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Update on the management of gastrointestinal varices

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Abstract

Cirrhosis of liver is a major problem in the western world. Portal hypertension is a complication of cirrhosis and can lead to a myriad of pathology of which include the development of porto-systemic collaterals. Gastrointestinal varices are dilated submucosal veins, which often develop at sites near the formation of gastroesophageal collateral circulation. The incidence of varices is on the rise due to alcohol and obesity. The most significant complication of portal hypertension is life-threatening bleeding from gastrointestinal varices, which is associated with substantial morbidity and mortality. In addition, this can cause a significant burden on the health care facility. Gastrointestinal varices can happen in esophagus, stomach or ectopic varices. There has been considerable progress made in the understanding of the natural history, pathophysiology and etiology of portal hypertension. Despite the development of endoscopic and medical treatments, early mortality due to variceal bleeding remains high due to significant illness of the patient. Recurrent variceal bleed is common and in some cases, there is refractory variceal bleed. This article aims to provide a comprehensive review of the management of gastrointestinal varices with an emphasis on endoscopic interventions, strategies to handle refractory variceal bleed and newer endoscopic treatment modalities. Early treatment and improved endoscopic techniques can help in improving morbidity and mortality.

Key words: Portal hypertension; Esophageal varices; Gastric varices; Ectopic varices;

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Core tip: Cirrhosis of liver can lead to gastrointestinal varices. Gastrointestinal bleed from varices can be debilitating and can cause morbidity and mortality if not well controlled. This is a detailed review on the endoscopic management of variceal bleed and gives an insight into some of the new endoscopic techniques that can be helpful in treating variceal bleed.

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INTRODUCTION

Less than 1% of the United States population have cirrhosis of liver^[1]. In the western world, the most common etiology of portal hypertension is cirrhosis due to alcoholic liver disease, nonalcoholic steatohepatitis (NASH), and hepatitis C infection^[2]. According to a recent estimate 15 million people in the United States have alcohol abuse disorder, nearly 88000 people die annually due to alcohol, and 10%-15% of people with alcoholism develop cirrhosis^[3]. Another 3 million people have chronic hepatitis C infection^[4], and 25%-28% of these patients go on to develop cirrhosis^[5,6]. Nonalcoholic fatty liver disease (NAFLD) is a spectrum of chronic liver disease consisting of mild to an advanced form of fatty degeneration of the liver described as NASH. Prevalence of NASH is estimated to be around 3%-8% of the general population, and 10%-25% of these patients progress to cirrhosis^[7]. Moreover, the rate of NASH is rising due to the increasing prevalence of obesity, insulin resistance, and diabetes. NASH is the second most common cause among patients with cirrhosis who are currently waiting for liver transplant. Recent trends have indicated that NAFLD is expected to overtake hepatitis C and alcohol as the most common etiology of liver cirrhosis and indication for liver transplants in the western countries by year 2030^[8,9]. Therefore, in order to reduce morbidity and mortality, as well as the overall burden on healthcare, it is essential to develop cost-effective screening and management strategies for portal hypertension related to cirrhosis.

NATURAL HISTORY OF GASTROINTESTINAL VARICES

Gastrointestinal varices are abnormally dilated submucosal veins in the digestive tract due to portal hypertension and can potentially cause life-threatening bleeding. Prevalence of varices increases with the severity of liver disease (Child-Pugh class A 42.7%, class B 70.7% and class C 75.5%)^[2,10]. The Child-Pugh score is described in [Table 1](#). The incidence of esophageal varices in cirrhotic patients is around 5% at the end of one year and 28% at the end of three years. Small varices progress to large varices at a rate of 10% to 12% annually^[11]. Approximately 50% of all patients with a new diagnosis of cirrhosis have gastrointestinal varices^[2]. Annual risk of variceal bleeding among small and large varices is 5% and 15% respectively^[12]. The six-week mortality rate among patients with index variceal bleeding is approximately 20%^[13]. Risk of rebleeding without endoscopic intervention is almost 60% with an increased mortality rate (33%)^[14].

PATHOPHYSIOLOGY

The development of portal hypertension in cirrhosis is a multifactorial process with changes in both the portal and systemic circulation. This is shown in [Figure 1](#). The majority of patients in western countries with portal hypertension have underlying cirrhosis. Non-cirrhotic portal hypertension is typically less common and

Table 1 Child-Pugh scoring and classification

	Child-Pugh scoring		
	1 point	2 points	3 points
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)
Ascites	None	Mild	Moderate to severe
PT/INR	< 1.7	1.71-2.30	> 2.30
Serum albumin (g/L)	> 35	28-35	< 28
Total bilirubin (μmol/L)	< 34	34-50	> 50

Class A (score 5-6), class B (score 7-9), and class C (score 10-15). PT/INR: Prothrombin time/international standardized ratio.

encompasses a broad range of pathology, typically vascular in origin^[15]. Portal hypertension is defined as hepatic vein pressure gradient (HVPG) more than 5 mmHg. The HVPG is a surrogate means to measure pressure in the portal veins. Normal HVPG (= hepatic vein wedge pressure - free hepatic vein pressure) is around 3-5 mmHg. Varices usually develop when patients have HVPG >10 mmHg and presence of HVPG > 12 mmHg is a risk factor for variceal bleeding. Reduction in HVPG to less than 12 mmHg or by $\geq 20\%$ from baseline reduces the risk of initial bleeding, and other complications of portal hypertension (ascites, encephalopathy)^[14].

Porto-systemic shunting due to portal hypertension causes diversion of the portal blood into systemic circulation and results in variceal formation. Presence of ongoing liver injury due to alcohol, viral hepatitis (hepatitis B and C), or NASH can lead to increase in the size of the varices, whereas elimination of etiological factor can lead to decrease in the size or disappearance of varices in patients with alcoholic cirrhosis^[16,17].

Intrahepatic hemodynamics

Architectural distortion: Hepatocellular injury causes transformation of hepatic stellate cells into myofibroblasts. Increased expression of pro-inflammatory genes and fibrotic activity, as a result, promotes neoangiogenesis and interstitial collagen deposition resulting in distortion of the hepatic sinusoidal architecture^[18,19]. Architectural damage and regenerative nodules are responsible for nearly 2nd/3rd of the increase in intrahepatic resistance.

Increased vascular resistance: In addition to the known anatomical disruption in the sinusoidal architecture, it is now understood that there are changes in the neurohormonal regulation of vascular tone within the portal circulation. The hepatic injury causes increased production of vasoconstrictors (endothelin 1^[20,21] and thromboxane A2^[22,23]) and reduction in nitric oxide (NO) synthesis due to sinusoidal endothelial dysfunction^[24]. The imbalance in the production of vasoconstrictors and vasodilators causes impaired vasomotor control leading to further increase in resistance and is responsible for approximately 1st/3rd of the increase in intrahepatic resistance^[25,26].

Extrahepatic hemodynamics

Portal hypertension induces neurohormonal changes in the splanchnic circulation as well. Overproduction of NO from splanchnic endothelium leads to reduced splanchnic and systemic vascular resistance^[27-29]. Furthermore, a compensatory activation of the renin-angiotensin mechanism leads to increased cardiac output and hepatic blood flow. Increased portal pressure is also suspected to result in overproduction of angiogenic factors such as vascular endothelial growth factor, platelet-derived growth factor at the microcirculatory level, contributing to angiogenesis and collateral formation resulting in varices^[30,31].

ETIOLOGY

Gastrointestinal varices develop as a consequence of portal hypertension. Most common etiology of portal hypertension in the United States is cirrhosis due to alcohol, NASH, and hepatitis C. The exact prevalence of portal hypertension is not known. Causes of portal hypertension are classified as below.

