World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i21.6481

World J Gastroenterol 2014 June 7; 20(21): 6481-6494
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Historical overview and review of current day treatment in the management of acute variceal haemorrhage

Neil Rajoriya, Dhiraj Tripathi

Neil Rajoriya, Dhiraj Tripathi, Department of Hepatology, The New Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom
Author contributions: All the authors contributed equally to this manuscript.
Correspondence to: Dr. Neil Rajoriya, Department of Hepatology, The New Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH,
United Kingdom. nrajoriya@hotmail.com
Telephone: +44-121-3714672 Fax: +44-121-6272449
Received: November 13, 2013 Revised: January 14, 2014
Accepted: April 2, 2014
Published online: June 7, 2014

Abstract

Variceal haemorrhage is one of the most devastating consequences of portal hypertension, with a 1-year mortality of 40%. With the passage of time, acute management strategies have developed with improved survival. The major historical treatment landmarks in the management of variceal haemorrhage can be divided into surgical, medical, endoscopic and radiological breakthroughs. We sought to provide a historical overview of the management of variceal haemorrhage and how treatment modalities over time have impacted on clinical outcomes. A PubMed search of the following terms: portal hypertension, variceal haemorrhage, gastric varices, oesophageal varices, transjugular intrahepatic portosystemic shunt was performed. To complement this, Google™ was searched with the aforementioned terms. Other relevant references were identified after review of the reference lists of articles. The review of therapeutic advances was conducted divided into pre-1970s, 1970/80s, 1990s, 2000-2010 and post-2010. Also, a summary and review on the pathophysiology of portal hypertension and clinical outcomes in variceal haemorrhage was performed. Aided by the development of endoscopic therapies, medication and improved radiological interventions; the management of variceal haemorrhage has changed over recent decades with improved survival from an often-terminating event in recent past.

Key words: Variceal haemorrhage; Oesophageal varices; Gastric varices; Portal hypertension

Core tip: This review article focuses on how the management of variceal haemorrhage, has changed and evolved over the decades. A novel historical approach detailing changes per decades is taken - with a review of each therapies and its impact on outcome.

Rajoriya N, Tripathi D. Historical overview and review of current day treatment in the management of acute variceal haemorrhage. *World J Gastroenterol* 2014; 20(21): 6481-6494 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i21/6481.htm
DOI: http://dx.doi.org/10.3748/wjg.v20.i21.6481

INTRODUCTION

Gastro-oesophageal variceal haemorrhage is a life-threatening complication of portal hypertension. Historically, overall mortality rates have been reported up to 30%-50%[1] and 1-year mortality as high as 70%[2]. Chronic liver disease of any aetiology can result in portal hypertension, the key event leading to formation of portosystemic collaterals including gastro-oesophageal varices. An increase in portal pressure is the most important risk factor for the development of varices[2]. The onset of portal hypertension can not only cause variceal haemorrhage, but also herald the development of other complications of liver cirrhosis such as ascites formation and hepatic encephalopathy. Therapies to reduce portal hypertension, along with improved resuscitation techniques and the advent of broad-spectrum antibiotics in variceal haemorrhage have improved outcomes[1]. Novel endoscopic and

radiological therapies have also improved outcomes and now play a pivotal role in the management of variceal haemorrhage. Injection sclerotherapy with sclerosant agents have been largely superseded by endoscopic variceal band ligation (EVBL) for oesophageal variceal haemorrhage whilst for gastric variceal haemorrhage, tissue adhesives have become increasing used and incorporated into consensus guidelines as 1st line therapies[2]. In addition to direct endoscopic therapies, measures have been introduced such as increased access to endoscopy including 24-h "bleeding rotas" performed by skilled endoscopists. These have coincided with the decline in use of tamponade equipment such as the Minnesota, Linton-Nachlas and Sengstaken-Blakemore tubes, and virtual extinction of emergency surgical procedures such as oesophageal transection or portocaval shunt formation, which had high associated mortality[1,3]. With all the pharmacological, radiological and endoscopic developments, mortality has fallen in the last 3 decades, and in one study mortality rates fell from 42%[4] in 1981 to recent actual rates ranging from 6%-12%[3]. New radiological procedures such as transjugular intrahepatic portosystemic stent-shunts (TIPSS) and balloon retrograde transvenous obliteration (BRTO) have a role in acute variceal haemorrhage often as "rescue therapy" when endoscopic therapies have failed. The emerging role of TIPSS in an "early" setting, within 72 h after haemostasis following the index bleed in high-risk patients has been recently studied[4]. The excellent results could lead to new paradigm in the utility of TIPSS following variceal bleeding.

This article aims to focus on the outcomes following variceal bleeding and how, over time, these have improved with the advent of new medical therapies and endoscopic and radiological therapies. A PubMed search was performed using the following keywords: portal hypertension, variceal haemorrhage, gastric varices, oesophageal varices, transjugular intrahepatic portosystemic shunt, TIPS and TIPSS. From this search 37431 articles were found, however 127 articles/abstracts were studied for the writing of this review article. This search was complemented by a search of the keywords using www.google.com™.

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION AND UTILITY OF HEPATIC VENOUS PRESSURE GRADIENT

Portal hypertension results from 3 principal events. The first is of a purely mechanical obstruction due to fibrosis or regenerative nodules resulting in increased resistance to flow. The second mechanism accounts for 20%-30% of increased intrahepatic resistance to portal inflow. There is contraction of sinusoidal and extra sinusoidal contractile cells (stellate cells and VSMCs) with intrahepatic imbalance between vasoconstrictors (such as endothelin-1 and angiotensin) and vasodilators (such as nitric oxide and glucagon). This imbalance leads to reduced intrahepatic eNOS activity. This second event is modifiable with medications such including beta-blockers and nitrates. These events together result in the development of the portosystemic collateral circulation with the aim of decompressing the portal circulation. However, the opposite occurs, with splanchnic vasodilatation in response to a relatively ischaemic liver or extrahepatic excess of NO, with sGC-PKG signalling and smooth muscle cell relaxation[3]. The increased portal blood flow maintains portal hypertension. A hyperdynamic circulation results due to these haemodynamic changes in cirrhosis and portal hypertension. This manifests as high cardiac output with low systematic vascular resistance and arterial hypotension[5].

Portal pressure can be derived from the hepatic venous pressure gradient (HVPG), which is normally in the range 1-5 mmHg. This is performed by advancing a catheter until it is wedged into a hepatic vein thus gaining a wedged hepatic vein pressure (WHVP)[6].

Initial studies on estimation of portal pressure from an occluded hepatic venule date as far back as 1951[2]. HVPG = WHVP - free hepatic venous pressure (FHVP) where HVPG represents the gradient between portal and caval pressure. FHVP cancels out variations in abdominal pressure and acts as an internal zero. Sinusoidal and post sinusoidal, but not pre-sinusoidal portal hypertension results in a raised HVPG as the resistance to flow extends from the hepatic venous system to the portal vein. It has been demonstrated that varices are more likely to develop if the HVPG is > 10 mmHg[7].

CLINICAL VARIABLES OF OUTCOME IN VARICEAL HAEMORRHAGE

Variceal haemorrhage is a life-threatening emergency, with a mortality of up to 20% at 6-wk[2,8]. It is now considered that any death occurring within 6 wk from a hospital admission for variceal haemorrhage be considered a variceal bleed-related death[2]. Other end-points are the advent of rebleeding after 1st variceal bleed (index bleed) or failure to control bleeding, which are often used to define outcomes. Rebleeding is an important predictive factor of mortality and a good indicator of the success of intervention directly targeted at upper gastrointestinal (GI) bleeding[9]. The factors contributing to outcome often from an upper GI bleed in patients with cirrhosis can be broadly divided into those correlating to severity of bleed and then also those relating to severity of liver disease.

The most applicable measurement of portal hypertension is the HVPG, which has been shown to be of prognostic benefit in patients having an acute variceal haemorrhage. Moitinho *et al*[10] found HVPG the only independent predictor of 5-d treatment failure after variceal bleed (rebleeding or death) with the best cut-off of HVPG of 20 mmHg. HVPG has also been found to be an independent predictor of 6-wk and 1 year mortality (38% *vs* 5% in those with HVPG < 20, and 65% *vs* 20%

Table 1 Predictors of day 5 treatment failure

Variable	OR	95%CI
Transfusion in 24 h (units)	1.35	1.13-1.61
CTP class	2.27	1.22-4.22
AST (per 10 U increase)	1.03	1.01-1.06
PV thrombosis	2.75	1.25-6.04

Adapted from D'Amico *et al*[14]. AST: Aspartate aminotransferase; PV: Portal vein; CTP: Child–Turcotte–Pugh.

Table 2 Predictors of 6-wk mortality

Variable	OR	95%CI
Albumin (per 1 g reduction)	2.33	1.32-4.00
Bilirubin (per 1 mg increase)	1.23	1.10-1.37
Transfusion total (units)	1.40	1.19-1.66
Hepatocellular carcinoma	3.44	1.64-7.24
Encephalopathy	2.30	1.39-3.70

Adapted from D'Amico *et al*[14].

at 1 year)[10,11]. A single HVPG measurement 2 wk after a variceal bleed has been shown to be an independent predictor for survival[12] with those patients having a measurement < 16 mmHg having a 35% 2 year survival (compared to 15% in those with HVPG > 16 mmHg). In those patients on vasoactive therapy, a HVPG response to treatment (*i.e.,* > 20% drop from baseline of to < 12 mmHg)[13] are independent predictors of survival.

The severity of liver disease can also be measured by a number of easily clinically accessible scoring systems including the Child-Pugh Turcotte (CPT) score/grade and the MELD scores. In an Italian study of 465 patients[14], prognostic parameters for 6-wk mortality and also day 5 failure (*i.e.,* uncontrolled bleeding, rebleeding or death) were studied in patients with cirrhosis and an upper gastrointestinal bleed (Tables 1 and 2). The variables in this study could be divided into three variables: (1) severity of underlying liver disease (CTP and its components); (2) specific features of liver disease (HCC and portal vein thrombosis); and (3) severity of bleeding (transfusion requirement and rise in aspartate aminotransferase as reflected by hypotension causing ischaemic hit to liver).

In another study by Carbonell *et al*[3] patients presenting to a centre with variceal bleeding were studied over 2 decades with 523 episodes of GI bleeding encountered in 468 patients with cirrhosis (319 episodes of variceal bleeding in 295 patients). On multivariant analysis, independent predictors of survival were: younger age (P = 0.04), antibiotic prophylaxis (P = 0.01), endoscopic therapy (P = 0.008), lower CPT score (P < 0.0001) and absence of hypovolemic shock (P = 0.005). In this same study, persistent bleeding at admission and absence of endoscopic therapy were independent predictors of rebleeding (P = 0.004 and P = 0.01 respectively). Interestingly, mortality fell from 9%-0% in CPT-A patients and 46%-0% in CPT-B over 20 years. Even in the patients CPT-C disease, mortality fell from 70% to 32%.

