceal technique, the first injection is made just below the bleeding site. Injection of the sclerosing agent is usually started at the time of the diagnostic endoscopy and is repeated every 1–2 weeks until complete obliteration of the varices (9,33). There are some technical variations associated with EIS, such as type and concentration of agent, number of sessions, interval between sessions, volume injected per session, use of an over-tube, time of injection, and others (33). The most frequently used sclerosants are sodium morrhuate, sodium tetradecyl sulfate, polidocanol, and ethanolamine oleate (33). EIS is inexpensive, easily performed, and is an effective method, but use of EIS is associated with different complications, which can be divided into complications of early and late onset (33). The most common complications of early onset are retrosternal chest pain, transient dysphagia, fever, and superficial ulcerations. Among complications with late onset, the most common are strictures, deep ulcerations, perforating ulcers, motility disorders, and sclerosant spreading (33). However, this method can be highly reliable in the control of variceal bleeding as it was shown by Romano *et al.*(34). In this retrospective study, rebleeding after first treatment with endoscopic sclerotherapy occured in 3.9% of patients, and in other 9.9% of patients within a 5-days period after the treatment (34).

Endoscopic variceal ligation (EVL)

Endoscopic variceal ligation, or endoscopic variceal band ligation **(**EVL) is a technique that was first used in the control of variceal hemorrhage in 1988 (35). It currently represents the standard endoscopic therapy in the control of bleeding. In contrast to EIS, EVL obliterates varices by causing mechanical strangulation with rubber bands (9). There are two main ways of placing rubber bands – the single-shot band technique and the multi-shot band technique.

Single-shot versus multi-shot band ligation

Single-shot band technique require removal of the endoscope after each band application in order to reload with a new band. Repeated insertion of the endoscope can prolong the entire procedure of variceal ligation and may cause esophageal injury. This disadvantage led to the development of the multi-band application. Multi-shot ligatures can carry up to ten bands simultaneously and they have a transparent outer cap that improves visibility (33). Multi-band ligatures showed better results than single-band ligatures in terms of sedation requirements, level of discomfort, and duration of entire ligation (36). Although they are more practical for use, a considerable drawback of their routine use is their higher price in comparison with single-band ligators (33).

Technique of band ligation

First, diagnostic endoscopy should be performed to identify varices at risk of bleeding. After that, the

Table 1. — **Comparison of EIS and EVL between different studies**

Study		Number of patients	Initial hemostasis (%)	Variceal eradication (%)	Rebleeding (%)	Variceal recurance (%)	Complications (%)	Mortality (%)	Number of sessions (mean±SD)	Follow-up period (mean±SD)
Sarin *et al* (37)	EIS	48	86	---	20.8	7.5	---	6.25	5.2±1.8	8.5±4.4mo
	EVL	47	80	---	6.4	28.7	---	6.38	4.1±1.2	8.5±4.4mo
Lo *et al* (39)	EIS	34	76	---	33	---	29	35	---	1 mo
	EVL	37	97	---	17	---	5	19	---	1 mo
Baroncini *et al* (40)	EIS	54	---	92.5	---	13	31	---	4.0 ± 0.1	534 ± 42 d
	EVL	57	---	93	---	30	11	---	3.5 ± 0.1	496 ± 40 d
Masci *et al* (41)	EIS	50	---	82	42	22	36	---	5.29	3 mo
	EVL	50	---	88	12	28	10	---	3.41	3 mo
Zargar *et al* (42)	EIS	24	(2/2*) 100	91.7	25	10	25	---	6.1 ± 1.7	3 mo
	EVL	25	(2/2*) 100	96	4	17.4	4	---	3.9 ± 1.1	3 mo
Ferrari *et al* (43)	EIS	23	---	78.3	34.8	26.7	100	21.7	4.7 ± 3.0	1 yr
	EVL	23	---	73.9	8.7	42.9	82.6	13.9	2.9 ± 2.0	1 yr
Kuran *et al* (44)	EIS	47	---	93.6	16.3	44.7	---	---	6.6 ± 4.0	35±26 mo
	EVL	72	---	90.3	6.1	47.2	---	---	2.5 ± 1.6	35±26 mo
Luz *et al* (45)	EIS	50	86	---	14	---	---	20	---	6 wk
	EVL	50	78	---	22	---	---	23	---	6 wk

--- : Insufficient or no data available ; d : days ; wk : weeks ; mo : months ; yr : years ; * : number of patients with active variceal bleeding in which initial hemostasis was achieved with EIS or EVL.

on the stage of liver disease at the onset of hemorrhage (10-13). Over the past few decades, the mortality rate, as well as the rebleeding rate, has steadily decreased because of improvements in the therapy of this life-threatening condition (11,14,15).

Primary prophylaxis of variceal bleeding

In order to prevent first variceal hemorrhage and complications deriving from it, therapeutic intervention that aim at the prevention of first variceal hemorrhage should be performed (1). Cornerstone of primary prophylaxis of variceal hemorrhage are non-selective beta-blockers (NSBB), such as propranolol, carvedilol and nadolol. They exert their effect due to beta-1 and beta-2 adrenergic blockade, resulting in reduction of cardiac output and splanchnic vasoconstriction. This leads to a decrease of portal blood flow, thus reducing portal blood pressure and subsequently pressure within varices (1,4,16). NSBB should reduce hepatic venous pressure gradient (HVPG) to 12mmHg or below, or at least for 20% of its baseline value to efficiently diminish the risk of variceal hemorrhage (16). Propranolol has been shown as effective in terms of reducing the risk of variceal hemorrhage and mortality (17). However, significant shortcoming of propranolol is that not all patients respond with a reduction of HVPG (4,18,19). Carvedilol seems to be as effective as propranolol when reduction of HVPG is observed (20), while in a group of patients with haemodynamic non-response to propranolol, carvedilol seems to cause a greater reduction of HVPG than propranolol (21).

On the other side, non-selective beta-blocker may cause cardiac and non-cardiac adverse effects, such as the precipitation of heart failure, symptomatic bradycardia, exacerbation of bronchospastic diseases, fatigue and sexual dysfunction (16). Approximately 15-20% of patients have contraindications for NSBB or suffer from side-effects that require dose-reduction or cessation of therapy (22,23).

In cases of intolerance or contraindication for NSBB, variceal band ligation is recommended (1). Variceal band ligation seems to be as effective as NSBB in terms of primary prophylaxis (24,25), but given that the administration of NSBB is easier, less expensive and has an absence of procedure-related mortality, it is the cornerstone of primary prophylaxis of variceal bleeding (1,22).

Treatment of acute bleeding

The current standard therapy protocol of variceal hemorrhage includes a combination of hemodynamic stabilization, pharmacological treatment, and endoscopic procedures (1,4,22,26). In cases of refractory esophageal variceal bleeding, other therapy options must be considered. Rescue therapy options are balloon tamponade, self-expandable metal stents (SEMS), transjugular intrahepatic portosystemic shunt (TIPS), and surgical treatment (1,4,26).

Hemodynamic stabilization must be done in order to preserve tissue perfusion. To avoid volume overload, systolic blood pressure should be maintained at around 100 mm Hg (1,27). Blood transfusion should be used to obtain a hemoglobin level between 70 and 80 g/L (1,26,27). The clotting profile should be managed carefully because, in cirrhotic liver disease, there are usually disturbances in the values of both procoagulant and anticoagulant factors (1). Correction of clotting factor should be considered when the international normalized ratio (INR) is >1.5 times normal (1). Platelet transfusion may be given to patients who are actively bleeding and have a platelet count of $<50x10^9$/L (1).

Vasoactive drugs, such as terlipressin, somatostatin, octreotide, and vapreotide, can reduce portal pressure due to splanchnic vasoconstriction. If variceal hemorrhage is suspected, they should be administrated as soon as possible, i.e., during transport or at admission to hospital. Therapy with vasoactive drugs should be maintained up to 5 days (1,2,26).

Antibiotic prophylaxis is the standard therapy for cirrhotic patients that present with esophageal hemorrhage, and it should be administered from admission to the hospital (22,26). It has been shown that prophylactic use of antibiotics in circumstances of variceal bleeding can prevent infection and the risk of rebleeding (28,29). In most patients, quinolones are the antibiotics of first choice (26). High-risk patients with advanced cirrhosis or patients in areas with a high prevalence of quinolone-resistant bacterial infections should receive ceftriaxone (8,26,30,31). According to another study, longterm prophylactic admission of rifaximin can reduce the risk of variceal bleeding and hepatic encephalopathy, and improves survival of patients (32).

Endoscopy procedures

If variceal bleeding is suspected, upper gastrointestinal endoscopy has to be done in the first 24 h after patient's admission, just after hemodynamic stabilization if possible (1,26). Endoscopic therapies for varices aim to diminish the wall tension of varices by obliteration of the varix. This therapy has no effect on the underlying pathophysiological mechanisms of portal hypertension and varices may re-emerge after endoscopic treatment (9). Therefore, patients need to receive lifelong endoscopic follow-up to detect variceal recurrence. The two primary endoscopic methods used in the control of acute variceal bleeding are endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL).