Presinusoidal

Extrahepatic: Portal vein thrombosis, splenic vein thrombosis.

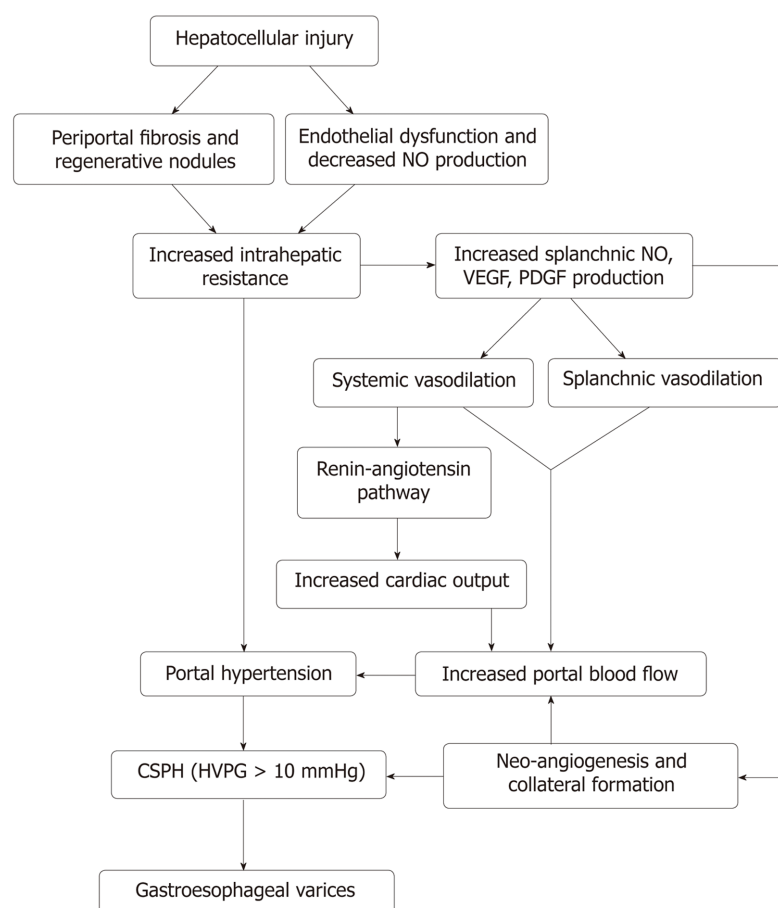


Figure 1 Mechanism of portal hypertension and the development of gastrointestinal varices. VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; NO: Nitric oxide; HVPG: Hepatic venous pressure gradient.

Intrahepatic: Schistosomiasis, congenital hepatic fibrosis, and sarcoidosis. (1) **Sinusoidal:** Cirrhosis due to viral hepatitis (hepatitis B and C), NASH, alcohol, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease, and cytotoxic drugs; and (2) **Postsinusoidal:** Budd-Chiari syndrome, caval web, constrictive pericarditis, and veno-occlusive disorders.

MECHANISM OF VARICEAL BLEEDING

Increased blood flow through the portosystemic collaterals due to portal hypertension causes dilation of the submucosal venous plexus resulting in elevated intravariceal pressure and wall tension. The mechanism of variceal rupture can be explained by Frank's modified Laplace's law^[32]. This is shown in [Figure 2](#).

Wall tension (T) = [Transmural pressure (P_{varices-Plumen}) × variceal radius (R)]/[Variceal wall thickness (WT)].

RISK STRATIFICATION FOR VARICEAL BLEEDING

HVPG > 12 mmHg

Rise in portal pressure causes increased flow through the varices and thus increased intravariceal pressure. In a randomized control trial (RCT) patients with HVPG < 12 mmHg did not develop variceal bleeding^[33], and presence of HVPG > 20 mmHg was associated with high risk of failed hemostasis and death^[34]. Whereas, a decrease in HVPG > 20% from the baseline reduces complications of portal hypertension including bleeding, ascites, encephalopathy, and death^[35-37].

Variceal size

Large varices (> 5 mm) have a higher tendency to bleed due to increased wall tension

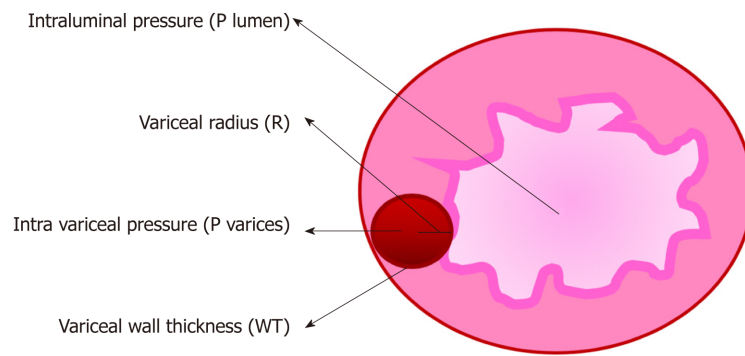


Figure 2 Mechanism of variceal bleeding. P: Pressure; R: Radius; WT: Wall thickness.

as explained above.

Wall tension

Increased wall tension and the presence of 'red wale sign' (dilated capillaries on the variceal wall) indicate a high risk for bleeding.

Other factors

Presence of coagulopathy, infection, and decompensated cirrhosis are other risk factors for variceal bleeding.

DIAGNOSTIC TESTS FOR GASTROINTESTINAL VARICES

Endoscopy

Esophago-gastro duodenoscopy (EGD) is the gold standard procedure used in the diagnosis of gastroesophageal varices (GOVs). Based on the endoscopic assessment, GOVs are classified into small (< 5 mm), and large varices(> 5 mm)^[38] for clinical management. Disadvantages of endoscopy include the risk of sedation, higher cost, bleeding and risk of aspiration.

Endoscopic ultrasound

Endoscopic ultrasound (EUS) has been evaluated as a diagnostic tool in assessing GOVs. EUS is better than EGD in detecting gastric varices (GVs), and its ability to evaluate the anatomy of collateral and perforating veins makes it an excellent choice in monitoring treatment response to endoscopic variceal ligation (EVL) and predicting recurrence^[39-41]. Currently, EUS is not considered as a primary diagnostic modality due to limited availability of local expertise.

Capsule endoscopy

A recent meta-analysis reviewed the use of capsule endoscopy for the diagnosis and grading of esophageal varices and noted a diagnostic accuracy of 90% with a pooled sensitivity and specificity of 83% and 85%, respectively^[42]. The inability of capsule endoscopy to detect GVVs is a significant drawback. Even though capsule endoscopy is relatively less invasive and does not require sedation, the diagnostic sensitivity is not adequate to advocate for index surveillance. It may be a consideration for a select subgroup of high-risk patients who are unwilling to undergo more invasive traditional endoscopic evaluation^[43,44]. One study showed that 97% of the patients preferred capsule endoscopy over endoscopy with or without sedation^[44].

Noninvasive testing

Various clinical findings, laboratory tests, and imaging studies have been considered as predictors of clinically significant portal hypertension (CSPH) (HVPG > 12 mmHg); however, they are not accurate enough to either reliably diagnose or exclude CSPH. Specifically, transient elastography, platelet count, spleen size, magnetic resonance elastography, and splenic stiffness are the most commonly used parameters to predict the presence of CSPH and varices in patients with cirrhosis. The presence of portosystemic collaterals on ultrasound, computed tomography, or magnetic resonance imaging is indicative of CSPH and necessitate screening endoscopy^[38]. Liver stiffness measured by transient elastography in combination with platelet count can rule out presence high-risk varices^[45]. A liver stiffness < 20 kPa and platelet count > 150000/ μ L indicate < 5% chance of having high-risk varices, and screening

endoscopy can be safely deferred as long as ongoing clinical monitoring can be assured^[46].