The advent of infection, encephalopathy and acute kidney injury (AKI) have been shown to be important late prognostic markers after the 1st index bleed[15] with AKI, rebleeding, HCC and encephalopathy all independent predictors of mortality in 403 patients presenting with an upper GI bleed in liver cirrhosis (of which 187 episodes were from varices). In this retrospective study, predictors of rebleeding included CPT class (P < 0.001) and severity of bleeding (P < 0.005) with rebleeding more common in those with oesophageal varices (OR = 4.3, 95%CI: 2.6-7.2). In a retrospective study by Thomopoulos *et al*[16] identified clinical predictors for early and late mortality in patients with variceal haemorrhage. Child-Pugh C (and haemodynamic shock - another marker of severity of bleed) on admission were independent predictors of 6-wk mortality (P = 0.003 and 0.0037 respectively). Predictors of 1 year mortality at initial admission included: Child-Pugh C (P = 0.028), presence of hepatocellular carcinoma (P = 0.04) and partial thromboplastin time (P = 0.021) Mortality however in this series was not affected by the presence of active bleeding at endoscopy or infection. Thus with set parameters in measuring outcomes from acute variceal bleeding - in severity of liver disease and also severity of haemorrhage; different therapeutic strategies over the years have evolved, improving outcomes in this potentially life threatening condition.

MANAGMEMENT STRATEGIES AND THEIR INFLUENCE ON OUTCOME

Pre-1970s

Sclerotherapy for the management of oesophageal varices was described initially by Crafoord and Freckner[17] in 1939 with injection of Quinine. However, it was not until later in the 20th century that this therapy became commonplace in the management of variceal haemorrhage, especially with the advent of fibre-optic endoscopy. Surgery was the mainstay of therapy for variceal haemorrhage prior to the 1970s. Surgical techniques such as oesophageal stapling or oesophagectomy were used, but with high mortality rates from complications such as sepsis, liver failure and renal failure[18]. In patients with portal hypertension, devascularisation procedures were shown to reduce variceal bleeding and mortality in primary prophylaxis in the 1980s, although there was heterogeneity in one such study by Inokuchi *et al*[19] with recruitment from a total of 22 centres. Shunt formation such as a splenorenal shunt was also performed with rebleeding rates varying from 5%-40%[20,21]. The role of splenectomy was and continues to be useful in patients with segmental portal hypertension secondary to an isolated splenic vein thrombosis. However, this surgical procedure was established later in the 20th century. Surgical therapies in present guidelines are reserved for patients who fail endoscopic therapies, and have been superseded by either TIPSS as rescue therapy or early TIPSS post index variceal bleeding, which will be discussed later[2].

Another method used prior to the advent of endo-

scopic therapy pre-1970s was balloon tamponade. The Sengstaken-Blakemore tube's use was first described in 1950 by Sengstaken and Blakemore[22] although the role of balloon tamponade was initially described in 1930[23]. Its place has largely been superseded by endoscopic therapies, however 21st century guidelines[24] still suggest a role for balloon tamponade, being used in massive haemorrhage as a bridge until definitive treatment can be instituted (for a maximum of 24 h). Although developed pre-1970s, its role in variceal haemorrhage was secured later in the century with effectiveness in controlling acute bleeding in up to 90% of patients, however with up to 50% rebleeding rates when the balloon was deflated[25]. Complications of balloon tamponade include aspiration pneumonia (often compounded by variceal haemorrhage event itself in encephalopathic patients) and oesophageal ulceration or rupture[26] in up to 15%-20%.

1970/1980s

The Linton-Nachlas balloon was developed in the 1970s[27] with a single 600 mL gastric balloon. The safety of this tube compared to Sengstaken Blakemore tube was identified in controlled trial of 79 patients with oesophagogastric variceal haemorrhage[28]. Both types of tamponade therapies resulted in primary haemostasis rates of 86%, but when bleeding from oesophageal varices was assessed, the Sengstaken Blakemore tube achieved permanent haemostasis in 52% compared the Linton-Nachlas tube 30%. The latter was more effective at controlling gastric variceal haemorrhage with 50% primary haemostasis rates compared to total failure in the Sengstaken Blakemore arm. The use of balloon tamponade as definitive therapy however was to be revolutionised by the advent of the fibre-optic endoscope and the therapies that could be delivered with it.

Rigid endoscopes were replaced by narrow fibre-optic endoscopes allowing therapy to be deployed through accessory channels. With a new and easier method for not only diagnosis of variceal haemorrhage but also therapeutic manoeuvres, new therapies were developed. The use of the overtube was phased out, patient comfort was improved and twin channel endoscopes were developed. The first reported case series of endoscopic sclerotherapy[29] was published in the early 1970s with its use becoming more established in the 1980s and thereafter. The concept was that the bleeding varix would "thrombose off" by internal injection of sclerosant causing vascular thrombosis and vascular obliteration[30]. Ethanolamine oleate, sodium tetradecyl sulphate, polidocanol, sodium morrhuate and ethanol have been used for injection sclerotherapy and successfully used in controlled trials[31]. In Europe the most common agents used were ethanolamine oleate and polidocanol, whereas in the United States sodium morrhuate was preferred[32,33]. Paravariceal injection involved injection around the varix causing variceal occlusion by tamponade and subsequent submucosal fibrosis of tissue around the varix, whereas intra-variceal injection induced thrombosis and subsequent occlusion of the lumen[34]. A meta-analysis by D'Amico *et al*[1] showed the type and volume of sclerosant did not seem to affect the efficacy.

Another issue of trials using injection sclerotherapy in the late 1980s (and 1990s) was the confounding factor that some trials had patients who were not actively bleeding at the time of initial endoscopy[1,35]. Furthermore, the optimal doses of sclerosing agents is unknown, with heterogeneity in scheduled follow-up endoscopies, and also differences between para- and intra-variceal injections[36,37]. There was however no doubt of sclerotherapy efficacy in the role of variceal bleeding. Sclerotherapy was compared to placebo in a controlled trial, with 56 patients having sclerotherapy injection and 60 placebo in patients with variceal bleeding. Survival was significantly better in those treated by sclerotherapy ($P < 0.001$)[38]. Sclerotherapy was also compared with oesophageal transection in 4 randomised trials[39-42] with similar mortality rates but rebleeding rates higher in the sclerotherapy arms. Only one trial showed a statistically significant reduction in failure to control bleeding with surgery[39]. When sclerotherapy was compared to balloon tamponade in 4 trials[43-46], 2 trials showed significantly higher control of bleeding with sclerotherapy[43,44].

In 1988, the first human cases were described of the use of EVBL in patients with oesophageal varices, based on the concept of banding haemorrhoids with elastic O-rings[47]. This technique was initially applied to canine models in the late 1980s[48,49] and then to patients with portal hypertension by Van Stiegmann *et al*[50]. EVBL was then successfully incorporated into the management of oesophageal variceal bleeding in the 1990s.

1990s

In the 1990s, further trials were carried out with injection sclerotherapy in not only oesophageal but also gastric variceal haemorrhage. Endoscopic therapy with sclerotherapy was found to control active bleeding from oesophageal varices in more than 90% of patients, and effective in reducing the frequency of rebleeding[51-53]. Injection sclerotherapy agents were compared, however most studies found them to have similar efficacy, although with some differences in cost[54,55] and time to obliteration[54,56]. The choice of sclerosant was dependant often on the operator and availability in the endoscopy units. A meta-analysis of 5 studies (Laine L, personal communication[24]) of 251 patients, showed significant benefits of sclerotherapy in terms of initial haemostasis rates compared to sham sclerotherapy, vasopressor therapy alone or balloon tamponade. In another meta-analysis, sclerotherapy was found to be the "gold standard" in acute variceal bleeding[57] with survival benefit seen when used in combination with vasoconstrictors than vasoconstrictors alone. Thus its role in the management of variceal bleeding became established. Injection sclerotherapy use was also extended to the treatment of gastric varices initially by Gotlib and Zimmerman[58] in 1984. The mechanism of action became clearer in the 1980s and 1990s

Table 3 Comparison of vasoactive pharmacological therapies used in variceal haemorrhage

	Octreotide	Somatostatin	Terlipressin
Mode of administration	Bolus followed by Ⅳ infusion	Bolus followed by Ⅳ infusion	Ⅳ bolus
Class	Somatostatin analogue		Synthetic analogue of Vasopressin
Indication	Variceal haemorrhage	Variceal haemorrhage	Variceal haemorrhage Hepatorenal syndrome
Proposed mechanism of action	Mechanism unclear Inhibition of glucagon-mediated splanchnic vasodilatation and reduction of postprandial gut hyperemia	Amino-acid peptide that reduced splanchnic blood flow (especially azygous). Prevent release of vasoactive peptides	V1 receptors blockade causing splanchnic vasoconstriction
Dose	Bolus of 50 μg, followed by an infusion of 50 μg per hour for up to 5 d	Infusion of 250-500 μg/h	2 mg bolus followed by 1 mg every 4 h for 3-5 d
Side effects/cautions	Vomiting, abdominal pain, nausea, hepatitis, abnormal LFTs, diahorrea, hypoglycaemia. Rarely arrhythmias, dyspnoea, pancreatitis, rash and alopecia	Loss of appetite, nausea, vomiting, abdominal, diahorrea and fatigue	Vasoconstrictive side-effects: myocardial ischemia, limb ischemia (avoid if peripheral vascular disease), nausea and diahorrea. Hyponatraemia

LFTs: Liver function tests.

with reports of gastric variceal endothelial damage with subsequent sclerosis[58]. Sarin *et al*[59] reported a 71.6% variceal obliteration rate in patients with gastric variceal haemorrhage treated with sclerotherapy. However, high re-bleeding rates of up to 60%-90% were reported[26,60]. The combination of ethanolamine sclerosant and cyanoacrylate glue was reported to produce rapid eradication of oesophagogastric varices, with fewer number of injection sessions[61,62].