Endoscopic injection sclerotherapy (EIS)

EIS is a technique that has existed for over 50 years, and it was widely adopted to treat variceal hemorrhage in the 1980s when rigid endoscopes were replaced

endoscope is withdrawn, and the ligation device is loaded on top of the endoscope. The endoscope/ligation device is then inserted into the esophagus. When the targeted varix is visualized, the tip of the device is moved toward the varix until it makes complete contact with it. When complete contact is made, continuous suction is applied in order to draw the varix into the banding area. To facilitate this action, a smooth movement of the device to the left and right is needed. When the varix completely fills the banding chamber, endoscopic visibility completely disappears, which is known as the "red out" sign. At that moment, the rubber band can be released, thus causing strangulation of the varix (9,33). Rubber bands over esophageal varices usually fall off within 1–10 days, leaving behind superficial ulceration that heals faster than ulcerations caused by EIS (9). Subsequent ligations are performed from the most distal variceal columns in the esophagus, progressing upwards in a helical fashion to avoid circumferential placement of bands at the same level (33). Eradication of varices usually requires two to four EVL sessions (9).

A possible shortcoming of this method is the higher recurrence of varices after EVL compared with EIS (37). The most common complications of EVL include esophageal laceration or perforation, transient dysphagia, retrosternal pain, esophageal stricture, and ulcer bleeding (9). In addition, there are reports that use of this method might increase the incidence of portal hypertensive gastropathy and fundal varices (38).

Table 1 shows that EIS compared with EVL has, in most cases, lower variceal recurrence rates, but higher rates of rebleeding and complications, and that it took more sessions to achieve variceal eradication.

EVL versus EIS – meta-analysis

Dai *et al.* (46) conducted a meta-analysis in which they compared the efficiency of EVL versus EIS in control of variceal hemorrhages. The meta-analysis included 14 studies comprising 1236 patients. The overall rebleeding rate in the EVL group was 21.7% and it was lower than that in the EIS group, where it was 33.1% (RR = 0.68; 95%CI: 0.57-0.81). The rate of complications in the EVL group was significantly lower than that in the EIS group (RR = 0.28, 95%CI: 0.13–0.58). The variceal eradication rate in the EVL group was significantly higher than that in the EIS group (RR = 1.06, 95%CI: 1.01-1.12). The mortality rate showed no significant difference between the EVL group and the EIS group (RR = 0.95, 95%CI: 0.77-1.17). This meta-analysis showed that EVL is better than EIS in terms of the lower rate of rebleeding and complications and the higher rate of variceal eradication. Therefore, this meta-analysis supports current guidelines according to which EVL should be the first-line endoscopic therapy, while EIS can be a therapeutic option in cases when EVL is not available (26).

Endoscopic treatment versus combined endoscopic and pharmacologic treatment – meta-analysis

Banares *et al.* (47) conducted a meta-analysis in which they compared the efficiency of endoscopic treatment versus combined endoscopic and pharmacologic treatment for acute variceal bleeding. The meta-analysis included eight trials with 939 patients. The results showed that combined treatment improved the initial control of bleeding (RR = 1.12; 95%CI: 1.02-1.23) and 5-day hemostasis (RR = 1.28; 95%CI: 1.18-1.39). In spite of this improvement, combined therapy did not significantly decrease mortality (RR = 0.73; 95%CI: 0.45–1.18). This meta-analysis showed that combined therapy had better initial control of bleeding and 5-day hemostasis, but did not have a significant effect on mortality.

Endoscopic variceal obturation (EVO)

Endoscopic variceal obturation is a method that represents an application of cyanoacrylate glues, and it is used for control of acute variceal hemorrhage and obliteration of varices (48,49). It is effective in control of esophageal variceal bleeding and represents a valid treatment option for acute bleeding episode in patients with Child-Pugh class C (50,51). Endoscopic variceal obturation represents a first-line endoscopic therapy for gastric variceal bleeding (1,22). Therefore, it is further described below in section of gastric varices and their management.

Rescue therapies

The standard therapy protocol is unable to control acute variceal bleeding or rebleeding in 10–20% of patients with variceal hemorrhage (27). If bleeding is not severe and the patient is hemodynamically stable, a second endoscopic therapy should be performed. If this fails or bleeding is severe, rescue therapies must be considered (27).

Balloon tamponade

Balloon tamponade as a treatment of esophageal variceal bleeding was first presented in 1949 (52). Unlike many methods that had been used till then, balloon tamponade with a Sengstaken-Blakemore tube may be an effective method to achieve hemostasis (Table 2) (52). The balloon tamponade achieves hemostasis in up to 90% of patients (53). It cannot be placed for longer than 24 h due to several severe side effects, such as aspiration pneumonia, necrosis, and rupture of the esophagus (1,2). Another drawback of this method is the high rate of rebleeding after the balloon is removed (2). Therefore, this method should be used only as a bridging therapy until permanent therapy options are available (1,2).

Self-expendable metal stent

Covered self-expandable metal stents (SEMS) are an alternative to balloon tamponade (Table 3) (54-56). New types of stents, such as the SX-Ella Danis stent, have been introduced in the last decade (55-57). This stent is usually inserted into the esophagus over an endoscopicaly placed guide-wire. It controls bleeding by tamponade of varices in the lower esophagus (58). It has been reported that this stent can effectively stop refractory bleeding from esophageal varices, with a low risk of rebleeding (Table 4). The stent can be left in place no more than 2 weeks in order to minimize the risk of migration and esophagus wall injury (58). Limitations and complications include the required training and expertise in setting the stent, distal stent migration, and aspiration. Although data are still limited, it seems that SEMS can be considered as an alternative to balloon tamponade (58). Similar to balloon tamponade, this method is only a bridging therapy until permanent treatment is possible (58).

Table 2. — **Efficiency of balloon tamponade in management of variceal bleeding**

Study	Sarin *et al* (59)	Panes *et al* (53)	
Type of balloon tamponade	Sengstaken-Blakemore tube	Sengstaken-Blakemore tube	Linton-Nachlas balloon
Number of patients	63	118	33
Primary hemostasis (%)	87	91.5	88
Overall or permanent hemostasis (%)	75	47.7	
Major complications (%)	15	10	

Transjugular intrahepatic portosystemic shunt (TIPS)

Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure that involves the creation of a portocaval conduit by deployment of an intrahepatic expandable stent between the hepatic vein and the intrahepatic branch of the portal vein (64-66), which leads to immediate decompression of portal hypertension (64,65). TIPS is used in resistant acute variceal bleeding or in cases of rebleeding that cannot be controlled with endoscopic therapy. TIPS is an effective procedure, as shown in Table 5 and Table 6. Control of bleeding can be achieved in up to 95% of patients (66). Rebleeding occurs in 10–20% of patients (66-68). The main drawbacks of this procedure are the relatively high rate of portal encephalopathy (up to 35%), and potential stent dysfunction or occlusion, which is the most common cause of rebleeding (67).

Early TIPS

Although TIPS is rescue therapy, there is a group of patients that seems to have benefit from the preemptive TIPS placement. This group includes patients with high-risk of treatment failure, such as patients with advanced liver disease and patients with severe portal hypertension (1,26).

Several studies have suggested that patients with high-risk factors that underwent early TIPS have better

Table 3. — **Comparison of esophageal balloon tamponade and SEMS**

Study	Type of procedure	Number of patients	Success of therapy*	Control of bleeding (%)	Serious adverse events (%)
Escorsell *et al* (60)	Balloon tamponade	15	20	47	47
	Esophageal stent	13	66	85	15

* : Success is defined as survival at day 15 with control of bleeding and without serious adverse events (%).

Table 4. — **Efficiency of SEMS in the control of gastroesophageal variceal bleeding**

Study	Number of patients	Successful stent deployment (%)	Hemostasis (%)	Rebleeding during stent treatment (%)	Complications (%)	Mortality during stent treatment (%)	Time of stent implantation in days
Hubmann *et al* (54)	20	100	100	0	0	0	2–14
Zehetner *et al* (55)	34	---	100	0	0	0	5 (1–14)
Wright *et al* (56)	10	90	70	---	10	40	9
Dechene *et al* (61)	8	---	100	0	---	0	11
Zakaria *et al* (62)	16	93.8	87.5	---	---	25	2–4
Muller *et al* (63)	11	---	100	9	---	27*	12 (5–24)

--- : Insufficient or no data available ; * : mortality for a follow-up period of 42 days after stent deployment.