ESOPHAGEAL VARICES

Epidemiology

Esophageal varices are the most common type of gastrointestinal varices, and their prevalence in Child-Pugh class A is 42.7%, around 70.7% in class B, and 75.5% in class C^[2]. The bleeding risk for small varices and large varices is around 5% and 15% per year respectively. Early mortality rate (6 wk) is approximately 20%^[47] in esophageal varices after index bleeding.

Anatomy

Venous drainage from the sub-mucosal venous plexus of the esophagus drains into the collateral veins around the esophagus. The interconnected collateral venous plexus runs longitudinally along the esophagus and communicates with submucosal venous plexus through perforating veins in the palisading area. The cervical esophagus drains into inferior thyroid vein, the thoracic esophagus drains to azygous, hemizygous, intercostal, and bronchial veins, whereas the abdominal portion of the esophagus drains into the left gastric vein, which in turn empties into the portal vein. Portal hypertension leads to shunting of blood from the portal circulation into these low pressure, thin-walled submucosal systemic veins and manifest as varices.

Modified Paquet classification

Grade I: Varices extending just above the mucosal level.

Grade II: Varices projecting by one-third of the luminal diameter that cannot be compressed with air insufflation.

Grade III: Varices projecting up to 50% of the luminal diameter and in contact with each other.

Screening and surveillance EGD for esophageal VARICES

Shown in **Figure 3**. All patients who are newly diagnosed with cirrhosis should be screened for esophageal varices. Patients with compensated cirrhosis without varices in the absence of ongoing liver injury, endoscopy should be done every three years. Those who have compensated cirrhosis without varices, but have an ongoing liver injury (alcohol abuse, hepatitis C) and/or other cofactor diseases (alcohol/obesity) screening endoscopy should be repeated every two years.

Patients with small varices without ongoing liver injury or cofactor disease endoscopy is recommended every two years, and every year if either ongoing liver injury or cofactor disease is present. Patients with medium and large size varices should be started on nonselective beta-blockers or considered for EVL. If the patient is on nonselective beta blockers, no further surveillance endoscopy is needed.

On the other hand, if EVL is considered for primary prophylaxis endoscopy should be done every 1-2 wk until eradication and then repeated every 6-12 mo.

Management of patients with esophageal varices that have not bled

Either nonselective beta blockers or EVL (**Figure 4**) can be used as primary prophylaxis of variceal hemorrhage in patients with medium/large esophageal varices. Only approved nonselective beta-blockers are propranolol, nadolol, and carvedilol^[38,48-52]. The choice should be made based on the cost, contraindications, availability, and patient preference. Nonselective beta-blockers are preferred over EVL due to their low cost, easy availability, ability to reduce the HVPG. Nonselective beta-blockers reduce the risk of hemorrhage and other complications (ascites, encephalopathy, and death) of portal hypertension^[37]. Based on the currently available data, beta-blockers do not prevent the development of varices or their progression from small to large varices, although there is some reported benefit of reduction in risk of bleeding.

The effect of nadolol on the progression of variceal size was studied in a prospective randomized study. A total of 161 patients were randomized into nadolol ($n = 83$) and placebo ($n = 78$) groups. All patients had yearly screening endoscopy and with a mean follow up of 36 mo. The cumulative probability of bleeding and progression of small varices was lower in nadolol group (20%) when compared to placebo (51%) ($P < 0.001$) (absolute risk difference: 31%; 95% CI: 17%-45%)^[53]. However, this benefit has not been proven in other studies.

In a recent meta-analysis of 6 RCTs, the effect of nonselective beta-blockers in

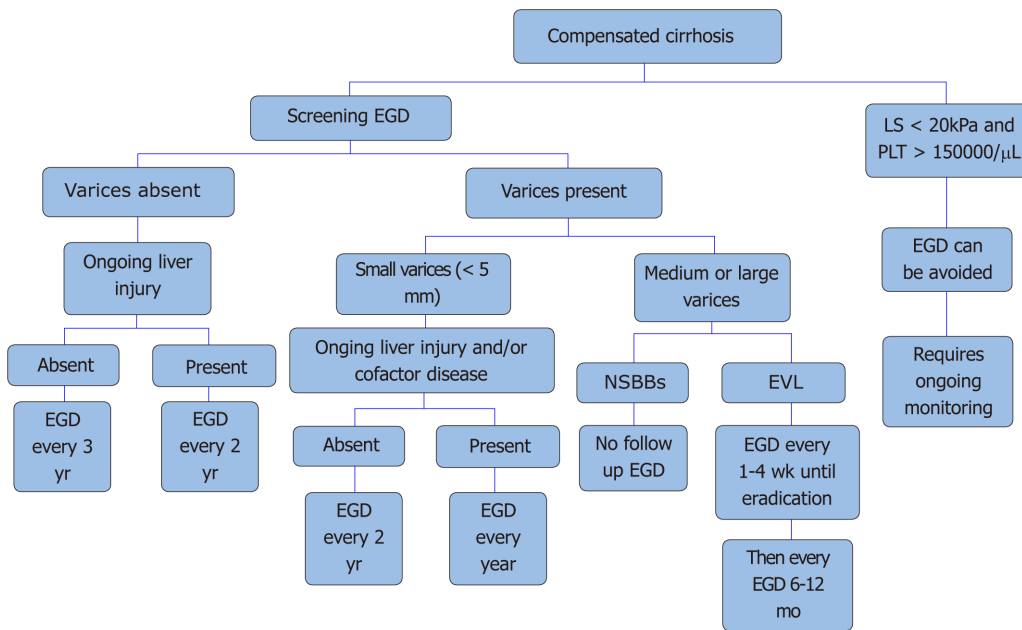


Figure 3 Screening endoscopy for esophageal varices per practice society guidelines^[38,48]. NSBBs: Nonselective beta-blockers; EVL: Endoscopic variceal ligation; EGD: Esophago-gastro duodenoscopy; LS: Liver stiffness; PLT: Platelet.

cirrhotic patients with no or small varices was analyzed. The incidence of large varices (OR = 1.05, 95% CI: 0.25-4.36; $P = 0.95$), first variceal bleeding (OR = 0.59, 95% CI: 0.24-1.47; $P = 0.26$) and death (OR = 0.70, 95% CI: 0.45-1.10; $P = 0.12$) were similar in both nonselective beta-blocker group and placebo group. However, the incidence of adverse events in the nonselective beta-blockers group was significantly higher than the placebo group. Notably, nonselective beta-blockers did not reduce the incidence of large varices or prevent the progression of small varices to large varices^[54].

On the other hand, when compared to nonselective beta blockers, EVL has a higher rate of recurrence of varices, lacks the benefit of HVP reduction, and needs further endoscopic surveillance. EVL has lower but more severe side effects (bleeding, ulcers, and strictures) compared to nonselective beta-blockers (weakness, tiredness, shortness of breath). However, there is no significant difference in the mortality rate between the two^[46].

In a prospective randomized study, the combination of EVL and propranolol was compared to EVL alone among high-risk patients. One hundred forty-four patients in total were randomized into EVL + propranolol ($n = 72$) group and EVL alone ($n = 72$) group respectively. Addition of propranolol to EVL did not reduce the risk of first variceal bleed (7% vs 11%, $P = 0.72$) or death (8% vs 15%, $P = 0.37$). However, the combination group had significant adverse effects due to propranolol in 22% of the patients. Combination of nonselective beta-blockers and EVL is not recommended as primary prophylaxis due to a higher rate of side effects. However, the recurrence of varices was significantly lower when propranolol was added ($P = 0.03$)^[55]. Recent practice society guidelines suggest the use of nonselective beta-blockers as a recommended therapy for primary prophylaxis for small varices with high-risk features (presence of 'red wale' signs or decompensated cirrhosis)^[38,46].