The 1990s also saw the role of EVBL developed to the forefront of oesophageal variceal haemorrhage. EVBL however is not without complications including: oesophageal ulceration, chest pain, transient dysphagia and occasionally oesophageal stricturing seen at follow-up endoscopy. EVBL however evolved in the 1990s and into the 21st century as the recommended standard treatment for bleeding oesophageal varices[24]. In a meta-analysis of 10 randomised controlled trials comparing sclerotherapy with EVBL, there was a non-significant benefit of EVBL in achieving initial haemostasis *vs* sclerotherapy (pooled relative risk of 0.53 with 95%CI: 0.28-1.01)[63]. In one particular study, HVPG increased significantly immediately after both therapies but remained elevated for the duration of the 5 d in the sclerotherapy group whilst returning to baseline levels by 48 h after EVBL group[64] thus potentially identifying a rationale for the use of EVBL over sclerotherapy. In another meta-analysis there was no difference in initial haemostasis rates between both modalities (RR = 1.1, 95%CI: 0.4-2.9)[65], but actively bleeding patients represented only a small subset from larger trials[24].

To complement endoscopic therapies, pharmacological therapies were developed for optimising outcomes in variceal bleeding (Table 3). The lowering of portal pressure, even prior to endoscopy, if the source of upper gastrointestinal bleeding was suspected to be variceal[2,66] became an important issue. To that end, vasopressin and terlipressin were developed and deployed in such a setting. Terlipressin (triglycyl-lysine vasopressin) is a synthetic analogue of vasopressin with longer half-life negating the need for continuous infusion and acts on V1 receptors leading to splanchnic vasoconstriction. This in turn reduces portal inflow and pressure. Consequently there is an improvement in renal blood flow and reduction in portal pressure. Blockade of the V2 receptors can also result in free water absorption in the renal collecting ducts. Vasopressin (mainly used in the United States due to the unavailability in terlipressin) had been shown to achieve haemostasis in 60%-80%[67] of patients, but compared with terlipressin had less effect on the reduction of early rebleeding and did not improve survival from active variceal haemorrhage. Terlipressin was shown to reduce all-cause mortality when compared to placebo in meta-analyses[68,69] and guidelines recommend early treatment, which should be continued for up to 5 d[24] when potential for rebleeding is greatest. Side-effects include peripheral or coronary ischaemia, nausea and diahorrea. Blocking activation of the V2 receptors of the renal tubules can cause a dilutional hyponatraemia, an effect that reverses rapidly on discontinuation of the drug. When compared to somatostatin analogues such as octreotide, the haemodynamic effects of terlipressin on portal pressure were found to be more sustained[69] suggesting terlipressin might have a more prolonged benefit in bleeding varices. Thus vasoactive drugs became a key part of the initial therapy in variceal haemorrhage.

One of the major radiological advances in the management of variceal haemorrhage in the 1990's was the advent of TIPSS. Although first described in 1983 by Colapinto *et al*[70], it was largely in the 1990s and thereafter that its place in the management of portal hypertensive complications was secured. TIPSS involves the placement of a stent between the portal and hepatic vein to reduce portal pressure, thus stemming variceal haemorrhage or preventing rebleeding. Complications of TIPSS include haemorrhage, infection, intravascular haemolysis, liver dysfunction, shunt dysfunction and worsening of hepatic encephalopathy[71,72]. Initial TIPSS were

bare-metal stents with rebleeding rates of up to 20% at 2 years[73]. TIPSS was initially used for uncontrolled bleeding with control of bleeding in 90%-95% of patients and a 4-wk survival of 50%-60%[74]. In a review of 15 studies, immediate haemostasis rates of 93% were found with rebleeding rates of 12%[75]. In another meta-analysis of 11 randomised controlled trials, although TIPSS reduced risk of rebleeding, TIPSS was found to not affect survival in patients with variceal haemorrhage[76]. TIPSS was also found to be successful in the management of bleeding gastric varices[77-79].

2000-2010

With the dawn on the 21st century, pharmacological, endoscopic and radiological therapies for variceal haemorrhage improved outcomes. The role of antibiotics in variceal bleeding became clear in the early 21st century. Primary or secondary bacterial infections are common in cirrhotic patients[80,81] due to bacterial translocation into the portal system from impaired mucosal integrity and an impaired immune function. Antibiotics were found to reduce bacterial infections, recurrent bleeding and improve mortality in patients bleeding from oesophageal varices[82-84]. Current guidelines recommend broad-spectrum antibiotic prophylaxis[2,24,26] in patients with suspected and proven variceal haemorrhage. Local antibiotic policy can vary and a patient's "nil-by mouth" status can influence the choice of antibiotic. However, oral quinolones are recommended, or a 3rd generation cephalosporin in patients who received quinolone prophylaxis, have advanced cirrhosis, or live in areas of high quinolone resistance[2]. Another area of interest recently in resuscitation has been that of transfusion. In a study by Villanueva *et al*[85] the role of over-transfusion in GI bleeding has been explored and its effects on portal pressure. In patients with a liberal transfusion strategy [transfused when haemoglobin (Hb) fell to less than 9 g/dL] there was a significant rise in portal pressure gradient in the 1st five d post bleed compared to patients with a restrictive transfusion strategy (transfused when Hb fell to less than 7 g/dL). Thus is could be argued that patients with a variceal bleed are not as aggressively resuscitated/over-transfused as they may have previously been, however further clarification in this area is required.

Endoscopic therapy developed further in the 21st century, with obturation therapies for gastric variceal bleeding coming of age in the new millennium. Gastric varices account for 10%-30% of variceal haemorrhage, and although less common than oesophageal varices, when bleeding occurs it can often be torrential and associated with a high mortality[86-89]. Gastric varices can also bleed at a lower portal pressure than oesophageal varices[86-89]. There is limited data on EVBL in the management of gastric variceal bleeding with high rates of gastric variceal recurrence following EVBL due to a more superficial effect compared with obturation therapy[86]. Technical difficulty of banding in a retroflexed endoscope position and a theoretical risk of gastric rupture has meant EVBL for gastric varices has largely been superseded by obturation therapies using thrombin and *N*-butyl-2-cyanoacrylate (Histoacryl ™) injection. *N*-butyl-2-cyanoacrylate is a long-chain cyanoacrylate glue that polymerises and solidifies within seconds following contact with blood in a gastric varix. It is mixed with the oily agent Lipiodol delaying polymerisation. Complications of its use include: endoscope damage due to blockage of the injection channel, sticking of the injection needle into a varix, mediastinitis, local abscesses, and cerebral/pulmonary embolisms or splenic infarcts from glue migration. Immediate haemostasis rates of 92%-100% have been reported with variable re-bleeding rates[86-93]. Cyanoacrylate glue when compared with ethanol injection in a randomised study had faster rates of variceal obliteration, required smaller injection volumes, had improved efficacy in control of acute gastric variceal bleeding and reduced need for rescue surgery[92,93]. Thrombin was another obturation therapy developed in the 21st century used in acutely bleeding gastric varices. It is a haemostatic agent converting fibrinogen to a fibrin clot and causing platelet aggregation[94]. Initially in the late 1980s and 1990s there were small case-series of its use with haemostasis rates between 70%-100% using bovine thrombin[95-99]. Bovine thrombin was discontinued because of the potential risk of prion transmission. Thus, short-term small uncontrolled studies of human-derived thrombin have demonstrated initial haemostasis rates of 100% but often a high mortality from re-bleeding[99-101]. A recent retrospective study from Edinburgh, United Kingdom demonstrated in 33 patients treated with human thrombin for gastric variceal bleeding rebleeding rates of 10.8%[102]. It is worth noting to date there have been no controlled trials with thrombin *vs* other obturation treatments such as *N*-butyl-2-cyanoacrylate) to our knowledge.

Radiological interventions in variceal haemorrhage improved in the new century too. In 2004, the advent of covered TIPSS stent (with an expanded polytetrafluoroethylene cover) was hailed as a breakthrough and approved by the United States Food and Drug Administration. The covered stent improved shunt patency by reducing tissue ingrowth by minimising transmural bile permeation[103]. The primary patency of covered stents at 1-year were found to be up to 80%-90%[104-107] with reduction of rebleeding post "index bleed" to less than 10%[105,107,108]. Other studies confirmed the role of a rescue TIPSS in variceal bleeding which could not be controlled by endoscopy or vasoactive drugs[67,68]. The early TIPSS placement has been shown to have beneficial effect in patients with a HVPG > 20 mmHg presenting with a variceal bleed[11]. In this study published in 2004, patients who were considered high risk (HVPG > 20 mmHg) were selected and randomised to early uncovered TIPSS or standard of care within 24 h of presentation. Treatment failure was deemed as failure to control acute variceal bleeding and/or early rebleeding after the first endoscopic therapy. TIPPS reduced rebleeding and treatment failure, and was associated with superior in-hospital and 1-year survival. However, the therapy used in the control arm was endoscopic sclerotherapy alone, which

is not the accepted standard of care. The other major issue translating this study into real world practice was the availability of HVPG in routine clinical practice.

Interventional radiological procedures for the treatment of gastric varices in the 2000s included the advent of BRTO[109-111] as salvage or rescue therapy when endoscopic obturation therapy fails. BRTO is an interventional radiological technique for gastric variceal bleeding whereby a splenorenal shunt often seen in such patients can be occluded with sclerosant using a balloon catheter approached *via* the left renal vein[109-111]. BRTO may potentially become an alternative to TIPSS in patients with active gastric variceal bleeding in whom a gastrorenal shunt is present[110]. However, it is not commonly used out-with the Far East or large tertiary referral centres. There is also an increased risk of the development of oesophageal varices after its use[109]. Its role has not been incorporated in any European or United States guidelines to date[2,24].

Liver transplantation is the only curative treatment for liver cirrhosis at this point in time, although its role in bleeding variceal haemorrhage has not been established. In some centres it has been proposed as a treatment in patients with advanced liver disease who fail endoscopic therapies[112]. These studies were however in the era prior to EVBL, combined pharmacological and endoscopic therapies and TIPSS. In a trial by Orloff *et al*[113] unselected consecutive patients with advanced cirrhosis and bleeding oesophageal varices were studied who had either sclerotherapy (n = 106) or emergency direct portocaval shunt (n = 105). The 3-, 5-, 10- and 15-year survival rates were significantly higher in the portocaval shunt group (P < 0.001). On the follow-up, 6% of patients were referred for liver transplant assessment, 3% listed and only a total of 2% actually underwent liver transplantation for progressive liver failure. A conclusion drawn from the study authors was that transplantation was infrequently required in this setting (even prior to the TIPSS era) and if initial bleeding was controlled (in 100% of the portocaval shunt arm) then survival was similar or better than that following transplant. It should be remembered that such centre-specific data however often differs from centres with less experience in portocaval shunts. However to our knowledge there are no randomised trials of endoscopic therapy with radiological therapy and liver transplantation in the setting for acute variceal haemorrhage and this is certainly not current practice. It could be argued that transplantation should only be reserved in those patients whom combined pharmacological and endoscopic therapy fails along with a trial of radiological intervention such as TIPSS or BRTO, or even surgery. However, patients with poor liver function or in whom liver function does not recover should always be considered at an early stage for liver transplant assessment where appropriate based on local scoring systems such as MELD in the United States and UKELD in the United Kingdom.