Table 5. — **Efficiency of TIPS in control of gastroesophageal variceal bleeding**

Study	Number of patients	Technical success of TIPS (%)	Hemostasis (%)	Rebleeding (%)	Encephalopathy (%)	30-day survival rate (%)
Sanyal *et al* (68)	30	96.7	100	20	26.7	63
Gaba *et al* (69)	128	100	---	9 (30 d)	14 (30 d)	80

d : days

treatment outcomes (70-72). Garcia-Pagan *et al.* (71) showed that patients with cirrhosis in Child-Pugh class C or in Child-Pugh class B with active bleeding benefit from early TIPS in terms of reduced risk of treatment failure, improved survival without increased risk of hepatic encephalopathy. Monescillo *et al.* (72) showed that patients with hepatic venous pressure gradient above 20mmHg and acute variceal bleeding had reduced treatment failure and improved survival if they underwent early TIPS placement.

According to Baverno V guidelines, an early TIPS within 72 hours should be considered in patients with Child-Pugh class C <14 points or Child class B with active bleeding after initial pharmacological and endoscopic therapy has been performed (26).

TIPS versus endoscopic treatment – meta-analysis

Papatheodoridis *et al.* (67) conducted a meta-analysis in which they compared the efficiency of TIPS versus endoscopic treatment (ET) in the prevention of variceal rebleeding. The meta-analysis included 11 trials with 811 patients. Variceal rebleeding was significantly higher in the ET group (47% of patients) compared with TIPS (19% of patients; OR = 3.8 ; 95% CI : 2.8-5.2; P < 0.001). Post-treatment encephalopathy was significantly lower after ET (19%) than after TIPS (34% ; OR = 0.43; 95% CI : 0.30-0.60; P < 0.001). There was no significant difference in mortality (OR = 0.97 ; 95% CI : 0.71-1.34). On the other hand, Qi *et al.* (109) conducted a meta-analysis in which they compared the efficiency of TIPS versus combined medical/endoscopic therapy in the control of variceal bleeding. Six trials were included, and TIPS was significantly more effective than medical/endoscopic therapy in decreasing the incidence of treatment failure (OR = 0.22 ; 95% CI : 0.11-0.44), improving overall survival (HR = 0.55 ; 95% CI : 0.38-0.812), and decreasing the incidence of bleeding-related death (OR = 0.19 ; 95% CI : 0.06-0.59). TIPS did not significantly decrease the incidence of rebleeding (OR = 0.27 ; 95% CI : 0.06-1.29) or increase the incidence of post-treatment hepatic encephalopathy (OR = 1.37; 95% CI: 0.63-2.99).

Secondary prophylaxis of variceal bleeding

Aim of secondary prophylaxis is to prevent new episodes of variceal bleeding after the initial bleeding episode has been under control for at least 5 days (80). Patients that survive the first bleeding incident have rebleeding risk of 60% in the first year after bleeding event with a mortality of up to 33% (81). Secondary prophylaxis should be performed as soon as possible after the initial bleeding episode (26).

Pharmacological treatment with only NSBB has been shown as beneficial in reducing the risk of variceal rebleeding, although it didn't show significant reduction in mortality (82). The addition of ISMN to NSBB results in higher decrease of portal pressure (4). In spite of, combined drug therapy of ISMN and NSBB did not differ from treatment alone with NSBB when the risk of rebleeding is observed (83). When comparing endoscopic therapy versus combined drug therapy in terms of prevention of variceal rebleeding, it seems that there is no superiority of one therapy over another (84-86).

For the majority of patients the therapy of choice is lifelong pharmacological therapy with non-selective beta-blockers, combined with endoscopic variceal ligation conducted until complete obliteration of varices (1,26). Thiele et al (87) showed that combined EVL and drug

Table 6. — **Comparison of TIPS and other therapeutic modalities in the treatment of variceal bleeding**

Study	Type of therapeutic modality	Number of patients	Rebleeding (%)	Encephalopathy rate after 2 years (%)	Survival rate after 2 years (%)	Follow-up period (mean±SD)
Merli *et al* (73)	TIPS	38	24	55	73	74±7 wk
	EIS	43	51	26	79	78±7 wk
Sauer *et al* (74)	TIPS	42	14.3	29	69	1.6 yr
	EIS + propranolol	41	51.2	13	67	1.45 yr
Pomier-Layrargues *et al* (75)	TIPS	41	18 (2 yr)	47	57	678 d
	EVL	39	66 (2 yr)	44	56	581 d
Sauer *et al* (76)	TIPS	43	19.4	40.5*	75.9*	4.1 yr
	EVL + propranolol	42	29.9	20.5*	82.2*	3.6 yr
Luo *et al* (77)	TIPS	37	22.2	---	72.9	23±8 mo
	EVL + propranolol	36	57.1	---	57.2	21±9 mo
Xue *et al* (78)	TIPS	64	17	81.2	79	21±1.3 mo
	Endoscopic therapy	62	50	91.8	64.9	19±1.3 mo
Sauerbruch *et al* (79)	TIPS	90	7 (2 yr)	18	76	2.48 yr
	Pharmaco-therapy**	95	26 (2 yr)	8	81	1.32 yr

--- : Insufficient or no data available ; TIPS : Transjugular intrahepatic portosystemic shun t; EIS : endoscopic injection sclerotherapy ; EVL : endoscopic variceal band ligation ; d : days ; wk : weeks ; mo : months ; yr : years ; * : unknown time frame of encephalopathy rate or survival rate ; ** : pharmacotherapy included propranolol and isosorbide-5-mononitrate.

therapy reduced the risk of rebleeding from esophageal varices when compared with treatment alone with EVL or drug therapy. However, mortality wasn't different when combined therapy was compared with EVL alone or medical treatment alone (87). Puente et al (88) showed that, when compared with EVL alone, combined therapy with EVL and NSBB ± ISMN significantly reduced overall rebleeding, with non-significant reduction of mortality. On the other hand, when combined therapy was compared with drug therapy alone, there was non-significant reduction of rebleeding or mortality (88). Therefore, non-selective beta-blockers remain the mainstay of secondary prophylaxis of variceal bleeding. Patients who fail endoscopic and pharmacological treatment for the prevention of rebleeding should undergo TIPS placement. In terms of prevention of variceal rebleeding, use of TIPS with covered stents is more efficient than standard secondary prophylaxis, but it doesn't have an impact on survival and it is associated with higher rates of hepatic encephalopathy (79,89). This group of patients, as well as patients that underwent TIPS placement in the initial bleeding episode, should be referred to transplant center to assess the possibility of transplantation (26,81).

Gastric varices and their management

General overview

Gastric varices occur in approximately 20% of patients with portal hypertension (90). In this group of patients, they are the most common cause of upper gastrointestinal bleeding after esophageal varices (48,91). Similar to esophageal varices, the mortality of gastric variceal bleeding has steadily decreased over the past years, but still it remains relatively high (92) and exceeds 15% in the first 6 weeks after the bleeding episode (93).

The most common classification system for gastric varices is the Sarin Classification system, which is based on endoscopic appearance and location of varices (94). According to this classification system, varices can be divided into four groups. Type 1 gastroesophageal varices (GOV1) are extensions of the esophageal varices into lesser curvature varices. Type 2 gastroesophageal varices (GOV2) represent an extension of the esophageal varices over the gastroesophageal junction toward the fundus. Type 1 isolated gastric varices (IGV1) represent isolated fundal varices, and type 2 isolated gastric varices (IGV2) include ectopic varices in the antrum, corpus, and around the pylorus (48,91,94).

GOV1 are the most common type of gastric varices, and they account for almost 75% of all gastric varices (48,94). On the other hand, bleeding from gastric varices occurs mostly from fundal varices, IGV1 and GOV2 (91). The cumulative risk for variceal bleeding from fundal varices goes from 16% per year to 44% for a 5-year period (95). Factors that could indicate a higher risk of bleeding include the size of varices, red marks on the surface, and the severity of liver disease (91).

Management of bleeding from gastric varices

The first-line treatment, as with esophageal variceal bleeding, is hemodynamic stabilization of the patient. When the patient is hemodynamically stabilized, control of bleeding can be attempted. Management of gastric variceal bleeding is not uniform for all cases of bleeding due to diverse underlying pathologies and the lack of large, randomized controlled trials (49).

Management of GOV-1 is same as for esophageal varices (1). On the other hand, optimal therapy for GOV-2 and IGV is endoscopic variceal obturation, endoscopic therapy with cyanoacrylate injection (1,22).

Endoscopic therapies

Gastric variceal sclerotherapy (GVS)

GVS represents a form of endoscopic sclerotherapy used for obliteration of gastric varices. Intra- or paravariceal application of sclerosing agent may result in control of bleeding from gastric varices (48). This method seems to have satisfying results for the treatment of GOV1 as they represent the extensions of esophageal varices (48,96). However, due to higher blood flow through gastric varices, GVS requires larger volumes of sclerosant agents. This shortcoming of GVS results with higher rates of side effects, such as fever and retrosternal and abdominal pain (48).