Isosorbide mononitrate, sclerotherapy, glue injection, and transjugular intrahepatic portosystemic shunt (TIPS) shunt are not used as primary prophylaxis due to a higher rate of side effects without mortality benefit.

Use of nonselective beta-blockers among patients who have cirrhosis with refractory ascites is controversial. A prospective case study showed that the use of nonselective beta-blockers in this patient group was associated with increased mortality^[56]. Another study also showed the increased risk of renal injury, hospital stay and mortality with the use of nonselective beta-blockers with spontaneous bacterial peritonitis due to post-paracentesis circulatory dysfunction^[57]. However, a meta-analysis of 3 RCTs and 13 observational studies ($n = 8279$) showed no significant difference in mortality or incidence of hepatorenal syndrome and spontaneous bacterial peritonitis among cirrhosis patients with refractory ascites, when treated with nonselective beta blockers^[58]. Due to concern for possible deleterious effects in patients with advanced cirrhosis, many physicians now prefer EVL over nonselective beta blockers. Larger RCTs are required before nonselective beta-blockers are

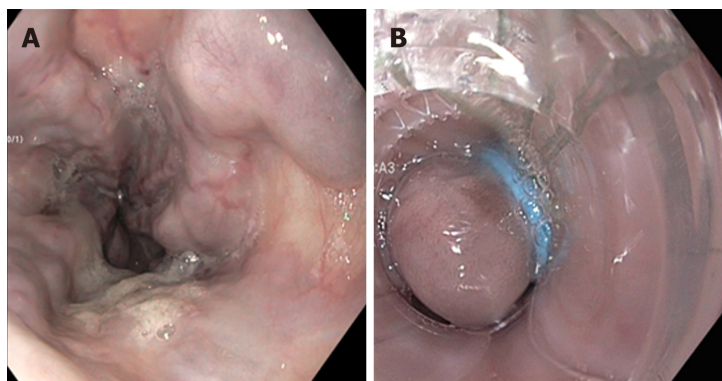


Figure 4 Endoscopic variceal ligation for primary prophylaxis. A: Esophageal varices before banding; B: Esophageal varix post banding.

considered as a contraindication in this subgroup.

Management of acute esophageal variceal bleeding

General measures: All patients with acute variceal bleeding should be resuscitated at an early stage to protect the airway and achieve hemodynamic stability, preferably in a medical intensive care unit. Prognostic indicators for early mortality due to acute variceal bleeding are HVPg, Child-Pugh score, and model for end-stage liver disease (MELD) score. A MELD score of > 19 showed 20% mortality due to index variceal bleeding^[34,47,59]. When measured within 24 h of acute bleeding, HVPg > 20 mmHg predicts a high risk of early rebleeding and death^[38,48,60]. The Child-Pugh score is also a significant predictor of early mortality and can help guide patient risk stratification^[61]. Medical management with vasoactive agents, antibiotics, blood transfusion, combined with EVL is the standard of care in treating acute variceal bleeding.

Restrictive transfusion strategy: All patients with Hb ≤ 7 g/dL should get packed red blood cells to maintain hemoglobin at 7-8 g/dL. Previous RCTs have shown a survival benefit, reduced need for blood transfusion, and a lower rate of adverse events with a restrictive strategy when compared to liberal transfusion^[62].

Most patients with acute variceal bleeding have elevated HVPg (> 12 mmHg). Further elevation of HVPg due to liberal transfusion can increase the risk of rebleeding. In a recent meta-analysis, the incidence of death (OR = 0.52, 95%CI: 0.31-0.87, $P = 0.01$), blood transfusion requirement (standard mean difference: -0.74, 95%CI: -1.15--0.32, $P = 0.0005$) and hospital stay (standard mean difference: -0.17, 95%CI: -0.30--0.04, $P = 0.009$) were significantly lower in the restrictive transfusion group compared to the liberal transfusion group^[63].

Therefore, a restrictive transfusion strategy should be employed in managing patients with acute variceal bleeding. The current practice society guidelines do not recommend routine use of plasma products and platelet transfusion in this setting due to inconsistent data on the use of plasma products and reliability of prothrombin time (PT)/international normalized ratio (INR) in patients with cirrhosis^[38,46]. However, platelet and plasma transfusion can be done in select patients who are hemodynamically unstable with active variceal bleeding (goal: platelet count $> 50000/\mu\text{L}$ and INR < 1.5)^[47].

Vasoactive agents: Vasoactive agents such as octreotide, terlipressin, somatostatin, and vasopressin cause splanchnic vasoconstriction and thus reduce portal pressure. All patients with confirmed or suspected variceal bleeding should be started on vasoactive agents as early as possible and should be continued for 2-5 d. They can be stopped early if the patient undergoes a TIPS procedure.

Terlipressin is a synthetic analog of vasopressin. The role of terlipressin in acute variceal bleeding was analyzed in a meta-analysis involving 1609 patients from 22 studies. Among those 22 studies, seven studies (443 patients) compared the effect of terlipressin to a placebo group. Terlipressin group was noted to have a statistically significant reduction in all-cause mortality (relative risk = 0.66, 95%CI: 0.49-0.88). Remaining studies compared terlipressin to somatostatin, octreotide, vasopressin or balloon tamponade. There was no significant difference in mortality or adverse events between the groups^[64,65].

Use of vasoactive agents has been shown to reduce acute bleeding, need for transfusion, and seven-day all-cause mortality^[66]. There was no significant difference in their efficacy or benefits noted between these agents^[67].

Antibiotics: Short-term antibiotics should be started in all patients with suspected or confirmed variceal bleeding to reduce bacterial infection, recurrent bleeding, and mortality^[38,48,68,69]. Bacterial infection is also considered to be an independent risk factor for variceal rupture. Choice of antibiotics should be based on local resistance pattern. However, third-generation cephalosporins with gram-negative coverage are commonly used. Intravenous ceftriaxone 1 g, every 24 h for a maximum of 7 d is preferred over oral fluoroquinolones^[38,46].

Other considerations: Most patients with variceal bleeding have loss of intravascular volume, and it is paramount to prevent hypotension. Due to the risk of hypotension and hemodynamic deterioration, nonselective beta-blockers should not be started during acute variceal bleeding and should be discontinued if the patient is already taking. However, nonselective beta-blockers should be restarted after the acute event, once hemostasis is achieved and vasoactive agents are discontinued.

Endoscopic management

Endoscopic intervention should be performed as early as possible but should be within 12 h from the time of presentation as per practice society guidelines. The diagnosis of variceal bleeding as the etiology of acute upper gastrointestinal bleeding is made when any of the following is noted on upper endoscopy: (1) Actively bleeding varices (Figure 5); (2) Signs of recent bleeding noted on varices or high-risk stigmata; *e.g.*, telangiectasia, red color signs, platelet-fibrin plug (white nipple sign), red wale marking or varices on varices (Figure 6); (3) Presence of varices and blood is noted in the stomach, with no other source of bleeding noted.

EVL (Figure 7) was first proposed for the treatment of esophageal varices in 1988 by Van Stiegmann *et al*^[70]. Currently, EVL is considered to be the first line of endoscopic treatment for the management of bleeding esophageal varices. EVL has better hemostasis, a lower rate of side effects (ulcer, stricture), a reduced rate of early rebleeding, and a lower rate of early mortality compared to sclerotherapy. Higher rebleeding in sclerotherapy is thought to be due to sustained elevation of HVPG, whereas HVPG returned to baseline with EVL^[71-73]. The slightly higher rate of variceal recurrence after EVL, when compared to sclerotherapy is due to its inability to affect the blood flow through perforators and esophageal collateral veins.