Post-2010

Areas of recent interest that required future clarification and further study include the early role of TIPSS in variceal haemorrhage, oesophageal stents and new agents for haemostasis.

The exact and optimal role of TIPSS in variceal haemorrhage has been particularly under the spotlight recently. In 2004, the early placement of TIPSS was shown to have beneficial effect in patients with a HVPG > 20 mmHg presenting with a variceal bleed[11]. In a recent seminal multi-centre European study in 2010[4], 63 cirrhotic patients with oesophageal variceal bleeding were treated with vasoactive drugs plus endoscopic therapy and then randomised to one of two treatment arms if they had Child's C disease or active bleeding and Child's B disease. The first arm was covered TIPSS within 72 h ("early-TIPSS"), and the second arm continuation of vasoactive drugs for 3 to 5 d followed by non-selective beta-blockers and with long-term EVBL (with the insertion of a TIPSS only if required as a rescue therapy). Rebleeding or failure to control bleeding occurred in only one patient in the "early TIPSS" arm, and in 14 patients in the control arm (P < 0.001). Overall mortality was lower in the "early-TIPSS" group (12 *vs* 4 patients, P = 0.01) with 1-year survival of 61% in the control group *vs* 86% in the "early-TIPSS" group (P < 0.001). There was no difference in the incidence of hepatic encephalopathy. A post RCT surveillance study from the same group published last year, aimed to confirm the results in a clinical setting[114] (Table 4). Patients admitted with acute variceal bleeding and high risk of treatment failure (Child C < 14 or Child B plus active bleeding) were thereafter treated with early covered TIPSS (n = 45) or combined pharmacology/endoscopic therapy (n = 30). The patients treated with "early-TIPSS" had lower rates of rebleeding or failure to control bleeding than patients receiving combined therapy (3 *vs* 15, P < 0.001). There was a tendency also towards reduced mortality in the "early-TIPSS" group (P = 0.056). Criticisms of the "early TIPSS" trial however included that recruitment was prolonged (3 years) to recruit 63 patients *via* 9 centres[4], with a high exclusion rate (296 patients excluded). The second issue is that of the inclusion of patients with ongoing bleeding following index endoscopy. This might arguably be termed a "rescue" TIPSS and although no studies have been done in this area it is intuitive to suggest that survival would be improved if haemostasis has not been achieved. Thirdly, survival at 1 year with "early TIPSS" was remarkably high (86% *vs* 61% in the medical management group)[4]. Thus the current Baveno V guidelines[2] suggest considering the "early TIPSS" approach, but clearly further studies are necessary where patients requiring an "early TIPSS" as a rescue therapy are excluded.

Another novel area of interest recently is the use of self-expanding oesophageal stents, which again will require further study to clarify their role in influencing outcome from variceal haemorrhage. The stent acts by applying direct tamponade to the distal oesophageal mucosa and any associated bleeding varices. Such stents were used in a pilot study in 20 patients who failed to

Table 4 Summary of randomized controlled trials and meta-analysis of different therapies over time in variceal haemorrhage

Ref.	Trial design/therapy	Outcome/results
Surgical techniques		
Inokuchi *et al*[19]	Randomised controlled trial (RCT)/prophylactic surgical intervention (n = 60) *vs* non surgical intervention (n = 52) for oesophageal varices	5-yr cumulative survival rate at 5 yr in the operated group was 72% *vs* 45% (P < 0.05). 5-yr cumulative variceal bleeding rate at 5 yr was 7% in the operated group v46% (P < 0.001)
Balloon tamponade		
Terés *et al*[28]	RCT/comparison of SB *vs* Linton-Nachlas (LN)	Primary haemostasis rates of 86%. In oesophageal variceal bleeding SB tube achieved permanent haemostasis in 52% *vs* 30% in LN tube
Sclerotherapy		
The Copenhagen esophageal varices sclerotherapy project[46]	Randomised multicentre trial/187 unselected patients with oesophageal variceal bleed randomly assigned to medical treatment including balloon tamponade or to medical treatment supplemented with paravariceal sclerotherapy	Overall mortality in the sclerotherapy group (hazard) was 76% (95%CI: 10%-54%) of that in the medical-regimen group (relative mortality in the sclerotherapy group was 63% of that in the medical-regimen group)
Westaby *et al*[38]	RCT of sclerotherapy (n = 56) *vs* placebo (n = 60)	Survival was significantly better in those treated by sclerotherapy (P < 0.001)
Burroughs *et al*[39]	Randomised trial/a comparison of sclerotherapy (n = 5) with staple transection (n = 51) of the oesophagus for the emergency control of bleeding from oesophageal varices	Total mortality did not differ significantly between the two groups. Mortality at six wk was 44% among those assigned to sclerotherapy and 35% assigned to staple transection. Complication rates were similar for the two groups
D'Amico *et al*[126]	Cochrane database systematic/meta-analysis of 17 trials, assessing the benefits of sclerotherapy *vs* vasoactive drugs in patients with variceal bleeding	Authors concluded no convincing evidence to support the use of emergency sclerotherapy as the first, single treatment when compared with vasoactive drugs
Thakeb *et al*[62]	Randomised controlled trial/assess the role of the combined N-butyl-2-cyanoacrylate and ethanolamine oleate (n = 58) *vs* ethanolamine sclerotherapy (n = 56) for management of bleeding esophagogastric varices	Arrested acute bleeding in 66.7% of patients with gastric variceal bleeding. Recurrent bleeding in 8.6% in the combined therapy group *vs* 25% in the sclerosis group (P < 0.01). The mortality in the combined therapy group less than sclerosis group (3.5% and 8.8% respectively, P > 0.05)
Endoscopic variceal band ligation (EVBL)		
Laine *et al*[65]	Meta-analysis of 7 RCTs/comparison of the effect of EVBL *vs* sclerotherapy in the treatment of patients with bleeding esophageal varices	EVBL (*vs* sclerotherapy) reduced the rebleeding rate (OR = 0.52, 95%CI: 0.37-0.74), the mortality rate (OR = 0.67, 95%CI: 0.46-0.98), and the rate of death due to bleeding (OR = 0.49, 95%CI: 0.24-0.996)
Garcia-Pagán *et al*[63]	Meta-analysis of 10 RCTs comparing sclerotherapy with EVBL	Non-significant benefit of EVBL in achieving initial haemostasis *vs* sclerotherapy (pooled relative risk of 0.53 with 95%CI: 0.28-1.01)
Radiological transjugular intrahepatic portosystemic stent-shunts (TIPSS)		
Monescillo *et al*[11]	RCT of patients (116) divided into low risk/high risk of rebleeding based on hepatic venous pressure gradient (HVPG)	Early TIPSS placement in patients with HVPG > 20 within 24 h of admission reduced in-patient and 1 yr mortality
García-Pagán *et al*[4]	RCT/role of early TIPSS in patients with oesophageal variceal haemorrhage (n = 32) within 72 h of admission *vs* continuation of vasoactive Tx and B-blocker/EVBL (n = 31) thereafter	Rebleeding or failure to control bleeding in 14 patients in the pharmacotherapy-EVBL group *vs* 1 patient in the early-TIPS group (P = 0.001)
Garcia-Pagán *et al*[114]	Post-RCT surveillance study/retrospective review of patients admitted for acute variceal bleeding and high risk of treatment failure treated with early-TIPSS (n = 45) or drugs/endoscopic therapy (ET) (n = 30)	Early-TIPSS group had a much lower incidence of failure to control bleeding/rebleeding than drug + ET (3 *vs* 15, P < 0.001). 1-yr actuarial survival was 86% *vs* 70% respectively (P = 0.056)
Yang *et al*[127]	Mata-analysis of 6 studies of covered stents *vs* bare metal stents	Use of polytetrafluoroethylene-covered stent-grafts associated with improved shunt patency without increasing the risk of hepatic encephalopathy and with a trend towards better survival

achieve haemostasis with pharmacological or endoscopic techniques[115], and achieved 100% immediate haemostasis rates in such a rescue setting. There was a stent migration in 25% of patients in this initial study and 10% of patients died within 5 d. Three other studies have further been published[116-118], with a combined total of 57 patients. Successful stent placement ranged from 90%-100% and control of bleeding ranging between 70%-100%. Stent migration rates varied from 0%-18% with a total of 4 patients rebleeding. Such stents may be a promising option in refractory oesophageal haemorrhage as bridge therapy to definite treatment such as TIPSS. However, randomized controlled trials with comparison to other interventions or even as an adjunct to current standard of care are necessary before they can be considered standard of care. Their mechanism of action would make them comparable to balloon tamponade and there is currently a study group in Barcelona exploring this (NCT01242280). Another United Kingdom study entitled "Effective haemostasis using self-expandable covered mesh-metal oeosphageal stents *vs* standard endoscopic therapy in the emergency treatment of oesophageal variceal hemorrhage: A multicenter, open, prospective, randomized, controlled study-ISRCTN 98310189" is under way and recruiting. Preliminary data was recently presented in the use of stents compared to balloon tam-

ponade in variceal bleeding refractory to endoscopic and medical therapy. Escorsell *et al*[119] reported on 28 patients (15 Sengstaken and 13 metal stents) with the intention to treat analysis showing more frequent success of therapy in the stent arm (46% *vs* 3%, $P = 0.005$). There was a trend towards better control of bleeding ($P = 0.1$) and less transfusion requirements ($P = 0.08$) in the stent arm. Survival rates were comparable ($P = 0.4$). The authors concluded that oesophageal stents were indeed more effective than balloon tamponade for temporary control of variceal haemorrhage in treatment failures. The stents however do not have a role in gastric variceal bleeding in their current form.

Another new area of interest that has been the development of haemostatic powders/sprays. TC-325 (Hemospray, Cook Technology™) is a granular non absorbable mineral powder used in the management of arterial wounds. It achieves hemostasis by activating platelets and increasing the concentration of clotting factors and also by forming a mechanical barrier over the wall of a bleeding vessel[120] thus forming a mechanical plug at site of bleeding[121]. It contains no proteins from animals or humans. The spray device kit contains an application catheter, a propellant CO_2 canister and also a chamber containing 20 g of powder. Its role has been studied in patients bleeding from peptic ulcers[122].