In terms of acute gastric variceal bleeding, GVS can achieve a relatively high percentage of bleeding control (Table 7). However, GVS of gastric variceal bleeding has been associated with high rebleeding rates after treatment, especially when it comes to treatment of fundal variceal bleeding (96,97).

Gastric variceal ligation (GVL)

According to some studies, endoscopic band ligation of gastric varices or gastric variceal ligation (GVL) is an efficient method in the control of gastric variceal bleeding (98). However, some other studies have shown that GVL is inferior to some other methods (Table 8) and, therefore, this method is not widely used in the treatment of gastric variceal hemorrhage.

Endoscopic variceal obturation (EVO)

EVO entails the application of tissue adhesives, such as histoacryl (n-butyl-2-cyanoacrylate) or bucrylate (isobutyl-2-cyanoacrylate), which induce thrombosis in the varices after their application (48,99). Cyanoacrylate injections are based on the same principles as injection schlerotherapy, but additional caution is needed in order to protect the endoscope from glue damage. Once a variceal bleeding is under control, follow-up treatment should be done every 3-4 weeks until the varices are completely obliterated (100). The efficiency of this method has been shown in several studies (101-105).

Table 7. — **Comparison of gastric variceal sclerotherapy and gastric variceal ligation**

Study	Sarin *et al* (96)	Shiha & El-Sayed (98)
Type of technique	GVS	GVL
Number of patients	71	27
Initial hemostasis (%)	(12/18*) 66.7	(16/18*) 88.8
Variceal eradication after repeated sessions (%)	71.6	100
Rebleeding (%)	5.5-53	18.5
Mortality (%)	24	22.2
Follow-up period (mean±SD)	24.2 ± 22.9 mo	---

--- : Insufficient or no data available ; * : number of patients with active variceal bleeding ; mo : months.

When compared with other therapeutic options, EVO has a higher rate of initial bleeding control and a lower risk of rebleeding (Table 8). Therefore, this method has been proposed as the first-line treatment for gastric variceal bleeding by several renowned guidelines, such as the UK guidelines and the Baverno V consensus (1,8,26). However, this method can be associated with some complications. Application of cyanoacrylates can cause fever, pain, embolization of pulmonary or systemic vessels, and tissue necrosis if applied paravariceally (49,105). In order to diminish the risk of these incidents, the standard injection technique should be used, which includes the use of a precisely defined amount of sclerosing agents in order to prevent embolism, then the use of repeated intravariceal injections in order to achieve hemostasis, the obliteration of all variceal tributaries, and control gastroscopy in 1-4 days in order to confirm complete obliteration (49,106).

Hemostatic powder (Hemospray)

Endoscopic hemostatic powder is a novel hemostatic technology in the management of upper GI bleeding (107,108). It represents inorganic hemostatic powder that becomes coherent and adhesive when in contact with blood. This results in a mechanical boundary over the bleeding site, thus enhancing the clotting factor concentration and clot formation (107).

The advantage of this method is its simplicity of use. It does not require high technical expertise in therapeutic endoscopy (110). The powder is used in intervals in short bursts over the bleeding area. It does not require direct contact with the exact place of bleeding, thus allowing less precise aiming of the bleeding site (107,108). However, there is a theoretical risk of venous embolisation dut to high-pressure delivery system of hemostatic powder (110-112).

The efficiency of this method in control of non-variceal gastrointestinal bleeding has been shown in several studies (113-116). This method has also been shown as effective in control of acute variceal bleeding (110,117). Although hemostatic powder is promising agent, further studies are needed to elucidate the strengths and weaknesses of this method among other treatment modalities of variceal bleeding (108).

Rescue therapies

If endoscopic treatment is unable to control bleeding from gastric varices, second–line or rescue therapies should be used. Among them, the most popular are balloon tamponade as a bridge therapy, TIPS, and B-RTO (100).

Balloon-occluded retrograde transvenous obliteration of gastric varices (B-RTO)

B-RTO is an interventional radiologic method that can be used to obliterate gastric varices. The method is based on the insertion of a balloon catheter into the gastrorenal or gastrocaval shunt through the femoral or internal jugular vein. After performing a retrograde venogram in order to identify and occlude collateral blood vessels, the sclerosant is injected into the varices and left there to coagulate. If repeated venograms show insufficient clot formation, B-RTO can be reattempted (119). Sclerosants that are used in this procedure are ethanolamine oleate, sodium tetradecyl sulfate, and polidocanol, and they can be used as a foam or in a liquid version (119,120).

Table 8. — **Comparison between endoscopic therapy with tissue adhesives (EVO - endoscopic variceal obturation) and gastric variceal ligation (GVL)**

Study	Lo *et al* (102)		Tan *et al* (101)		Tantau *et al* (103)		Hong *et al* (118)	
Type of technique	EVO	GVL	EVO	GVL	EVO	GVL	EVO	GVL
Number of patients	31	29	49	48	19	18	64	20
Control of active bleeding (%)	(13/15*) 87	(5/11*) 45	(14/15*) 93	(14/15*) 93	100	89	97	90
Rebleeding (%)	31	54	22.4	43.8	31.6	72.2	27.4(6wk)	16.7(6wk)
Variceal eradication (%)	51	45	63.3	66.7	84.2	66.7	---	---
Variceal recurrence (%)	---	---	22.6	59.4	57.9	77.7	---	---
Complications (%)	19	38	22.4	22.9	26.3	27.8	---	---
Mortality (%)	29	48	14.6(30d)	16.3(30d)	10.5	11.1	19.4(1yr)	5.6(1yr)

--- : Insufficient or no data available ; * : number of patients with active variceal bleeding ; d : days ; wk : weeks ; yr : years.

Table 9. — **Efficiency of B-RTO in control of gastric variceal bleeding**

Study	Number of patients	Success of procedure after 1 or 2 sessions (%)	Rebleeding rate (%)	Variceal eradication (%)	Variceal recurrence (%)	Development or worsening of esophageal varices (%)	Survival rate (%)
Kitamoto *et al* (122)	24	88	9 (1wk)	100	0	33.3	---
Arai *et al* (123)	11	100	0	90.9	0	54.5	91 (1yr)
Ninoi *et al* (124)	78	---	1.5 (5yr)	---	2.6	37.1	93 (1yr)
Park *et al* (125)	28	89.3	0	78.3	4.3	30.4	55 (2yr)
Akahoshi *et al* (126)	68	92.6	3.2	96.6	---	17	---
Sabri *et al* (127)	22	91	0	89	---	---	---
Sonomura *et al* (128)	17	94.1	0	94.1	0	29.4	---

--- : Insufficient or no data available ; wk : weeks ; yr : years.

However, obliteration of gastric varices can redirect portal blood to the esophageal varices (121), and therefore, the unintended consequence of this method can be enlargement of esophageal varices. Risk factors that could indicate a higher risk of enlargement or even rupture of esophageal varices are total bilirubin and the hepatic venous pressure gradient (121). Patients that are at higher risk should undergo follow-up evaluation that includes endoscopy (121).

This method has been demonstrated in a large number of trials (126,128-132), and efficiency of this method can be seen in Table 9 and Table 10. According to a meta-analysis conducted by Park *et al.* (133), B-RTO is a highly effective method. The meta-analysis included 24 studies with 1016 patients who underwent B-RTO treatment of gastric varices. The clinical success, which was defined as variceal obliteration or absence of rebleeding episodes, was 97% and the rate of complications was 2.6%. The recurrence rate of esophageal varices was 33.3% (133).

Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS has been shown to be an effective therapy for gastric variceal bleeding that cannot be controlled with standard endoscopic therapies (134). In the control of gastric variceal bleeding, TIPS is as effective as endoscopic therapies based on cyanoacrylate injection (Table 11). However, use of TIPS is associated with a higher risk of hepatic encephalopathy (135,136).

In order to compare TIPS and B-RTO in the control of gastric variceal bleeding, further studies are needed (137).

Table 10. — **Comparison between balloon-occluded retrograde transvenous obliteration (B-RTO) and endoscopic injection sclerotherapy (EIS)**

Study	Emori *et al* (130)	
Type of procedure	B-RTO	EIS
Number of patients	49	63
Gastric variceal bleeding during follow-up (%)	0	14.3
Variceal recurrence (%)	0	19.9
Complications (%)	12.2	15.8
Worsening of esophageal varices (%)	32.7	23.8
Number of sessions	1.4 ± 0.6	2.3 ± 1.8
3-year survival rate (%)	76.3	58.4
Mortality rate (%)	34.7	42.9
Follow-up period	50 ± 36 mo	35 ± 32 mo

mo : months.