Treatment failure

Sengstaken-Blakemore tube: Whenever variceal bleeding is not controlled by EVL, temporary hemostatic measures should be used as a bridge to more definitive treatment, such as TIPS or variceal shunt surgery. Sengstaken-Blakemore tube is inserted through the mouth or nose and then distended to achieve hemostasis during active variceal bleeding by tamponading varices. The rate of hemostasis with Sengstaken-Blakemore tube varies (47%-80%). It is associated with a high rate of serious adverse events including aspiration, esophageal ulceration, and rarely esophageal rupture. Sengstaken-Blakemore tubes cannot be left in place for more than 24 h due to an increased risk of adverse events and a high rate of rebleeding (50%)^[72,73].

Metal stents: Endoscopically placed self-expanding fully covered metal stents (Figure 8) can achieve hemostasis in most cases (80%-96%). The stents expand inside the esophagus and tamponade the varices to achieve hemostasis. They can be left in place for up to 2 wk and have a lower rate of serious adverse events and transfusion requirements when compared to balloon tamponade^[74,75]. Adverse events associated with this modality of treatment include stent migration (28%), rebleeding (16%) and ulcers. However, there was no significant difference in mortality compared to balloon tamponade^[76,77].

In a meta-analysis of 12 studies ($n = 155$) hemostasis was achieved in 96% (95%CI: 0.90-1.00) of the patients within 24 h with 97% technical success (95%CI: 0.91-1.00). Adverse events (rebleeding, ulceration and stent migration) were noted in 36% (95%CI: 0.23-0.50) of the patients. Pooled survival rate at 30 d and 60 d were 68% (95%CI: 0.56-0.80) and 64% (95%CI: 0.48-0.78) respectively^[78]. Similar results were noted in another meta analysis of 5 studies ($n = 80$) with technical success of 96.7% (95%CI: 91.6%-99.5%) and hemostasis of 93.9% (95%CI: 82.2%-99.6%). Rebleeding was observed in 13.2% (95%CI: 1.8%-32.8%) and the overall mortality was 34.5% (95%CI: 24.8%-44.8%)^[79].

Based on the above evidence, self-expanding metal stents are a better choice for bridge therapy in uncontrolled esophageal variceal bleeding and should be used whenever available.

TIPS

Patients with uncontrolled variceal hemorrhage despite the combination of medical

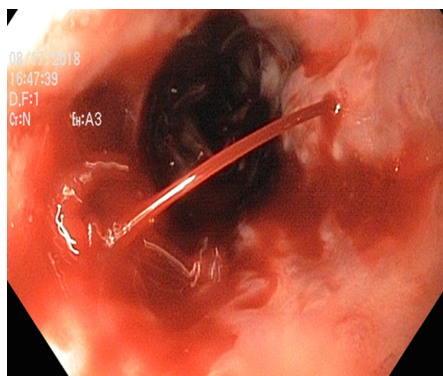


Figure 5 Bleeding esophageal varices.

and endoscopic treatment should be considered for early TIPS within (24 h) with covered PTFE (polytetrafluoroethylene) stents. TIPS is a shunt created by placing a stent between the portal vein and hepatic vein to reduce the portal pressure and thereby portal hypertension. Also, early rebleeding (within five days of initial bleeding) can be treated with repeat endoscopic intervention or covered TIPS stent^[38,46,48].

TIPS vs pharmacotherapy and endoscopic treatment

In a meta-analysis of six comparative studies, TIPS was compared with medical and endoscopic treatment for acute variceal bleeding. In this study, the survival rate (HR = 0.55; 95%CI: 0.38-0.812) was better in TIPS patients, and the incidence of bleeding-related death (OR = 0.19; 95%CI: 0.06-0.59) was lower compared to medical/endoscopic treatment. There was no significant increase in hepatic encephalopathy (OR = 1.37; 95%CI: 0.63-2.99) in TIPS patients. Although there was no significant difference in rebleeding rate between the two groups, it was evident that rebleeding in the high-risk patients was higher on subgroup analysis^[80].

Early TIPS vs pharmacotherapy and endoscopy in high-risk patients

Patients with Child-Pugh class B with active bleeding and class C are considered high-risk due to increased risk of treatment failure and rebleeding.

In a 2010 study, early TIPS was compared with pharmacotherapy (vasoactive agents) and EVL in Child-Pugh class C patients and class B patients with a high risk of treatment failure. Sixty-two patients were randomized into the treatment group (early TIPS, $n = 32$), and control group (pharmacotherapy and EVL, $n = 31$). Rescue TIPS was used in control group as needed for treatment failure. Rebleeding or failure to control bleeding occurred in one patient in the early TIPS group and 14 patients in the control group ($P = 0.001$). The one-year actuarial survival rate was 61% in the control group *vs* 86% in the early-TIPS group ($P < 0.001$)^[81].

In another international multicenter observational study (671 patients from 34 centers) patients who were admitted for acute variceal bleeding with Child-Pugh class C, and Child-Pugh class B with active bleeding were included in the study. Patients were treated with either pharmacotherapy and endoscopic interventions or preemptive TIPS. Preemptive TIPS was associated with significantly lower one-year mortality (22% *vs* 47%, $P = 0.002$), treatment failure and rebleeding (92% *vs* 74%, $P = 0.017$) when compared to patients treated with pharmacotherapy and endoscopic interventions. TIPS also prevented the development of new ascites or worsening of pre-existing ascites^[82]. Even though these results are encouraging, it was an observational study, and patients were not randomized. Each center chose to treat the patient with either preemptive TIPS or medications and endoscopy at its discretion. Therefore, the results may not be generalized. However, large RCTs can determine the use of preemptive TIPS in this high-risk population^[82].

Complications from TIPS include hepatic encephalopathy, heart failure, and stent stenosis. The incidence of hepatic encephalopathy is close to 50% without a significant difference in mortality^[83]. Absolute contraindications for TIPS include heart failure, severe pulmonary hypertension, severe tricuspid valve regurgitation, sepsis, and unrelieved biliary obstruction. Relative contraindications are portal vein thrombosis, hepatoma, uncorrected coagulopathy, and severe thrombocytopenia (platelet count $< 20000/\mu\text{L}$).

Direct ultrasound-guided direct intrahepatic porto-caval shunt

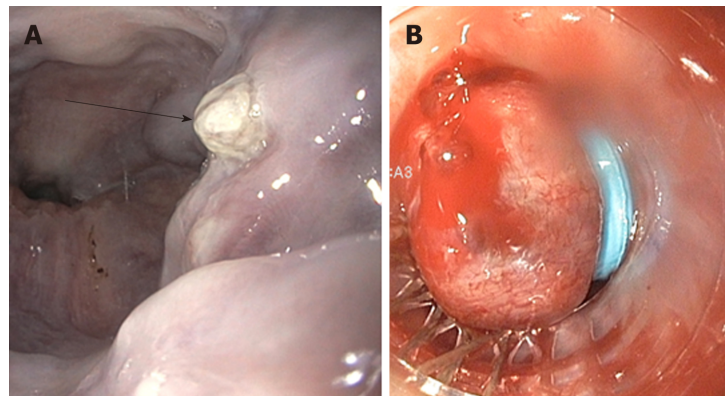


Figure 6 High-risk stigmata of bleeding from esophageal varices. A: Platelet-fibrin plug on esophageal varix (white nipple sign); B: Bleeding esophageal varix post banding.