In a pilot study by Ibrahim *et al*[123], the use of one such powder TC-325 (was studied in 2 tertiary care referral centres with primary haemostasis rates and rebleeding rates measured). Nine patients with confirmed variceal bleeding had treatment within 12 h of admission, with 21 g of haemostatic powder applied *via* a catheter in the accessory channel of the endoscope from the cardia up to 15 cm above the gastro-oesophageal junction. There was no rebleeding within 24 h and no mortality at 15 d. Although a small pilot study, further larger trials needed to secure its position in variceal haemorrhage. In another case series, its role in the management of portal hypertensive bleeding was studied in 4 patients - 3 with portal hypertensive gastropathies and 1 portal colopathy[124]. All patients had cessation of bleeding with Hemospray and reduced transfusion requirements thereafter however in 1 patient a complication of viscus perforation was encountered and the patient died shortly after endoscopy - however it was unclear if perforation was secondary to instrumentation during the procedure or the spray itself. Its use has also been studied in small case reports in the management of bleeding gastric varices[125]. This remains a promising area requiring further large trials securing its position in the management of variceal haemorrhage.

CONCLUSION

Variceal haemorrhage from oesophageal or gastric varices remains a life-threatening emergency requiring urgent specialist care. The development over the years of endoscopic access and therapies has transformed the management of variceal haemorrhage. This coupled with improved medical management of variceal bleeding patients has resulted in improved mortality and rebleeding rates. However the delivery of optimal management of these patients in the "real-world" setting remains variable. With firm guidelines in place for the management of variceal haemorrhage and general management of upper gastrointestinal bleed patients, it is paramount that local centres aim to deliver such standards. Currently the gold standard management involves adequate and early resuscitation including airway support if required. The optimal circulating volume should allow good perfusion pressures however over transfusion recently has been contentious with further studies required in this area. Vasopressor and antibiotic treatments are now well established in variceal haemorrhage and should be instituted early in a presumed (or confirmed) variceal haemorrhage. Definitive endoscopic treatment is required, however the timing of endoscopy often depends on local units and ease of endoscopic services out-of-h. To develop optimal endoscopic services local and national auditing of services is required, but also training of competent endoscopists who can manage acute variceal haemorrhage optimally pre-, peri- and post-endoscopy.

In the management of oesophageal variceal haemorrhage, endoscopic band ligation should be the favored definitive treatment, with sclerotherapy reserved potentially for those whom EVBL cannot be performed (Figure 1). In gastric varices the optimal treatment remains to be ascertained between *N*-butyl-2-cyanoacylate or thrombin, and a randomised controlled trial in this area would be helpful in the future. Much depends on the endoscopist familiarity with both injection methods, with thrombin being technically easier in our experience with potentially less complications. Other endoscopic therapies such as oesophageal stents and Hemospray are intriguing and may indeed have a role in patients who fail standard endoscopic treatments, however larger trials are also required for these agents.

If endoscopic therapy is difficult, or does not halt the bleeding in oesophageal variceal haemorrhage then a rescue TIPSS can be performed. The role of an "early" TIPPS in those who have had initial bleeding halted to prevent rebleeding and potentially improve mortality is something that requires further study and may potentially have significant implications for regional radiological centres offering TIPSS to other hospitals. Other interventional radiological procedures such as BRTO offer promise in refractory gastric variceal haemorrhage however there availability is dependent on the expertise of centre's radiologists.

In summary, over the last few decades, much has been achieved in the management of variceal haemorrhage from an almost always life terminating event, to now, an event that can be adequately and aggressively managed, with the aim to completely reduce mortality from variceal bleeding. The next decade will be indeed an exciting time in the management of variceal haemorrhage.

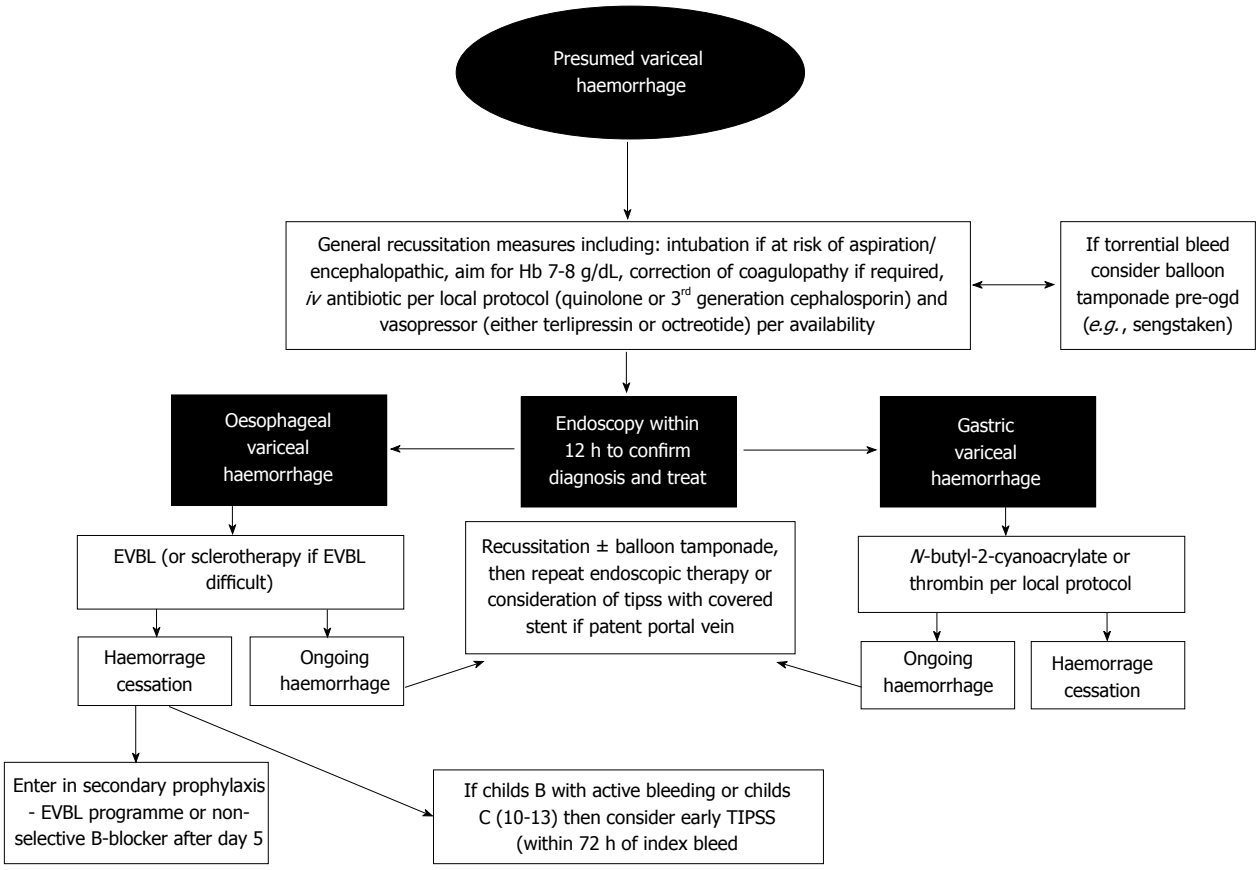

Figure 1 Summary in the management of acute variceal haemorrhage. EVBL: Endoscopic variceal band ligation; TIPSS: Transjugular intrahepatic portosystemic stent-shunts; Hb: Haemoglobin.

REFERENCES

1 **D'Amico G**, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995; **22**: 332-354 [PMID: 7601427 DOI: 10.1002/hep.1840220145]

2 **de Franchis R**. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; **53**: 762-768 [PMID: 20638742 DOI: 10.1016/j.jhep.2010.06.004]

3 **Carbonell N**, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology* 2004; **40**: 652-659 [PMID: 15349904 DOI: 10.1002/hep.20339]

4 **García-Pagán JC**, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, Abraldes JG, Nevens F, Vinel JP, Mössner J, Bosch J. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med* 2010; **362**: 2370-2379 [PMID: 20573925 DOI: 10.1056/NEJMoa0910102]

5 **Graham DY**, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; **80**: 800-809 [PMID: 6970703]

6 **Groszmann RJ**, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology* 2004; **39**: 280-282 [PMID: 14767976 DOI: 10.1002/hep.20062]

7 **Groszmann RJ**, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Gao H, Makuch R. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005; **353**: 2254-2261 [PMID: 16306522 DOI: 10.1056/NEJMoa044456]

8 **Chalasani N**, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ, Pandya P, Sitaraman S, Shen J. Improved patient survival after acute variceal bleeding: a multicenter, cohort study. *Am J Gastroenterol* 2003; **98**: 653-659 [PMID: 12650802 DOI: 10.1111/j.1572-0241.2003.07294.x]

9 **Jairath V**, Barkun AN. Improving outcomes from acute upper gastrointestinal bleeding. *Gut* 2012; **61**: 1246-1249 [PMID: 22267592 DOI: 10.1136/gutjnl-2011-300019]

10 **Moitinho E**, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, Bosch J. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* 1999; **117**: 626-631 [PMID: 10464138 DOI: 10.1016/S0016-5085(99)70455-5]

11 **Monescillo A**, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, Marrero JM, Buceta E, Sánchez J, Castellot A, Peñate M, Cruz A, Peña E. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology* 2004; **40**: 793-801 [PMID: 15382120 DOI: 10.1002/hep.20386]

12 **Patch D**, Armonis A, Sabin C, Christopoulou K, Greenslade L, McCormick A, Dick R, Burroughs AK. Single portal pressure measurement predicts survival in cirrhotic patients with recent bleeding. *Gut* 1999; **44**: 264-269 [PMID: 9895388 DOI: 10.1136/gut.44.2.264]

13 **D'Amico G**, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. *Gastroenterology* 2006; **131**: 1611-1624 [PMID: 17101332 DOI: 10.1053/j.gastro.2006.09.013]

14 **D'Amico G**, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003; **38**: 599-612 [PMID: 12939586 DOI: 10.1053/jhep.2003.50385]