Table 11. — **Comparison of TIPS and endoscopic treatment with cyanoacrylate**

Study	Kochnar *et al* (138)	
Type of procedure	TIPS	Endoscopic treatment
Number of patients	140	29
Rebleeding within 30 days (%)	17.4	17.2
Encephalopathy (%)	15.9	20.7
In-hospital mortality (%)	9.0	11.1

Primary and secondary prophylaxis of gastric variceal bleeding

It has been shown that primary prophylaxis of gastric variceal bleeding reduces the risk of first variceal bleeding (139). Use of NSBB can be considered to lower the risk of the initial bleeding episode in high-risk patients with large GOV-2, while use of cyanoacrilate injections is not recommended outside of clinical trials (1).

As for secondary prophylaxis, patients with GOV-1 should be treated with endoscopic variceal ligation until complete eradication of varices, followed by periodic endoscopic surveillance. On the other hand, patients with GOV-2 and IGV should enter endoscopic surveillance with cyanoacrylate injection, or should receive TIPS if rebleeding occurs despite cyanoacrylate injections (2). The role of non-selective beta-blockers in terms of secondary prophylaxis of gastric variceal bleeding is controversial (1).

Conclusion

Endoscopic procedures currently represent the standard therapy for both esophageal and gastric variceal

bleeding. If endoscopic therapy is unable to control variceal hemorrhage, several rescue therapies are available. Although these procedures are effective in the control of variceal bleeding, it is important to understand that none of these procedures resolves cirrhosis, which is the most common condition that leads to increased portal pressure and varices enlargement.

Source of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No potential conflict of interest was reported by the authors.

References

1. TRIPATHI D, STANLEY AJ, HAYES PC, PATCH D, MILLSON C, MEHRZAD H, *et al.* Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut*., 2015, **64** : 1680-704.
2. ASHKENAZI E, KOVALEV Y, ZUCKERMAN E. Evaluation and treatment of esophageal varices in the cirrhotic patient. *Isr. Med. Assoc. J*., 2013, **15** : 109-15.
3. CREMERS I, RIBEIRO S. Management of variceal and nonvariceal upper gastrointestinal bleeding in patients with cirrhosis. *Therap. Adv. Gastroenterol.,* 2014, **7** : 206-16.
4. MIÑANO C, GARCIA-TSAO G. Portal hypertension. *Gastroenterol. Clin. North Am.,* 2010, 39: 681-95.
5. KOVALAK M, LAKE J, MATTEK N, EISEN G, LIEBERMAN D, ZAMAN A. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. *Gastrointest. Endosc.,* 2007, **65** : 82-8.
6. MERLI M, NICOLINI G, ANGELONI S, RINALDI V, DE SANTIS A, MERKEL C, *et al.* Incidence and natural history of small esophageal varices in cirrhotic patients. *J. Hepatol*., 2003, **38** : 266-72.
7. D'AMICO G, GARCIA-TSAO G, PAGLIARO L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J. Hepatol.,* 2006, **44** : 217-31.
8. GARCIA-TSAO G, SANYAL AJ, GRACE ND, CAREY W. Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007, **46** : 922-38.
9. POZA CORDON J, FROILAN TORRES C, BURGOS GARCÍA A, GEA RODRIGUEZ F, SUÁREZ DE PARGA JM. Endoscopic management of esophageal varices. *World J. Gastrointest. Endosc*., 2012, **4** : 312-22.
10. Augustin S, Muntaner L, Altamirano JT, González A, Saperas E, Dot J, *et al.* Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. Clin Gastroenterol Hepatol. 2009, 7: 1347-54.
11. CARBONELL N, PAUWELS A, SERFATY L, FOURDAN O, LÉVY VG, POUPON R. Improved survival after variceal bleeding in patients with cirrhosis over past two decades. *Hepatology*, 2004, **40** : 652-9.
12. CHALASANI N, KAHI C, FRANCOIS F, PINTO A, MARATHE A, BINI EJ. *et al.* Improved patient survival after acute variceal bleeding: a multicenter, cohort study. *Am. J. Gastroenterol.,* 2003, **98** : 653-9.
13. D'AMICO G, DE FRANCHIS R. Cooperative Study Group (2003) Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology*. 2003, **38** : 599-612.
14. MCCORMICK PA, O'KEEFE C. Improving prognosis following a first variceal haemorrhage over four decades. *Gut,* 2001, **49** : 682-5.
15. VUACHET D, CERVONI JP, VUITTON L, WEIL D, DRITSAS S, DUSSAUCY A. *et al.* Improved survival of cirrhotic patients with variceal bleeding over the decade 2000-2010. *Clin. Res. Hepatol. Gastroenterol*., 2015, **39 :** 59-67.
16. GE PS, RUNYON BA. The changing role of beta-blocker therapy in patients with cirrhosis. *J. Hepatol.,* 2014, **60** : 643-53.
17. CHENG JW, ZHU L, GU MJ, SONG ZM. Meta analysis of propranolol effects on gastrointestinal hemorrhage in cirrhotic patients. *World J. Gastroenterol.,* 2003, **9** : 1836-1839.
18. TURNES J, GARCIA-PAGAN JC, ABRALDES JG, HERNANDEZ-GUERRA M, DELL'ERA A, BOSCH J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. *Am J Gastroenterol.* 2006, **101** : 506-12.
19. VILLANUEVA C, ARACIL C, COLOMO A, HERNÁNDEZ-GEA V, LÓPEZ-BALAGUER JM, ALVAREZ-URTURI C, *et al.* Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. *Gastroenterology*, 2009, **137** : 119-28.
20. HOBOLTH L, MØLLER S, GRØNBÆK H, ROELSGAARD K, BENDTSEN F, FELDAGER HANSEN E. Carvedilol or propranolol in portal hypertension? A randomized comparison. *Scand. J. Gastroenterol.,* 2012, **47** : 467-74.
21. REIBERGER T, ULBRICH G, FERLITSCH A, PAYER BA, SCHWABL P, PINTER M. *et al.* Vienna Hepatic Hemodynamic Lab. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. *Gut*. 2013, **62** : 1634-41.
22. BIECKER E. Portal hypertension and gastrointestinal bleeding: diagnosis, prevention and management. *World J. Gastroenterol.,* 2013, **19** : 5035-50.
23. BARI K, GARCIA-TSAO G. Treatment of portal hypertension. *World J. Gastroenterol.,* 2012, **18** : 1166-75.
24. SCHEPKE M, KLEBER G, NÜRNBERG D, WILLERT J, KOCH L, VELTZKE-SCHLIEKER W, *et al.* German Study Group for the Primary Prophylaxis of Variceal Bleeding. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology*, 2004, **40** : 65-72.
25. LO GH, CHEN WC, CHEN MH, LIN CP, LO CC, HSU PI, *et al.* Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. *Gastrointest. Endosc.,* 2004, **59** : 333-8.
26. DE FRANCHIS R; BAVERNO V Faculty. Revising consensus in portal hypertension: report of the Baverno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J. Hepatol.,* 2010, **53** :762-8.
27. BOSCH J, BERZIGOTTI A, GARCIA-PAGAN JC, ABRALDES JG. The management of portal hypertension: rational basis, available treatments and future options. *J. Hepatol.,* 2008, **48** Suppl 1 : S68-92.
28. HOU MC, LIN HC, LIU TT, KUO BI, LEE FY, CHANG FY, *et al*. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology*, 2004, **39 :** 746-53.
29. CHAVEZ-TAPIA NC, BARRIENTOS-GUTIERREZ T, TELLEZ-AVILA F, SOARES-WEISER K, MENDEZ-SANCHEZ N, GLUUD C, *et al.* Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review. *Aliment Pharmacol Ther*., 2011, **34** : 509-18.
30. FERNÁNDEZ J, RUIZ DEL ARBOL L, GÓMEZ C, DURANDEZ R, SERRADILLA R, GUARNER C, *et al.* Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology,* 2006, **131** : 1049-56.
31. LEE YY, TEE HP, MAHADEVA S. Role of prophylactic antibiotics in cirrhotic patients with variceal bleeding. *World J. Gastroenterol.,* 2014, **20 :** 1790-6.

32 VLACHOGIANNAKOS J, VIAZIS N, VASIANOPOULOU P, VAFIADIS I, KARAMANOLIS DG, LADAS SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J. Gastroenterol. Hepatol.,* 2013,28: 450-5.