Patients who failed TIPS, those who have altered anatomy due to previous surgery or congenital anomaly, or are otherwise not candidates for TIPS, can be treated with direct ultrasound-guided direct intrahepatic porto-caval shunt (DIPS)^[84]. The DIPS is a modified TIPS procedure, and it involves percutaneous ultrasound-guided puncture from the inferior vena cava to the portal vein through the caudate lobe of the liver.

Porto-caval shunt surgeries

Surgical shunts are considered when all other treatment modalities fail. Portocaval surgery has a very high rate of encephalopathy but does have good bleeding control. Most patients who undergo portocaval shunt surgery already have high morbidity and surgery adds to it further^[85]. In a recent RCT, emergency TIPS procedure was compared with emergency portocaval shunt surgery, and shunt surgery was noted to have superior bleeding control, long-term survival (10 years *vs* 1.99 years) and low rate of encephalopathy. However, this has not been replicated, and more evidence is required before using portocaval shunt surgery as a salvage procedure after failure of first-line treatment with medical therapy and EVL^[86].

Secondary prophylaxis

Patients who were treated with EVL and medical therapy without TIPS are at high risk for rebleeding. Approximately 60% of patients will experience rebleeding during the first year and have a high mortality rate (up to 33%) with no further intervention. Combination therapy with nonselective beta blockers (propranolol and nadolol) and EVL is the first line of treatment for secondary prophylaxis with a goal to eradicate varices and prevent recurrent bleeding^[87]. TIPS should be considered if patients do not tolerate or fail the combination of nonselective beta-blockers and EVL.

A multicenter RCT compared TIPS with the combination of EVL or glue injection and nonselective beta-blockers. Patients in the TIPS group had a significantly lower rebleeding rate (0%) compared to the EVL or glue injection and nonselective beta blockers group (29%) without a significant difference in survival benefit^[88].

GASTRIC VARICES

Epidemiology

GVs are less frequent compared to esophageal varices and are reported to be seen in 20% of the patients with portal hypertension^[38,89]. Bleeding from GV's account for 20% of all variceal bleeding^[48]. The annual bleeding rate in GV's, which have never bled before is reported to be as low as 16% per year. Sarin *et al*^[90] classified GV's based on their location.

Sarin classification

Shown in **Figure 9**. Gastroesophageal varix type 1 (GOV1): Extension of esophageal varices along lesser curvature (most common 75% of GV's); GOV2: Extension of esophageal varices along the greater curvature; Isolated gastric varix type 1 (IGV1): Isolated varices seen in the fundus of the stomach; IGV2: Isolated varices in the stomach (body, pylorus, antrum).

Predictors of bleeding from GV's

Location (IGV1 > GOV2 > GOV1); The severity of liver disease; Stigmata of high-risk

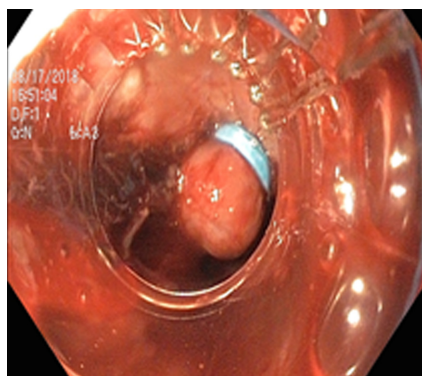


Figure 7 Endoscopic variceal band ligation.

bleeding such as 'red wale' sign.

GVs bleed less frequently but have high mortality due to the severity of bleeding. Bleeding from IGV is associated with the highest risk of death^[38,48,91].

Anatomy

GVs have complex anatomy and understanding the anatomy assists in the endoscopic management of GV. The most common type of GV is GOV1 and are usually associated with portal hypertension due to cirrhosis. They are a continuation of esophageal varices along the lesser curvature of the stomach. These are supplied by the esophageal collateral veins and are also treated similarly to esophageal varices.

On the other hand, GOV2 and IGV1 are supplied by the posterior and left gastric vein, which later drains into left renal vein due to porto-systemic shunting. Therefore GOV2 and IGV1 are together called cardiofundal varices^[91]. Isolated IGV1 can be associated with splenic vein thrombosis in the setting of pancreatitis or malignancy.

Diagnosis of GV

Diagnosis of GV (Figure 10) is commonly done with endoscopy. However, the recent use of EUS has increased the sensitivity of detecting GV. No guidelines are currently available regarding the use of endoscopy or EUS specifically to diagnose GV.

Management of patients with GV that have not bled

Primary prophylaxis for GV is not well established. Currently, nonselective beta-blockers are the first line of treatment as per practice society guidelines, in large part due to their ability to prevent other complications of cirrhosis. The role of endoscopic glue (N-butyl-2-cyanoacrylate) injection and EVL in primary prophylaxis are not clear. One study has shown glue injection was associated with lower bleeding and mortality due to GV when compared to nonselective beta blockers^[92]. Prophylactic EUS guided injection has also shown to be equally beneficial, and further studies are required to evaluate its role in primary prophylaxis for GV.

Management of acute gastric variceal bleeding

Medical management of suspected gastric variceal bleeding is similar to esophageal variceal bleeding as described above, including airway protection, admission to the intensive care unit, blood transfusion, vasoactive agents, and antibiotics (Figure 11).

Endoscopic interventions

Diagnosis of gastric variceal bleeding can be made based on endoscopic findings. Most practice guidelines recommend endoscopic glue injection as the first line of treatment in the management of acute gastric variceal bleeding. However, glue injection comes with the risk of several complications including venous and systemic thromboembolism (pulmonary embolism, stroke), ulcers, protracted bleeding, splenic and portal vein thrombosis^[93]. Portal vein thrombosis due to embolized glue can render a future plan for TIPS and liver transplantation ineffective. Embolized glue can also act as a nidus of infection and cause recurrent bacteremia^[94]. Successful glue injection requires experience due to gastric anatomy. Because of the drawbacks mentioned above, many centers use TIPS as the first line of treatment in managing acute gastric variceal bleeding.

A RCT compared efficacy and complication of TIPS and glue injection in treating GV. Rebleeding (11% *vs* 38%, $P = 0.014$; OR = 3.6, 95%CI: 1.2-11.1) and transfusion requirements were lower ($P < 0.01$) in TIPS compared to endoscopic glue injection with similar initial hemostasis, side effects, and mortality^[95].

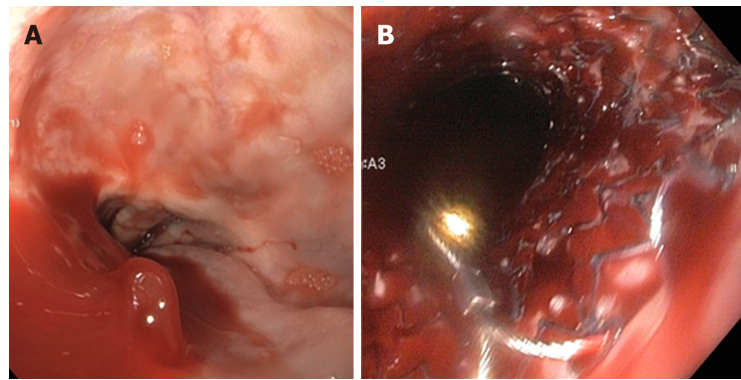


Figure 8 Metal stents for the treatment of bleeding esophageal varices. A: Bleeding esophageal varix before stenting; B: Esophageal varix after metal stent.