15 **del Olmo JA**, Peña A, Serra MA, Wassel AH, Benages A, Ro-

drigo JM. Predictors of morbidity and mortality after the first episode of upper gastrointestinal bleeding in liver cirrhosis. *J Hepatol* 2000; **32**: 19-24 [PMID: 10673062]
16 **Thomopoulos K**, Theocharis G, Mimidis K, Lampropoulou-Karatza Ch, Alexandridis E, Nikolopoulou V. Improved survival of patients presenting with acute variceal bleeding. Prognostic indicators of short- and long-term mortality. *Dig Liver Dis* 2006; **38**: 899-904 [PMID: 17005458 DOI: 10.1016/j.dld.2006.08.002]
17 **Crafoord CPF**. Surgical treatment of varicose veins of the esophagus. *Acta Otolaryngol* (Stockholm) 1939; **27**: 422-429 [DOI: 10.3109/00016483909123738]
18 **Krähenbühl L**, Seiler CA, Büchler MW. [Variceal hemorrhage in portal hypertension: role of surgery in the acute and elective situation]. *Schweiz Med Wochenschr* 1999; **129**: 631-638 [PMID: 10378247]
19 **Inokuchi K**. Improved survival after prophylactic portal nondecompression surgery for esophageal varices: a randomized clinical trial. Cooperative Study Group of Portal Hypertension of Japan. *Hepatology* 1990; **12**: 1-6 [PMID: 2197208 DOI: 10.1002/hep.1840120102]
20 **Orozco H**, Mercado MA, Granados Garcia J, Hernandez-Ortiz J, Tielve M, Chan C, Contreras JL. Selective shunts for portal hypertension: current role of a 21-year experience. *Liver Transpl Surg* 1997; **3**: 475-480 [PMID: 9346789 DOI: 10.1002/lt.500030501]
21 **Tsuchida S**, Ku Y, Fukumoto T, Tominaga M, Iwasaki T, Kuroda Y. Isolated gastric varices resulting from iatrogenic splenic vein occlusion: report of a case. *Surg Today* 2003; **33**: 542-544 [PMID: 14507002]
22 **Sengstaken RW**, Blakemore AH. Balloon tamponage for the control of hemorrhage from esophageal varices. *Ann Surg* 1950; **131**: 781-789 [PMID: 15411151 DOI: 10.1097/00000658-195005000-00017]
23 **Westphal K**. Ueber eine Kompressionsbehandlung der Blutungen aus Oesophagusvarizen. *Deutsch Med Wochenschr* 1930; **56**: 1135
24 **de Franchis R**. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005; **43**: 167-176 [PMID: 15925423 DOI: 10.1016/j.jhep.2005.05.009]
25 **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**: 454-459 [PMID: 3280273]
26 **Jalan R**, Hayes PC. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. British Society of Gastroenterology. *Gut* 2000; **46** Suppl 3-4: III1-III15 [PMID: 10862604]
27 **Chojkier M**, Conn HO. Esophageal tamponade in the treatment of bleeding varices. A decadel progress report. *Dig Dis Sci* 1980; **25**: 267-272 [PMID: 6967005 DOI: 10.1007/BF01308516]
28 **Terés J**, Cecilia A, Bordas JM, Rimola A, Bru C, Rodés J. Esophageal tamponade for bleeding varices. Controlled trial between the Sengstaken-Blakemore tube and the Linton-Nachlas tube. *Gastroenterology* 1978; **75**: 566-569 [PMID: 361485]
29 **Johnston GW**, Rodgers HW. A review of 15 years' experience in the use of sclerotherapy in the control of acute haemorrhage from oesophageal varices. *Br J Surg* 1973; **60**: 797-800 [PMID: 4542942 DOI: 10.1002/bjs.1800601011]
30 **Goldman MP**. Sodium tetradecyl sulfate for sclerotherapy treatment of veins: is compounding pharmacy solution safe? *Dermatol Surg* 2004; **30**: 1454-1456; discussion 1456 [PMID: 15606731 DOI: 10.1111/j.1524-4725.2004.30502.x]
31 **Helmy A**, Hayes PC. Review article: current endoscopic therapeutic options in the management of variceal bleeding. *Aliment Pharmacol Ther* 2001; **15**: 575-594 [PMID: 11328251 DOI: 10.1046/j.1365-2036.2001.00950.x]
32 **Park WG**, Yeh RW, Triadafilopoulos G. Injection therapies for variceal bleeding disorders of the GI tract. *Gastrointest Endosc* 2008; **67**: 313-323 [PMID: 18226695 DOI: 10.1016/j.gie.2007.09.052]
33 **Villanueva C**, Colomo A, Aracil C, Guarner C. Current endoscopic therapy of variceal bleeding. *Best Pract Res Clin Gastroenterol* 2008; **22**: 261-278 [PMID: 18346683 DOI: 10.1016/j.bpg.2007.11.012]
34 **Sarin SK**, Nanda R, Sachdev G, Chari S, Anand BS, Broor SL. Intravariceal versus paravariceal sclerotherapy: a prospective, controlled, randomised trial. *Gut* 1987; **28**: 657-662 [PMID: 3305185 DOI: 10.1136/gut.28.6.657]
35 **Alexandrino P**, Alves MM, Fidalogo P, Matos L, Esteves AV, Veloso J, Oliveira AG, Moura MC. Is sclerotherapy the first choice treatment for active variceal bleeding in cirrhotic patients? Final report of a randomised clinical trial. *J Hepatol* 1990; **11** (suppl 2): S1
36 **Larson AW**, Cohen H, Zweiban B, Chapman D, Gourdji M, Korula J, Weiner J. Acute esophageal variceal sclerotherapy. Results of a prospective randomized controlled trial. *JAMA* 1986; **255**: 497-500 [PMID: 3510333 DOI: 10.1001/jama.1986.03370040071026]
37 **Westaby D**. Emergency and elective endoscopic therapy for variceal haemorrhage. *Baillieres Clin Gastroenterol* 1992; **6**: 465-480 [PMID: 1421595 DOI: 10.1016/0950-3528(92)90033-B]
38 **Westaby D**, Macdougall BR, Williams R. Improved survival following injection sclerotherapy for esophageal varices: final analysis of a controlled trial. *Hepatology* 1985; **5**: 827-830 [PMID: 2993147 DOI: 10.1002/hep.1840050520]
39 **Burroughs AK**, Hamilton G, Phillips A, Mezzanotte G, McIntyre N, Hobbs KE. A comparison of sclerotherapy with staple transection of the esophagus for the emergency control of bleeding from esophageal varices. *N Engl J Med* 1989; **321**: 857-862 [PMID: 2788816]
40 **Cello JP**, Crass R, Trunkey DD. Endoscopic sclerotherapy versus esophageal transection of Child's class C patients with variceal hemorrhage. Comparison with results of portacaval shunt: preliminary report. *Surgery* 1982; **91**: 333-338 [PMID: 7036396]
41 **Terés J**, Baroni R, Bordas JM, Visa J, Pera C, Rodés J. Randomized trial of portacaval shunt, stapling transection and endoscopic sclerotherapy in uncontrolled variceal bleeding. *J Hepatol* 1987; **4**: 159-167 [PMID: 3295018 DOI: 10.1016/S0168-8278(87)80075-2]
42 **Huizinga WK**, Angorn IB, Baker LW. Esophageal transection versus injection sclerotherapy in the management of bleeding esophageal varices in patients at high risk. *Surg Gynecol Obstet* 1985; **160**: 539-546 [PMID: 3873713]
43 **Moretó M**, Zaballa M, Bernal A, Ibáñez S, Ojembarrena E, Rodriguez A. A randomized trial of tamponade or sclerotherapy as immediate treatment for bleeding esophageal varices. *Surg Gynecol Obstet* 1988; **167**: 331-334 [PMID: 3047893]
44 **Paquet KJ**, Feussner H. Endoscopic sclerosis and esophageal balloon tamponade in acute hemorrhage from esophagogastric varices: a prospective controlled randomized trial. *Hepatology* 1985; **5**: 580-583 [PMID: 3894199 DOI: 10.1002/hep.1840050409]
45 **Barsoum MS**, Bolous FI, El-Rooby AA, Rizk-Allah MA, Ibrahim AS. Tamponade and injection sclerotherapy in the management of bleeding oesophageal varices. *Br J Surg* 1982; **69**: 76-78 [PMID: 7037105 DOI: 10.1002/bjs.1800690206]
46 Sclerotherapy after first variceal hemorrhage in cirrhosis. A randomized multicenter trial. The Copenhagen Esophageal Varices Sclerotherapy Project. *N Engl J Med* 1984; **311**: 1594-1600 [PMID: 6390203 DOI: 10.1056/NEJM198412203112502]
47 **MacRae HM**, McLeod RS. Comparison of hemorrhoidal treatment modalities. A meta-analysis. *Dis Colon Rectum* 1995; **38**: 687-694 [PMID: 7607026 DOI: 10.1007/BF02048023]

48 **Van Stiegmann G**, Cambre T, Sun JH. A new endoscopic elastic band ligating device. *Gastrointest Endosc* 1986; **32**: 230-233 [PMID: 3487484 DOI: 10.1016/S0016-5107(86)71815-4]

49 **Stiegmann GV**, Sun JH, Hammond WS. Results of experimental endoscopic esophageal varix ligation. *Am Surg* 1988; **54**: 105-108 [PMID: 3341642]

50 **Van Stiegmann G**, Goff JS. Endoscopic esophageal varix ligation: preliminary clinical experience. *Gastrointest Endosc* 1988; **34**: 113-117 [PMID: 3259195 DOI: 10.1016/S0016-5107(88)71274-2]

51 **Chawla YK**, Dilawari JB, Dhiman RK, Goenka MK, Bhasin DK, Kochhar R, Singh K, Kaur U. Sclerotherapy in noncirrhotic portal fibrosis. *Dig Dis Sci* 1997; **42**: 1449-1453 [PMID: 9246045 DOI: 10.1023/A: 1018858525312]

52 **Bhargava DK**, Dasarathy S, Sundaram KR, Ahuja RK. Efficacy of endoscopic sclerotherapy on long-term management of oesophageal varices: a comparative study of results in patients with cirrhosis of the liver, non-cirrhotic portal fibrosis (NCPF) and extrahepatic portal venous obstruction (EHO). *J Gastroenterol Hepatol* 1991; **6**: 471-475 [PMID: 1932668 DOI: 10.1111/j.1440-1746.1991.tb00890.x]

53 **Kochhar R**, Goenka MK, Mehta SK. Outcome of injection sclerotherapy using absolute alcohol in patients with cirrhosis, non-cirrhotic portal fibrosis, and extrahepatic portal venous obstruction. *Gastrointest Endosc* 1991; **37**: 460-464 [PMID: 1916169 DOI: 10.1016/S0016-5107(91)70780-3]

54 **Sarin SK**, Mishra SP, Sachdev GK, Thorat V, Dalal L, Broor SL. Ethanolamine oleate versus absolute alcohol as a variceal sclerosant: a prospective, randomized, controlled trial. *Am J Gastroenterol* 1988; **83**: 526-530 [PMID: 3284336]

55 **Meirelles-Santos JO**, Carvalho AF, Callejas-Neto F, Magna LA, Yamanaka A, Zeitune JM, Brandalise NA, Ferraz JG. Absolute ethanol and 5% ethanolamine oleate are comparable for sclerotherapy of esophageal varices. *Gastrointest Endosc* 2000; **51**: 573-576 [PMID: 10805844 DOI: 10.1016/S0016-5107(00)70292-6]