33. HELMY A, HAYES PC. Review article: current endoscopic therapeutic options in the management of variceal bleeding. *Aliment. Pharmacol. Ther.,* 2001,**15** : 575-94.
34. ROMANO G, AGRUSA A, AMATO G, DE VITA G, FRAZZETTA G, CHIANETTA D, *et al.* Endoscopic sclerotherapy for hemostasis of acute esophageal variceal bleeding. *G. Chir.*, 2014, **35** : 61-4.
35. HALL RJ, LILLY JR, STIEGMANN GV. Endoscopic esophageal varix ligation: technique and preliminary results in children. *J. Pediatr. Surg.,* 1988, **23** : 1222-3.
36. WONG T, PEREIRA SP, MCNAIR A, HARRISON PM. A prospective, randomized comparison of the ease and safety of variceal ligation using a multiband vs. a conventional ligation device. *Endoscopy,* 2000, 32: 931-4.
37. SARIN SK, GOVIL A, JAIN AK, GUPTAN RC, ISSAR SK, JAIN M, *et al.* Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *J. Hepatol.,* 1997, **26** : 826-32.
38. YÜKSEL O, KÖKLÜ S, ARHAN M, YOLCU OF, ERTUĞRUL I, ODEMIŞ B, *et al.* Effects of esophageal varice eradication on portal hypertensive gastropathy and fundal varices: a retrospective and comparative study. *Dig. Dis. Sci*., 2006, **51** : 27-30.
39. LO GH, LAI KH, CHENG JS, LIN CK, HUANG JS, HSU PI, *et al.* Emergency banding versus sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology*, 1997, **25** : 1101-4.
40. BARONCINI D, MILANDRI GL, BORIONI D, PIEMONTESE A, CENNAMO V, BILLI P, et al. A prospective randomized trial of sclerotherapy versus ligation in the elective treatment of bleeding esophageal varices. *Endoscopy,* 1997, **29** : 235-40.

41. MASCI E, STIGLIANO R, MARIANI A, BERTONI G, BARONCINI D, CENNAMO V, *et al.* Prospective multicenter randomized trial comparing banding ligation with sclerotherapy of esophageal varices. *Hepatogastroenterology*. 1999, **46** : 1769-73.
42. ZARGAR SA, JAVID G, KHAN BA, YATTOO GN, SHAH AH, GULZAR GM, *et al.* Endoscopic ligation compared with sclerotherapy for bleeding esophageal varices in children with extrahepatical venous obstruction. *Hepatology*. 2002, **36 :** 666-72.
43. FERRARI AP, DE PAULO GA, DE MACEDO CM, ARAÚJO I, DELLA LIBERA E Jr. Efficacy of absolute alcohol injection compared with band ligation in the eradication of esophageal varices. *Arq. Gastroenterol.,* 2005, **42** : 72-6.
44. KURAN S, OĞUZ D, PARLAK E, ASIL M, CIÇEK B, KILIÇ M, *et al.* Secondary prophylaxis of esophageal variceal treatment: Endoscopic sclerotherapy, band ligation and combined therapy-long-term results. *Turk J. Gastroenterol*., 2006, 17: 103-9.
45. LUZ GO, MALUF-FILHO F, MATUGUMA SE, HONDO FY, IDE E, MELO JM, et al. Comparison between endoscopic sclerotherapy and band ligation for hemostasis of acute variceal bleeding. *World J. Gastrointest. Endosc.,* 2011, **3** : 95-100.
46. DAI C, LIU WX, JIANG M, SUN MJ. Endoscopic variceal ligation compared with endoscopic injection sclerotherapy for treatment of esophageal variceal hemorrhage: a meta-analysis. *World J. Gastroenterol.,* 2015, **21** : 2534-41.
47. BAÑARES R, ALBILLOS A, RINCÓN D, ALONSO S, GONZÁLEZ M, RUIZ-DEL-ARBOL L, *et al.* Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding : a meta-analysis. *Hepatology*. 2002, **35** : 609-15.
48. RYAN BM, STOCKBRUGGER RW, RYAn JM. A pathophysiologic, gastroenterologic, and radiologic approach to the management of gastric varices. *Gastroenterology,* 2004, **126** : 1175-89.
49. LIM YS. Practical approach to endoscopic management for bleeding gastric varices. *Korean J. Radiol*., 2012, **13** Suppl 1 : S40-4.
50. RIBEIRO JP, MATUGUMA SE, CHENG S, HERMAN P, SAKAI P, D'ALBUQUERQUE LA, *et al.* Results of treatment of esophageal variceal hemorrhage with endoscopic injection of n-butyl-2-cyanoacrylate in patients with Child-Pugh class C cirrhosis. *Endosc. Int. Open*., 2015, **3** : E584-9.
51. MALUF-FILHO F, SAKAI P, ISHIOKA S, MATUGUMA SE. Endoscopic sclerosis versus cyanoacrylate endoscopic injection for the first episode of variceal bleeding: a prospective, controlled, and randomized study in Child-Pugh class C patients. *Endoscopy,* 2001, **33** : 421-7.
52. SENGSTAKEN RW, BLAKEMORE AH. Balloon Tamponage for the Control of Hemorrhage from Esophageal Varices. *Ann. Surg*., 1950, **131** : 781-79.
53. PANÉS J, TERÉS J, BOSCH J, RODÉS J. Efficacy of balloon tamponade in treatment of bleeding gastric and esophageal varices. Results in 151 consecutive episodes. *Dig. Dis. Sci.,* 1988, **33** : 454-9.
54. HUBMANN R, BODLAJ G, CZOMPO M, BENKO L, PICHLER P, AL-KATHIB S, et al. The use of self-expendable metal stents to treat acute esophageal variceal bleeding. *Endoscopy,* 2006, **38** : 896-901.
55. ZEHETNER J, SHAMIYEH A, WAYAND W, HUBMANN R. Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. *Surg. Endosc*., 2008, **22** : 2149-52.
56. WRIGHT G, LEWIS H, HOGAN B, BURROUGHS A, PATCH D, O'BEIRNE J. A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. *Gastrointest. Endosc.,* 2010, **71** : 71-8.
57. MISHIN I, GHIDIRIM G, DOLGHII A, BUNIC G, ZASTAVNITSKY G. Implantation of self-expanding metal stent in the treatment of severe bleeding from esophageal ulcer after endoscopic band ligation. *Dis. Esophagus*, 2010, **23** : E35-8.
58. MAUFA F, AL-KAWAS FH. Role of self expandable metal stents in acute variceal bleeding. *Int. J. Hepatol.,* 2012, 418369.
59. SARIN SK, NUNDY S. Balloon tamponade in the management of bleeding oesophageal varices. *Ann. R. Coll. Surg. Engl*., 1984, **66** : 30-2.
60. ESCORSELL À, PAVEL O, CÁRDENAS A, MORILLAS R, LLOP E, VILLANUEVA C, GARCIA-PAGÁN JC, BOSCH J. Variceal Bleeding Study Group. Esophageal balloon tamponade Vs esophageal stent in controlling acute refractory variceal bleeding: A multicenter RCT. *Hepatology*, 2016, **63** : 1957-67.
61. DECHÊNE A, EL FOULY AH, BECHMANN LP, JOCHUM C, SANER FH, GERKEN G, *et al.* Acute management of refractory variceal bleeding in liver cirrhosis by self-expanding metal stents. *Digestion*, 2012, **85** : 185-91.
62. Zakaria MS, Hamza IM, Mohey MA, Hubamnn RG. The first Egyptian experience using new self-expandable metal stents in acute esophageal variceal bleeding: pilot study. *Saudi J. Gastroenterol.*, 2013, **19** : 177-81.
63. MÜLLER M, SEUFFERLEIN T, PERKHOFER L, WAGNER M, KLEGER A. Self-Expandable Metal Stents for Persisting Esophageal Variceal Bleeding after Band Ligation or Injection-Therapy : A Retrospective Study. *PLoS One*., 2015, **10** : e0126525.
64. LOFFROY R, ESTIVALET L, CHERBLANC V, FAVELIER S, POTTECHER P, HAMZA S, *et al.* Transjugular intrahepatic portosystemic shunt for the management of acute variceal hemorrhage. *World J. Gastroenterol.,* 2013, **19** : 6131-43.
65. GOYKHMAN Y, BEN-HAIM M, ROSEN G, CARMIEL-HAGGAI M, OREN R, NAKACHE R, et al. Transjugular intrahepatic portosystemic shunt: current indications, patient selection and results. *Isr. Med. Assoc. J*., 2010, **12** : 687-91.
66. BOYER TD, HASKAL ZJ. American Association for the Study of Liver Diseases. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. *Hepatology*, 2005, **41** : 386-400.
67. PAPATHEODORIDIS GV**,** GOULIS J, LEANDRO G, PATCH D, BURROUGHS AK. Transjugular intrahepatic portosystemic shunt compared with endoscopic treatment for prevention of variceal rebleeding: A meta-analysis. *Hepatology*, 1999, **30** : 612-22.
68. SANYAL AJ, FREEDMAN AM, LUKETIC VA, PURDUM PP, SHIFFMAN ML, TISNADO J, *et al.* Transjugular intrahepatic portosystemic shunts for patients with active variceal hemorrhage unresponsive to sclerotherapy. *Gastroenterology,* 1996, **111** : 138-46.
69. GABA RC, OMENE BO, PODCZERWINSKI ES, KNUTTINEN MG, COTLER SJ, KALLWITZ ER, *et al.* TIPS for treatment of variceal hemorrhage: clinical outcomes in 128 patients at a single institution over a 12-year period. *J. Vasc. Interv. Radiol*., 2012, **23** : 227-35.
70. Njei B, McCarty TR, Laine L. Early transjugular intrahepatic portosystemic shunt in US patients hospitalized with acuteesophageal variceal bleeding. *J. Gastroenterol. Hepatol.,* 2017, **32** : 852-8.
71. GARCÍA-PAGÁN JC, CACA K, BUREAU C, LALEMAN W, APPENRODT B, LUCA A, *et al.*; Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N. Engl. J. Med*., 2010, **362** : 2370-9.
72. MONESCILLO A, MARTÍNEZ-LAGARES F, RUIZ-DEL-ARBOL L, SIERRA A, GUEVARA C, JIMÉNEZ E, *et al.* Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology,* 2004, **40** : 793-801.
73. MERLI M, SALERNO F, RIGGIO O, DE FRANCHIS R, FIACCADORI F, MEDDI P, *et al.* Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal bleeding in cirrhosis: a randomized multicenter trial. Gruppo Italiano Studio TIPS (G.I.S.T.). *Hepatology*, 1998, **27** : 48-53.
74. SAUER P, THEILMANN L, STREMMEL W, BENZ C, RICHTER GM, STIEHL A. Transjugular intrahepatic portosystemic stent shunt versus sclerotherapy plus propranolol for variceal rebleeding. *Gastroenterology,* 1997, **113** : 1623-31.
75. POMIER-LAYRARGUES G, VILLENEUVE JP, DESCHÊNES M, BUI B, PERREAULT P, FENYVES D, *et al.* Transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: a randomised trial. *Gut*. 2001, **48** : 390-6.
76. SAUER P, HANSMANN J, RICHTER GM, STREMMEL W, STIEHL A. Endoscopic variceal ligation plus propranolol vs. transjugular intrahepatic portosystemic stent shunt: a long-term randomized trial. *Endoscopy,* 2002, **34** : 690-7.
77. LUO X, WANG Z, TSAUO J, ZHOU B, ZHANG H, LI X. Advanced Cirrhosis Combined with Portal Vein Thrombosis: A Randomized Trial of TIPS versus Endoscopic Band Ligation Plus Propranolol for the Prevention of Recurrent Esophageal Variceal Bleeding. *Radiology*, 2015, **276** : 286-93.
78. XUE H, ZHANG M, PANG JX, YAN F, LI YC, LV LS, *et al.* Transjugular intrahepatic portosystemic shunt vs endoscopic therapy in preventing variceal rebleeding. *World J. Gastroenterol.,* 2012, **18** : 7341-7.
79. SAUERBRUCH T, MENGEL M, DOLLINGER M, ZIPPRICH A, RÖSSLE M, PANTHER E, *et al.* German Study Group for Prophylaxis of Variceal Rebleeding. Prevention of Rebleeding From Esophageal Varices in Patients With Cirrhosis Receiving Small-Diameter Stents Versus Hemodynamically Controlled Medical Therapy. *Gastroenterology,* 2015, **149** : 660-8.
80. BRUNNER F, BERZIGOTTI A, BOSCH J. Prevention and treatment of variceal haemorrhage in 2017. *Liver Int*., 2017, **37** Suppl 1: 104-15.
81. GARCIA-TSAO G, BOSCH J. Varices and Variceal Hemorrhage in Cirrhosis: A New View of an Old Problem. *Clin. Gastroenterol. Hepatol.*, 2015, **13** : 2109-17.
82. GATTA A, MERKEL C, SACERDOTI D, BOLOGNESI M, CAREGARO L, ZUIN R, *et al.* Nadolol for prevention of variceal rebleeding in cirrhosis: a controlled clinical trial. *Digestion*, 1987, **37** : 22-8.
83. GLUUD LL, LANGHOLZ E, KRAG A. Meta-analysis: isosorbide-mononitrate alone or with either beta-blockers or endoscopic therapy for the