Even though initial hemostasis in both glue injection and EVL is similar for GOV1 GV, rebleeding is high in EVL. So EVL should be avoided^[96-98]. Combination of sclerotherapy and EVL is currently not recommended due to a higher rate of complications, and adverse events without mortality benefit^[99]. In a recent RCT, scleroligation (variceal ligation + sclerotherapy) compared to EVL alone, in the management of GOVs, the scleroligation group required a lower number of endoscopic procedures, transfusion, and bands used, without a significant difference in recurrence rate, major side effects, and mortality^[100]. Further research is needed to prove the benefits of scleroligation.

The recent emergence of EUS guided glue and coil injection in treating GV has shown a lower bleeding rate, transfusion requirements, and mortality when compared to glue injection. When EUS guided coil embolization alone was compared with EUS guided glue injection, both had similar hemostasis rates, but coil embolization had fewer adverse events and required a fewer number of endoscopies^[101]. When these two techniques were combined (glue + coil), the mean number of coils used, mean volume of glue used, and the recurrence rate was lower compared to either of them alone^[102].

Treatment failure

Patients with uncontrolled gastric variceal bleeding despite endoscopic intervention should be managed with balloon tamponade with Sengstaken-Blakemore tube or Linton-Nachlas tube as a bridge to definitive treatment. In a controlled trial Sengstaken-Blakemore tube failed to control gastric variceal bleeding in all the cases, and 50% hemostasis was achieved by Linton-Nachlas tube. Types of GV and their frequency between the two groups was not available^[73]. This difference could be attributed to a larger gastric balloon (500 mL) when compared to smaller gastric balloon in the Sengstaken-Blakemore tube. Therefore, Linton-Nachlas tube should be used whenever possible.

Hemostatic powder

Hemostatic powder (TC 325 - hemospray) and similar products have been used as bridging therapy in controlling acute peptic ulcer bleeding in the past. The hemostatic powder when sprayed at the bleeding site, it absorbs water and creates a mechanical barrier to achieve hemostasis. Recently one study assessed its role in acute variceal bleeding. Hemostasis in the study group was better than the control group, with fewer study group patients requiring rescue endoscopy (12%). Rescue endoscopy was performed if initial hemostasis was not achieved within the first 12 h with hemospray. All patients were later treated with definitive endoscopic intervention after 24 h. Larger RCTs are required to evaluate the role of hemostasis powder, and currently not approved by Food and Drug Administration^[103,104].

Patients with GV who fail to respond to the endoscopic treatment will require TIPS or shunt surgery to control acute variceal bleeding. Recurrent bleeding is noted in 11%-30% of the patients who undergo TIPS.

Balloon-occluded retrograde transvenous obliteration

Patients with GV and gastro-renal collaterals can be treated with balloon-occluded retrograde transvenous obliteration (BRTO). This procedure involves retrograde cannulation of the outflow channels which drain the GV through the femoral or jugular vein, and obliteration of the varices and collaterals assisted by balloon occlusion and followed by coil and sclerosant. Various studies have evaluated its

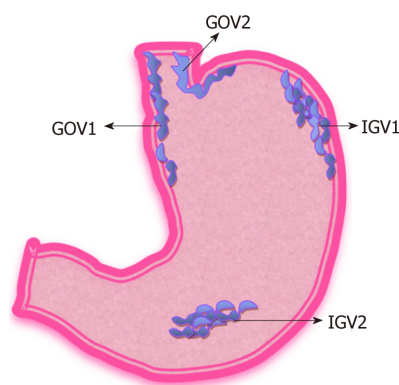


Figure 9 Sarin classification of gastric varices. GOV1: Gastroesophageal varix type 1; GOV2: Gastroesophageal varix type 2; IGV1: Isolated gastric varix type 1; IGV2: Isolated gastric varix type 2.

efficacy in treating GVs. A recent meta-analysis showed a success rate for obliteration was 97.3%, and 33.3% recurrence. BRTO can be considered as an alternative to TIPS in managing GVs. A retrospective review of 142 consecutive patients treated for acute gastric variceal bleeding comparing the efficacy of BRTO ($n = 95$) and TIPS ($n = 47$) showed significantly lower rebleeding rate in BRTO (8.6%) group compared to TIPS (19.8%)^[105] at the end of the first year. There was no significant difference in mortality. BRTO is mostly done in Asian countries, but recently it is gaining popularity in the United States^[38,48,106].

Secondary prophylaxis

Risk of rebleeding among patients who are treated with glue injection for gastric variceal bleeding was noted to vary from 15%-72%^[98,107,108]. TIPS is considered to be superior to endoscopic glue injection for secondary prophylaxis of GVs^[38]. However, there is no significant mortality benefit when compared to glue injection. The role of nonselective beta-blockers is not evident in secondary prophylaxis of GVs. Data on EUS guided glue injection and coiling for primary and secondary prophylaxis is lacking. Larger multicenter RCTs will help in understanding the role of EUS in the management of GVs.

ECTOPIC GASTROINTESTINAL VARICES

Gastrointestinal varices can develop in the duodenum, rectum, colon, small bowel, gallbladder and the retroperitoneal areas. The prevalence of ectopic gastrointestinal varices is unknown. According to one estimate, among patients with cirrhosis and portal hypertension who underwent angiography, 40% of patients had duodenal varices. Ectopic varices are responsible for up to 1%-5% of all variceal bleeding. Understanding the complex anatomy of ectopic varices, and their anastomosis with mesenteric veins is essential in managing ectopic varices^[91,109].

Duodenal varices

Duodenal varices are more commonly seen in noncirrhotic, extrahepatic portal hypertension (*e.g.*, portal vein thrombosis, splenic vein thrombosis) and their prevalence is around 0.4%^[109]. Duodenal varices form due to Porto-mesenteric and Porto-portal anastomosis. Duodenal varices are noted on endoscopy as submucosal dilated veins, usually arising from anastomosis between tributaries of the superior mesenteric vein and portal vein draining into inferior vena cava. EUS is notably superior in diagnosing duodenal varices compared to EGD^[110]. Acute duodenal variceal bleeding is usually treated with endoscopic glue injection. There have been no RCTs evaluating the treatment strategies for duodenal varices owing to their rarity. In the largest case series involving ten patients with duodenal variceal glue injection, 4 out of the five patients who presented with acute bleeding were treated with endoscopic glue injection and had 100% hemostasis rate without recurrence^[110]. Duodenal varices bleed at a lower hepatic venous pressure gradient, and therefore TIPS may not be sufficient to treat duodenal varices and need further definitive treatment with intravascular obliteration with glue injection, or embolization through BRTO. BRTO can also be used for patients who fail endoscopic therapy and are not candidates for TIPS^[111].

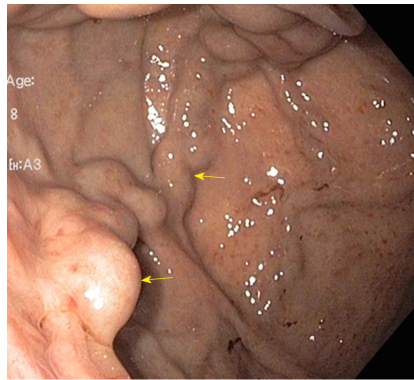


Figure 10 Gastric varices.