56 **Kochhar R**, Goenka MK, Mehta S, Mehta SK. A comparative evaluation of sclerosants for esophageal varices: a prospective randomized controlled study. *Gastrointest Endosc* 1990; **36**: 127-130 [PMID: 2185977]

57 **Triantos CK**, Goulis J, Patch D, Papatheodoridis GV, Leandro G, Samonakis D, Cholongitas E, Burroughs AK. An evaluation of emergency sclerotherapy of varices in randomized trials: looking the needle in the eye. *Endoscopy* 2006; **38**: 797-807 [PMID: 17001564]

58 **Gotlib JP**, Zimmerman P. Une nouvelle technique de traitement encoscopique des varices oesophagiennes: l'obriteration. *Endosc Dig* 1984; **7**: 10-12

59 **Sarin SK**. Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience. *Gastrointest Endosc* 1997; **46**: 8-14 [PMID: 9260698 DOI: 10.1016/S0016-5107(97)70202-5]

60 **Sarin SK**, Sachdev G, Nanda R, Misra SP, Broor SL. Endoscopic sclerotherapy in the treatment of gastric varices. *Br J Surg* 1988; **75**: 747-750 [PMID: 3262398 DOI: 10.1002/bjs.1800750809]

61 **Miyazaki S**, Yoshida T, Harada T, Shigemitsu T, Takeo Y, Okita K. Injection sclerotherapy for gastric varices using N-butyl-2-cyanoacrylate and ethanolamine oleate. *Hepatogastroenterology* 1998; **45**: 1155-1158 [PMID: 9756025]

62 **Thakeb F**, Salama Z, Salama H, Abdel Raouf T, Abdel Kader S, Abdel Hamid H. The value of combined use of N-butyl-2-cyanoacrylate and ethanolamine oleate in the management of bleeding esophagogastric varices. *Endoscopy* 1995; **27**: 358-364 [PMID: 7588349 DOI: 10.1055/s-2007-1005714]

63 **Garcia-Pagán JC**, Bosch J. Endoscopic band ligation in the treatment of portal hypertension. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 526-535 [PMID: 16355158 DOI: 10.1038/ncpgasthep0323]

64 **Avgerinos A**, Armonis A, Stefanidis G, Mathou N, Vlachogiannakos J, Kougioumtzian A, Triantos C, Papaxoinis C, Manolakopoulos S, Panani A, Raptis SA. Sustained rise of portal pressure after sclerotherapy, but not band ligation, in acute variceal bleeding in cirrhosis. *Hepatology* 2004; **39**: 1623-1630 [PMID: 15185303 DOI: 10.1002/hep.20236]

65 **Laine L**, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Intern Med* 1995; **123**: 280-287 [PMID: 7611595 DOI: 10.7326/0003-4819-123-4-199508150-00007]

66 **Burroughs AK**, Planas R, Svoboda P. Optimizing emergency care of upper gastrointestinal bleeding in cirrhotic patients. *Scand J Gastroenterol Suppl* 1998; **226**: 14-24 [PMID: 9595599]

67 **Ioannou G**, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev* 2003; **(1)**: CD002147 [PMID: 12535432]

68 **Gøtzsche PC**, Hróbjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. *Cochrane Database Syst Rev* 2008; **(3)**: CD000193 [PMID: 18677774]

69 **Baik SK**, Jeong PH, Ji SW, Yoo BS, Kim HS, Lee DK, Kwon SO, Kim YJ, Park JW, Chang SJ, Lee SS. Acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis: a randomized comparison. *Am J Gastroenterol* 2005; **100**: 631-635 [PMID: 15743362 DOI: 10.1111/j.1572-0241.2005.41381.x]

70 **Colapinto RF**, Stronell RD, Gildiner M, Ritchie AC, Langer B, Taylor BR, Blendis LM. Formation of intrahepatic portosystemic shunts using a balloon dilatation catheter: preliminary clinical experience. *AJR Am J Roentgenol* 1983; **140**: 709-714 [PMID: 6601376 DOI: 10.2214/ajr.140.4.709]

71 **Sanyal AJ**, Freedman AM, Luketic VA, Purdum PP, Shiffman ML, Tisnado J, Cole PE. Transjugular intrahepatic portosystemic shunts for patients with active variceal hemorrhage unresponsive to sclerotherapy. *Gastroenterology* 1996; **111**: 138-146 [PMID: 8698192 DOI: 10.1053/gast.1996.v111.pm8698192]

72 **Chau TN**, Patch D, Chan YW, Nagral A, Dick R, Burroughs AK. "Salvage" transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. *Gastroenterology* 1998; **114**: 981-987 [PMID: 9558287 DOI: 10.1016/S0016-5085(98)00640-4]

73 **Boyer TD**, Haskal ZJ. American Association for the Study of Liver Diseases Practice Guidelines: the role of transjugular intrahepatic portosystemic shunt creation in the management of portal hypertension. *J Vasc Interv Radiol* 2005; **16**: 615-629 [PMID: 15872315 DOI: 10.1097/01.RVI.0000157297.91510.21]

74 **Terés J**, Planas R, Panes J, Salmeron JM, Mas A, Bosch J, Llorente C, Viver J, Feu F, Rodés J. Vasopressin/nitroglycerin infusion vs. esophageal tamponade in the treatment of acute variceal bleeding: a randomized controlled trial. *Hepatology* 1990; **11**: 964-968 [PMID: 2114350 DOI: 10.1002/hep.1840110609]

75 **Vangeli M**, Patch D, Burroughs AK. Salvage tips for uncontrolled variceal bleeding. *J Hepatol* 2002; **37**: 703-704 [PMID: 12399244 DOI: 10.1016/S0168-8278(02)00321-5]

76 **Luca A**, D'Amico G, La Galla R, Midiri M, Morabito A, Pagliaro L. TIPS for prevention of recurrent bleeding in patients with cirrhosis: meta-analysis of randomized clinical trials. *Radiology* 1999; **212**: 411-421 [PMID: 10429698 DOI: 10.1148/radiology.212.2.r99au46411]

77 **Albillos A**, Ruiz del Arbol L. "Salvage" transjugular intrahepatic portosystemic shunt: gastric fundal compared with esophageal variceal bleeding. *Gastrointest Endosc* 1999; **50**: 294-295 [PMID: 10523141]

78 **Stanley AJ**, Jalan R, Ireland HM, Redhead DN, Bouchier IA, Hayes PC. A comparison between gastric and oesophageal variceal haemorrhage treated with transjugular intrahepatic portosystemic stent shunt (TIPSS). *Aliment Pharmacol Ther* 1997; **11**: 171-176 [PMID: 9042990 DOI: 10.1046/j.1365-2036.1997.106277000.x]

79 **Barange K**, Péron JM, Imani K, Otal P, Payen JL, Rousseau

H, Pascal JP, Joffre F, Vinel JP. Transjugular intrahepatic portosystemic shunt in the treatment of refractory bleeding from ruptured gastric varices. *Hepatology* 1999; **30**: 1139-1143 [PMID: 10534333 DOI: 10.1002/hep.510300523]

80 **Fernández J**, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; **35**: 140-148 [PMID: 11786970 DOI: 10.1053/jhep.2002.30082]

81 **Borzio M**, Salerno F, Piantoni L, Cazzaniga M, Angeli P, Bissoli F, Boccia S, Colloredo-Mels G, Corigliano P, Fornaciari G, Marenco G, Pistarà R, Salvagnini M, Sangiovanni A. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. *Dig Liver Dis* 2001; **33**: 41-48 [PMID: 11303974 DOI: 10.1016/S1590-8658(01)80134-1]

82 **Soares-Weiser K**, Brezis M, Tur-Kaspa R, Paul M, Yahav J, Leibovici L. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2003; **38**: 193-200 [PMID: 12678337 DOI: 10.1080/00365520310000690]

83 **Hou MC**, Lin HC, Liu TT, Kuo BI, Lee FY, Chang FY, Lee SD. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology* 2004; **39**: 746-753 [PMID: 14999693 DOI: 10.1002/hep.20126]

84 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922-938 [PMID: 17879356 DOI: 10.1002/hep.21907]

85 **Villanueva C**, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368**: 11-21 [PMID: 23281973 DOI: 10.1056/NEJMoa1211801]

86 **Lo GH**, Lai KH. Is endoscopic ligation therapy with large detachable snares and elastic bands really safe and effective? *Gastrointest Endosc* 2003; **57**: 438-439; author reply 439-440 [PMID: 12612544]

87 **Billi P**, Milandri GL, Borioni D, Fabbri C, Baroncini D, Cennamo V, Piemontese A, D'Imperio N. Endoscopic treatment of gastric varices with N-butyl-2-cyanoacrylate: a long term follow up. *Gastrointest Endosc* 1998; **47**: AB26 (abstract)

88 **Huang YH**, Yeh HZ, Chen GH, Chang CS, Wu CY, Poon SK, Lien HC, Yang SS. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. *Gastrointest Endosc* 2000; **52**: 160-167 [PMID: 10922085 DOI: 10.1067/mge.2000.104976]

89 **Seewald S**, Ang TL, Imazu H, Naga M, Omar S, Groth S, Seitz U, Zhong Y, Thonke F, Soehendra N. 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**: 447-454 [PMID: 18760173 DOI: 10.1016/S0016-5107(05)00632-2]

90 **Iwase H**, Maeda O, Shimada M, Tsuzuki T, Peek RM, Nishio Y, Ando T, Ina K, Kusugami K. Endoscopic ablation with cyanoacrylate glue for isolated gastric variceal bleeding. *Gastrointest Endosc* 2001; **53**: 585-592 [PMID: 11323583 DOI: 10.1067/mge.2001.113921]

91 **Rajoriya N**, Forrest EH, Gray J, Stuart RC, Carter RC, McKay CJ, Gaya DR, Morris AJ, Stanley AJ. Long-term follow-up of endoscopic Histoacryl glue injection for the management of gastric variceal bleeding. *QJM* 2011; **104**: 41-47 [PMID: 20871126 DOI: 10.1093/qjmed/hcq161]

92 **Sarin SK**, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002; **97**: 1010-1015 [PMID: 12003381 DOI: 10.1111/j.1572-0241.2002.05622.x]

93 **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**: 1060-1064 [PMID: 11343232 DOI: 10.1053/jhep.2001.24116]

94 **Tripathi D**, Ferguson JW, Therapondos G, Plevris JN, Hayes PC. Review article: recent advances in the management of bleeding gastric varices. *Aliment Pharmacol Ther* 2006; **24**: 1-17 [PMID: 16803599 DOI: 10.1111/j.1365-2036.2006.02965.x]