management of oesophageal varices. *Aliment Pharmacol Ther.,* 2010, **32** : 859-71.
84. PATCH D, SABIN CA, GOULIS J, GERUNDA G, GREENSLADE L, MERKEL C, *et al.* A randomized, controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal rebleeding in patients with cirrhosis. *Gastroenterology,* 2002, 123: 1013-9.
85. LI L, YU C, LI Y. Endoscopic band ligation versus pharmacological therapy for variceal bleeding in cirrhosis: a meta-analysis. *Can. J. Gastroenterol*., 2011, **25** : 147-55.
86. DING SH, LIU J, WANG JP. Efficacy of beta-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: a meta-analysis. *World J. Gastroenterol.,* 2009, **15** : 2151-5.
87. THIELE M, KRAG A, ROHDE U, GLUUD LL. Meta-analysis: banding ligation and medical interventions for the prevention of rebleeding from oesophageal varices. *Aliment Pharmacol Ther.,* 2012, **35** : 1155-65.
88. PUENTE A, HERNÁNDEZ-GEA V, GRAUPERA I, ROQUE M, COLOMO A, POCA M, ARACIL C, GICH I, GUARNER C, VILLANUEVA C. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. *Liver Int.*, 2014, **34** : 823-33.
89. HOLSTER IL, TJWA ET, MOELKER A, WILS A, HANSEN BE, VERMEIJDEN JR, *et al.* Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy + β-blocker for prevention of variceal rebleeding. *Hepatology*, 2016, **63** : 581-9.
90. SARIN SK, LAHOTI D, SAXENA SP, MURTHY NS, MAKWANA UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology*, 1992, **16**, 1343-9.
91. AL-OSAIMI AM, CALDWELL SH. Medical and endoscopic management of gastric varices. *Semin. Intervent. Radiol*., 2011, **28** : 273-82.
92. KIM MY, UM SH, BAIK SK, SEO YS, PARK SY, LEE JI, *et al.* Clinical features and outcomes of gastric variceal bleeding: retrospective Korean multicenter data. *Clin. Mol. Hepatol.,* 2013, **19** : 36-44.
93. Teng W, Chen WT, Ho YP, Jeng WJ, Huang CH, Chen YC, *et al.* Predictors of mortality within 6 weeks after treatment of gastric variceal bleeding in cirrhotic patients. *Medicine* (Baltimore), 2014, **93** : e321.
94. SARIN SK, KUMAR A. Gastric varices: profile, classification, and management. *Am J Gastroenterol.,* 1989, **84** : 1244-9.
95. KIM T, SHIJO H, KOKAWA H, TOKUMITSU H, KUBARA K, OTA K, *et al.* Risk factors for hemorrhage from gastric fundal varices. *Hepatology*, 1997, **25** : 307-12.
96. SARIN SK. Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience. *Gastrointest. Endosc.,* 1997, **46** : 8-14.
97. KORULA J, CHIN K, KO Y, YAMADA S. Demonstration of two distinct subsets of gastric varices. Observations during a seven-year study of endoscopic sclerotherapy. *Dig. Dis. Sci.,* 1991, **36** : 303-9.
98. SHIHA G, EL-SAYED SS. Gastric variceal ligation: a new technique. *Gastrointest. Endosc.,* 1999, **49** : 437-41.
99. SARASWAT VA, VERMA A. Gluing Gastric Varices in 2012: Lessons Learnt Over 25 Years. *J. Clin. Exp. Hepatol.*, 2012, **2** : 55–69.
100. Saad WE. Endovascular management of gastric varices. *Clin. Liver Dis*., 2014, **18** : 829-51.
101. TAN PC, HOU MC, LIN HC, LIU TT, LEE FY, CHANG FY, *et al.* A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation. *Hepatolog,*. 2006, **43** : 690-7.
102. LO GH, LAI KH, CHENG JS, CHEN MH, CHIANG HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology*, 2001, **33** : 1060-4.
103. TANTAU M, CRISAN D, POPA D, VESA S, TANTAU A. Band ligation vs. N-Butyl-2-cyanoacrylate injection in acute gastric variceal bleeding: a prospective follow-up study. *Ann. Hepatol*., 2013-2014, **13** : 75-83.
104. KUMAR A, SINGH S, MADAN K, GARG PK, ACHARYA SK. Undiluted N-butyl cyanoacrylate is safe and effective for gastric variceal bleeding. *Gastrointest. Endosc.,* 2010, **72** : 721-7.
105. CHENG LF, WANG ZQ, LI CZ, LIN W, YEO AE, JIN B. Low incidence of complications from endoscopic gastric variceal obturation with butyl cyanoacrylate. *Clin. Gastroenterol. Hepatol*., 2010, **8** : 760-6.
106. SEEWALD S, ANG TL, IMAZU H, NAGA M, OMAR S, GROTH S, *et al.* A standardized injection technique and regimen ensures success and safety of N-butyl-2-cyanoacrylate injection for the treatment of gastric fundal varices (with videos). *Gastrointest. Endosc.,* 2008, **68** : 447-54.
107. FUJII-LAU LL, LAW R, WONG KEE SONG LM, LEVY MJ. Novel techniques for gastric variceal obliteration. *Dig. Endosc*., 2015, **27** : 189-96.
108. LEUNG KI EL, LAU JY. New endoscopic hemostasis methods. *Clin. Endosc*., 2012, **45** : 224-9.
109. QI X, JIA J, BAI M, GUO X, SU C, GARCIA-PAGAN JC, *et al.* Transjugular Intrahepatic Portosystemic Shunt for Acute Variceal Bleeding; A Meta-analysis. *J. Clin. Gastroenterol*., 2015, **49** : 495-505.
110. IBRAHIM M, EL-MIKKAWY A, ABDALLA H, MOSTAFA I, DEVIÈRE J. Management of acute variceal bleeding using hemostatic powder. *United European Gastroenterol. J*., 2015, **3** : 277-83.
111. STANLEY AJ, SMITH LA, MORRIS AJ. Use of hemostatic powder (Hemospray) in the management of refractory gastric variceal hemorrhage. *Endoscopy,* 2013, **45** : E86-7.
112. HOLSTER IL, POLEY JW, KUIPERS EJ, TJWA ET. Controlling gastric variceal bleeding with endoscopically applied hemostatic powder (Hemospray™). *J. Hepatol.,* 2012, **57** : 1397-8.
113. CHEN YI, BARKUN AN, SOULELLIS C, MAYRAND S, GHALI P. Use of the endoscopically applied hemostatic powder TC-325 in cancer-related upper GI hemorrhage: preliminary experience (with video). *Gastrointest. Endosc.,* 2012, **75** : 1278-81.
114. SUNG JJ, LUO D, WU JC, CHING JY, CHAN FK, LAU JY, *et al.* Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. *Endoscopy,* 2011, **43** : 291-5.
115. HADDARA S, JACQUES J, LECLEIRE S, BRANCHE J, LEBLANC S, LE BALEUR Y, *et al.* A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the "GRAPHE" registry). *Endoscopy,* 2016, **48** : 1084-95.
116. GIDAY S, VAN ALSTINE W, VAN VLEET J, DUCHARME R, BRANDNER E, FLOREA M, *et al.* Safety analysis of a hemostatic powder in a porcine model of acute severe gastric bleeding. *Dig. Dis. Sci.,* 2013, **58** : 3422-8.
117. IBRAHIM M, EL-MIKKAWY A, MOSTAFA I, DEVIÈRE J. Endoscopic treatment of acute variceal hemorrhage by using hemostatic powder TC-325: a prospective pilot study. *Gastrointest. Endosc.,* 2013, **78** : 769-73.
118. HONG HJ, JUN CH, LEE DU H, CHO EA, PARK SY, CHO SB, *et al.* Comparison of Endoscopic Variceal Ligation and Endoscopic Variceal Obliteration in Patients with GOV1 Bleeding. *Chonnam Med. J*., 2013, **49** : 14-9.
119. PATEL A, FISCHMAN AM, SAAD WE. Balloon-occluded retrograde transvenous obliteration of gastric varices. AJR *Am. J. Roentgenol*., 2012, **199** : 721-9.
120. ITOU C, KOIZUMI J, HASHIMOTO T, MYOJIN K, KAGAWA T, MINE T, *et al.* Balloon-Occluded Retrograde Transvenous Obliteration for the Treatment of Gastric Varices: Polidocanol Foam Versus Liquid Ethanolamine Oleate. *AJR Am. J. Roentgenol*., 2015, **205** : 659-66.
121. JOGO A, NISHIDA N, YAMAMOTO A, MATSUI H, TAKESHITA T, SAKAI Y, *et al.* Factors associated with aggravation of esophageal varices after B-RTO for gastric varices. *Cardiovasc. Intervent. Radiol*., 2014, **37** : 1243-50.
122. KITAMOTO M, IMAMURA M, KAMADA K, AIKATA H, KAWAKAMI Y, MATSUMOTO A, *et al.* Balloon-occluded retrograde transvenous obliteration of gastric fundal varices with hemorrhage. *AJR Am. J. Roentgenol*., 2002, **178** : 1167-74.
123. ARAI H, ABE T, SHIMODA R, TAKAGI H, YAMADA T, MORI M. Emergency balloon-occluded retrograde transvenous obliteration for gastric varices. *J. Gastroenterol*., 2005, **40** : 964-71.
124. NINOI T, NISHIDA N, KAMINOU T, SAKAI Y, KITAYAMA T, HAMURO M, *et al.* Balloon-occluded retrograde transvenous obliteration of gastric varices with gastrorenal shunt: long-term follow-up in 78 patients. *AJR Am. J. Roentgenol*., 2005, **184** : 1340-6
125. PARK KS, KIM YH, CHOI JS, HWANG JS, KWON JH, JANG BK, *et al.* Therapeutic efficacy of balloon-occluded retrograde transvenous obliteration in patients with gastric variceal bleeding. Korean *J. Gastroenterol.*, 2006, **47** : 370-8.
126. AKAHOSHI T, HASHIZUME M, TOMIKAWA M, KAWANAKA H, YAMAGUCHI S, KONISHI K, *et al.* Long-term results of balloon-occluded retrograde transvenous obliteration for gastric variceal bleeding and risky gastric varices: a 10-year experience. *J. Gastroenterol. Hepatol.,* 2008, **23** : 1702-9.
127. SABRI SS, SWEE W, TURBA UC, SAAD WE, PARK AW, AL-OSAIMI AM, *et al.* Bleeding gastric varices obliteration with balloon-occluded retrograde transvenous obliteration using sodium tetradecyl sulfate foam. *J. Vasc. Interv. Radiol.*, 2011, **22** : 309-16.
128. SONOMURA T, ONO W, SATO M, SAHARA S, NAKATA K, SANDA H, *et al.* Emergency balloon-occluded retrograde transvenous obliteration of ruptured gastric varices. *World J. Gastroenterol.,* 2013, **19** : 5125-30.
129. CLEMENTS W, CAVANAGH K, ALI F, KAVNOUDIAS H, KEMP W, ROBERTS S, *et al.* Variant treatment for gastric varices with polidocanol foam using balloon-occluded retrograde transvenous obliteration: a pilot study. *J. Med. Imaging Radiat. Oncol*., 2012, **56** : 599-605.

130. EMORI K, TOYONAGA A, OHO K, KUMAMOTO M, HARUTA T, INOUE H, *et al.* Balloon-occluded retrograde transvenous obliteration versus endoscopic injection sclerotherapy for isolatedgastric varices: a comparative study. *Kurume Med. J*., 2014, **60** : 105-13.
131. NAESHIRO N, AIKATA H, KAKIZAWA H, HYOGO H, KAN H, FUJINO H, *et al.* Long-term outcome of patients with gastric varices treated by balloon-occluded retrograde transvenous obliteration. *J. Gastroenterol. Hepatol.,* 2014, **29** : 1035-42.
132. AKAHOSHI T, TOMIKAWA M, KAMORI M, TSUTSUMI N, NAGAO Y, HASHIZUME M, *et al.* Impact of balloon-occluded retrograde transvenous obliteration on management of isolated fundal gastricvariceal bleeding. *Hepatol. Res*., 2012, **42** : 385-93.
133. PARK JK, SAAB S, KEE ST, BUSUTTIL RW, KIM HJ, DURAZO F, *et al.* Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) for Treatment of Gastric Varices: Review and Meta-Analysis. *Dig. Dis. Sci.,* 2015, **60** : 1543-53.
134. TRIPATHI D, THERAPONDOS G, JACKSON E, REDHEAD DN, HAYES PC. The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: clinical and haemodynamic correlations. *Gut*, 2002, **51**: 270-4.
135. KHAN S, TUDUR SMITH C, WILLIAMSON P, SUTTON R. Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. *Cochrane Database Syst. Rev.*, 2006, (4) : CD000553.
136. BAI M, QI XS, YANG ZP, WU KC, FAN DM, HAN GH. EVS vs TIPS shunt for gastric variceal bleeding in patients with cirrhosis : A meta-analysis., 2014, **5** : 97-104.
137. SAAD WE, DARCY MD. Transjugular Intrahepatic Portosystemic Shunt (TIPS) versus Balloon-occluded Retrograde Transvenous Obliteration (BRTO) for the Management of Gastric Varices. *Semin. Intervent. Radiol*., 2011, **28** : 339-49.
138. KOCHHAR GS, NAVANEETHAN U, HARTMAN J, MARI PARUNGAO J, LOPEZ R, GUPTA R, *et al.* Comparative study of endoscopy vs. transjugular intrahepatic portosystemic shunt in the management of gastricvariceal bleeding. *Gastroenterol. Rep. (Oxf*), 2015, **3** : 75-82.
139. MISHRA SR, SHARMA BC, KUMAR A, SARIN SK. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial. *J. Hepatol.,* 2011, **54** : 1161-7.