95 **Kitano S**, Hashizume M, Yamaga H, Wada H, Iso Y, Iwanaga T, Sugimachi K. Human thrombin plus 5 per cent ethanolamine oleate injected to sclerose oesophageal varices: a prospective randomized trial. *Br J Surg* 1989; **76**: 715-718 [PMID: 2765808 DOI: 10.1002/bjs.1800760721]

96 **Przemioslo RT**, McNair A, Williams R. Thrombin is effective in arresting bleeding from gastric variceal hemorrhage. *Dig Dis Sci* 1999; **44**: 778-781 [PMID: 10219838 DOI: 10.1023/A:1026626212129]

97 **Snobl J**, Van Buuren HR, Van Blankenstein M. Endoscopic injection using thrombin: an effective and safe method for controlling oesophagogastric variceal bleeding. *Gastroenterology* 1992; **102**: A891 (abstract)

98 **Williams SG**, Peters RA, Westaby D. Thrombin--an effective treatment for gastric variceal haemorrhage. *Gut* 1994; **35**: 1287-1289 [PMID: 7959239 DOI: 10.1136/gut.35.9.1287]

99 **Heneghan MA**, Byrne A, Harrison PM. An open pilot study of the effects of a human fibrin glue for endoscopic treatment of patients with acute bleeding from gastric varices. *Gastrointest Endosc* 2002; **56**: 422-426 [PMID: 12196788 DOI: 10.1016/S0016-5107(02)70054-0]

100 **Datta D**, Vlavianos P, Alisa A, Westaby D. Use of fibrin glue (beriplast) in the management of bleeding gastric varices. *Endoscopy* 2003; **35**: 675-678 [PMID: 12929063 DOI: 10.1055/s-2003-41517]

101 **Yang WL**, Tripathi D, Therapondos G, Todd A, Hayes PC. Endoscopic use of human thrombin in bleeding gastric varices. *Am J Gastroenterol* 2002; **97**: 1381-1385 [PMID: 12094854 DOI: 10.1111/j.1572-0241.2002.05776.x]

102 **McAvoy NC**, Plevris JN, Hayes PC. Human thrombin for the treatment of gastric and ectopic varices. *World J Gastroenterol* 2012; **18**: 5912-5917 [PMID: 23139607 DOI: 10.3748/wjg.v18.i41.5912]

103 **Gaba RC**, Bui JT, Cotler SJ, Kallwitz ER, Mengin OT, Martinez BK, Berkes JL, Carrillo TC, Knuttinen MG, Owens CA. Rebleeding rates following TIPS for variceal hemorrhage in the Viatorr era: TIPS alone versus TIPS with variceal embolization. *Hepatol Int* 2010; **4**: 749-756 [PMID: 21286346 DOI: 10.1007/s12072-010-9206-2]

104 **Vignali C**, Bargellini I, Grosso M, Passalacqua G, Maglione F, Pedrazzini F, Filauri P, Niola R, Cioni R, Petruzzi P. TIPS with expanded polytetrafluoroethylene-covered stent: results of an Italian multicenter study. *AJR Am J Roentgenol* 2005; **185**: 472-480 [PMID: 16037523 DOI: 10.2214/ajr.185.2.01850472]

105 **Hausegger KA**, Karnel F, Georgieva B, Tauss J, Portugaller H, Deutschmann H, Berghold A. Transjugular intrahepatic portosystemic shunt creation with the Viatorr expanded polytetrafluoroethylene-covered stent-graft. *J Vasc Interv Radiol* 2004; **15**: 239-248 [PMID: 15028808 DOI: 10.1097/01.RVI.0000116194.44877.C1]

106 **Angermayr B**, Cejna M, Koenig F, Karnel F, Hackl F, Gangl A, Peck-Radosavljevic M. Survival in patients undergoing transjugular intrahepatic portosystemic shunt: ePTFE-covered stentgrafts versus bare stents. *Hepatology* 2003; **38**: 1043-1050 [PMID: 14512892 DOI: 10.1053/jhep.2003.50423]

107 **Charon JP**, Alaeddin FH, Pimpalwar SA, Fay DM, Olliff SP, Jackson RW, Edwards RD, Robertson IR, Rose JD, Moss JG. Results of a retrospective multicenter trial of the Viatorr expanded polytetrafluoroethylene-covered stent-graft for transjugular intrahepatic portosystemic shunt creation. *J*

Vasc Interv Radiol 2004; **15**: 1219-1230 [PMID: 15525740 DOI: 10.1097/01.RVI.0000137434.19522.E5]
108 **Tripathi D**, Ferguson J, Barkell H, Macbeth K, Ireland H, Redhead DN, Hayes PC. Improved clinical outcome with transjugular intrahepatic portosystemic stent-shunt utilizing polytetrafluoroethylene-covered stents. *Eur J Gastroenterol Hepatol* 2006; **18**: 225-232 [PMID: 16462534 DOI: 10.1097/00042737-200603000-00001]
109 **Kiyosue H**, Mori H, Matsumoto S, Yamada Y, Hori Y, Okino Y. Transcatheter obliteration of gastric varices. Part 1. Anatomic classification. *Radiographics* 2003; **23**: 911-920 [PMID: 12853665]
110 **Choi YH**, Yoon CJ, Park JH, Chung JW, Kwon JW, Choi GM. Balloon-occluded retrograde transvenous obliteration for gastric variceal bleeding: its feasibility compared with transjugular intrahepatic portosystemic shunt. *Korean J Radiol* 2003; **4**: 109-116 [PMID: 12845306 DOI: 10.3348/kjr.2003.4.2.109]
111 **Matsumoto A**, Hamamoto N, Nomura T, Hongou Y, Arisaka Y, Morikawa H, Hirata I, Katsu K. Balloon-occluded retrograde transvenous obliteration of high risk gastric fundal varices. *Am J Gastroenterol* 1999; **94**: 643-649 [PMID: 10086645 DOI: 10.1111/j.1572-0241.1999.00928.x]
112 **Iwatsuki S**, Starzl TE, Todo S, Gordon RD, Tzakis AG, Marsh JW, Makowka L, Koneru B, Stieber A, Klintmalm G. Liver transplantation in the treatment of bleeding esophageal varices. *Surgery* 1988; **104**: 697-705 [PMID: 3051474]
113 **Orloff MJ**, Isenberg JI, Wheeler HO, Haynes KS, Jinich-Brook H, Rapier R, Vaida F, Hye RJ, Orloff SL. Liver transplantation in a randomized controlled trial of emergency treatment of acutely bleeding esophageal varices in cirrhosis. *Transplant Proc* 2010; **42**: 4101-4108 [PMID: 21168637 DOI: 10.1016/j.transproceed.2010.09.035]
114 **Garcia-Pagán JC**, Di Pascoli M, Caca K, Laleman W, Bureau C, Appenrodt B, Luca A, Zipprich A, Abraldes JG, Nevens F, Vinel JP, Sauerbruch T, Bosch J. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. *J Hepatol* 2013; **58**: 45-50 [PMID: 22940408 DOI: 10.1016/j.jhep.2012.08.020]
115 **Hubmann R**, Bodlaj G, Czompo M, Benkö L, Pichler P, Al-Kathib S, Kiblböck P, Shamyieh A, Biesenbach G. The use of self-expanding metal stents to treat acute esophageal variceal bleeding. *Endoscopy* 2006; **38**: 896-901 [PMID: 16981106 DOI: 10.1055/s-2006-944662]
116 **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**: 71-78 [PMID: 19879564 DOI: 10.1016/j.gie.2009.07.028]
117 **Dechêne A**, El Fouly AH, Bechmann LP, Jochum C, Saner FH, Gerken G, Canbay A. Acute management of refractory variceal bleeding in liver cirrhosis by self-expanding metal stents. *Digestion* 2012; **85**: 185-191 [PMID: 22269340 DOI: 10.1159/000335081]
118 **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**: 2149-2152 [PMID: 18622540 DOI: 10.1007/s00464-008-0009-7]
119 **Escorsell A**, Cardenas A, Pavel O, Morillas RM, Albillos A, Llop E, de la Pena J, Vilanueava C, Garica-Pagan JC, Bosch J. Self-expandable esophageal metal stent vs Balloon tamponade in esophageal variceal bleeding refractory to medical and endoscopic treatment: a multicenter randomized controlled trial. *Hepatology* 2013: 1368A
120 **Babiuc RD**, Purcarea M, Sadagurschi R, Negreanu L. Use of Hemospray in the treatment of patients with acute UGIB - short review. *J Med Life* 2013; **6**: 117-119 [PMID: 23904868]
121 **Ward KR**, Tiba MH, Holbert WH, Blocher CR, Draucker GT, Proffitt EK, Bowlin GL, Ivatury RR, Diegelmann RF. Comparison of a new hemostatic agent to current combat hemostatic agents in a Swine model of lethal extremity arterial hemorrhage. *J Trauma* 2007; **63**: 276-283; discussion 283-284 [PMID: 17693824 DOI: 10.1097/TA.0b013e3180eea8a5]
122 **Sung JJ**, Luo D, Wu JC, Ching JY, Chan FK, Lau JY, Mack S, Ducharme R, Okolo P, Canto M, Kalloo A, Giday SA. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. *Endoscopy* 2011; **43**: 291-295 [PMID: 21455870 DOI: 10.1055/s-0030-1256311]
123 **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**: 769-773 [PMID: 24120338 DOI: 10.1016/j.gie.2013.07.037]
124 **Smith LA**, Morris AJ, Stanley AJ. The use of hemospray in portal hypertensive bleeding; a case series. *J Hepatol* 2014; **60**: 457-460 [PMID: 24140803 DOI: 10.1016/j.jhep.2013.10.008]
125 **Stanley AJ**, Smith LA, Morris AJ. Use of hemostatic powder (Hemospray) in the management of refractory gastric variceal hemorrhage. *Endoscopy* 2013; **45** Suppl 2 UCTN: E86-E87 [PMID: 23526533 DOI: 10.1055/s-0032-1326258]
126 **D'Amico G**, Pagliaro L, Pietrosi G, Tarantino I. Emergency sclerotherapy versus vasoactive drugs for bleeding oesophageal varices in cirrhotic patients. *Cochrane Database Syst Rev* 2010; **(3)**: CD002233 [PMID: 20238318]
127 **Yang Z**, Han G, Wu Q, Ye X, Jin Z, Yin Z, Qi X, Bai M, Wu K, Fan D. Patency and clinical outcomes of transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stents versus bare stents: a meta-analysis. *J Gastroenterol Hepatol* 2010; **25**: 1718-1725 [PMID: 21039832 DOI: 10.1111/j.1440-1746.2010.06400.x]

P- Reviewers: Amitrano L, de Franchis R, Lo GH
S- Editor: Gou SX **L- Editor**: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327