Rectal varices

Rectal varices usually arise from portosystemic anastomosis between superior hemorrhoidal veins (a tributary of the inferior mesenteric vein) and the middle or inferior hemorrhoidal veins (tributaries of iliac or pudendal veins). Prevalence of rectal varices patients with portal hypertension varies from 28%-56% in cirrhotic patients^[112], and are more common among patients with extrahepatic portal vein obstruction (up to 90%)^[113]. EUS has a higher sensitivity to detect rectal varices compared to endoscopy. Risk of bleeding from rectal varices is 8%-38%^[112]. Rectal varices bleed at the lower hepatic venous pressure gradient and may not disappear with TIPS. Endoscopic variceal band ligation is the preferred method of treatment for rectal varices compared to endoscopic sclerotherapy or glue injection, but the recurrence rate of rebleeding is high with Endoscopic variceal band ligation. Recurrent bleeding in endoscopic sclerotherapy (33%) was much lower compared to EVL (55.6%)^[114] but not commonly used due to the occurrence of severe ulcers. Endoscopic glue injection can be useful in managing rectal varices, but nearly 0.5%-4.3% of these patients develop embolization. EUS guided coil and glue embolization is also considered useful in large rectal varices that are not amenable to variceal ligation^[115]. Role of BRTO has been evaluated in small case series; no RCTs are available to compare its efficacy. Optimal management of rectal varices is not yet established.

Stomal varices

Stomal varices usually occur at the mucocutaneous junction of the stoma, due to portosystemic shunt between the portal circulation of the bowel and systemic circulation of the abdominal wall. Diagnosis of stomal varices is difficult, on physical exam, they appear as bluish discoloration of the skin. Visibly dilated veins and characteristic raspberry appearance of the stoma should prompt further evaluation for the cause of bleeding. Patients with stomal varices can be treated with a glue injection. Percutaneous sclerotherapy is not recommended due to increased risk of damaging the stoma. Gastrointestinal varices can also form in other parts of the gastrointestinal tract including jejunum, ileum, and colon as well. The actual prevalence of these varices is unknown but considered to be low.

CONCLUSION

In summary, development, and utilization of newer treatment modalities such as therapeutic EUS, BRTO, and hemospray in managing gastrointestinal varices will help to reduce further- the morbidity and mortality related to variceal bleeding. Further research in understanding the risk factors, mechanism of liver injury, and evaluation of antifibrotic agents to prevent architectural changes to the liver can revolutionize the management of portal hypertension and its complications.

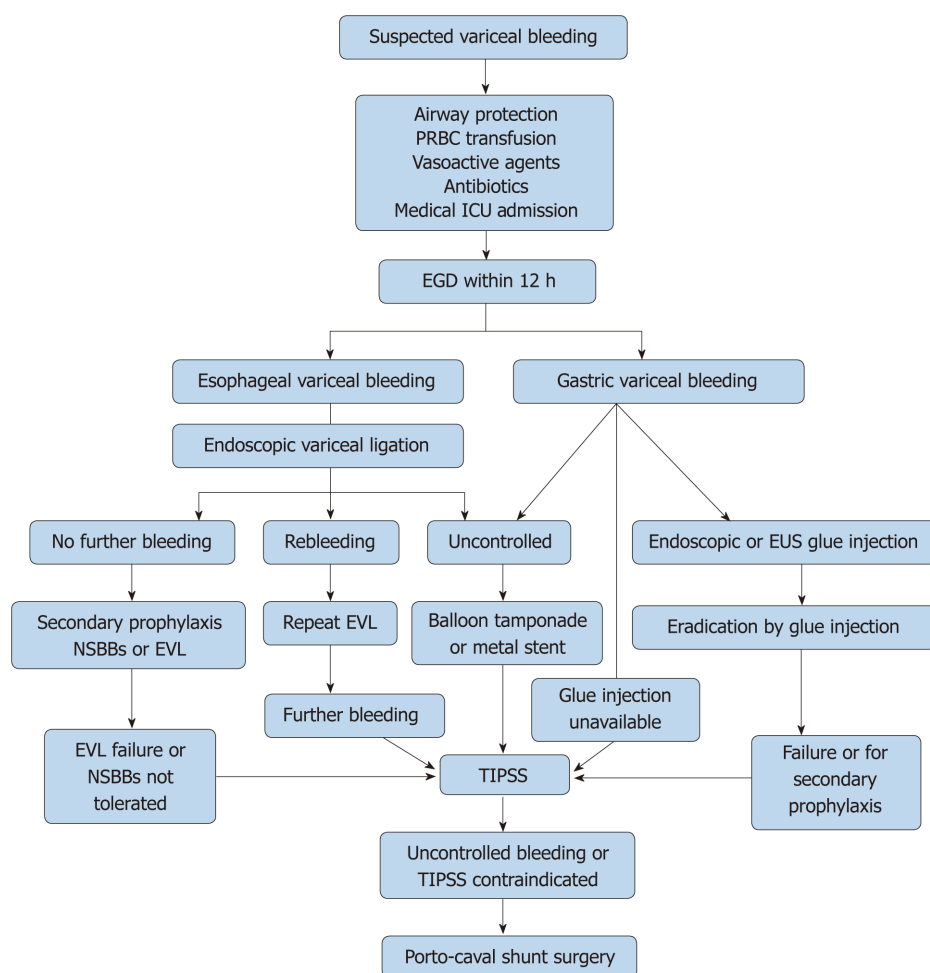


Figure 11 Algorithm for the management of acute variceal bleed. ICU: Intensive care unit; EGD: Esophago-gastro duodenoscopy; NSBB: Nonselective beta blockers; EVL: Endoscopic variceal ligation; TIPS: Transjugular intrahepatic portosystemic shunt.

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Retrospective Study

Opioid use and misuse in ulcerative colitis

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Institutional review board

statement: This study was reviewed and approved by the University of Virginia Institutional Review Board for Health Sciences Research (IRB-HSR).

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Patients were not required to give informed consent for this study as the analysis was conducted retrospectively and no identifying factors were used in the analysis.

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Abstract

BACKGROUND

Patients with ulcerative colitis (UC) may be exposed to opioids over their disease duration. The use of such medications carries significant risk, including intestinal dysmotility and potential for addiction. However, the rates of narcotic use and misuse in patients with UC have not been studied extensively. Functional gastrointestinal disorders (FGID) are prevalent in patients with UC, and have been shown to increase the risk of narcotic use and misuse in patients with Crohn's disease. We hypothesized that patients with UC and a concurrent diagnosis of FGID would have increased rates of both opioid use and misuse in our patient cohort.

AIM

To evaluate the prevalence of chronic opioid use and misuse in UC.

METHODS

A retrospective chart review of UC patients seen at the University of Virginia Digestive Health Center was performed on all patients evaluated between 2006 and 2011. Patient demographics, medical, surgical, and medication histories were obtained from the electronic medical record. Concomitant diagnosis of FGID was also noted at the time. The electronic prescription monitoring program was accessed to obtain prescription opioid filling histories. Prescription opioid misuse was defined as opioid prescriptions filled from four or more prescribers and four or more different pharmacies in a 12-mo period.

RESULTS

A total of 497 patients with UC were included. Patients with UC and FGID were

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more likely to be female, but no other demographic variables were associated with FGID. Of the UC patients who had FGID, a greater proportion were found to be using opioids chronically (36% with FGID *vs* 9% without FGID, $P < 0.0001$) and were misusing prescription opioids (12.8% *vs* 1.3%, $P < 0.001$). Multivariate logistic regression demonstrated a significant association with FGID and chronic opioid use (OR = 4.50; 95% CI: 1.91-10.59) and opioid misuse (OR = 5.19; 95% CI: 1.04-25.76). Tobacco use (OR 2.53; 95% CI: 1.06-6.08) and anxiety (OR 3.17; 95% CI: 1.08-9.26) were other variables associated with an increased risk of chronic narcotic use.

CONCLUSION

FGID was associated with a 4.5-fold increase in chronic opioid use and a 5-fold increased risk of opioid misuse in this patient cohort with UC.

Key words: Ulcerative colitis; Chronic opioid use; Opioid misuse; Narcotic; Functional gastrointestinal disorder

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Core tip: Rates of chronic opioid use and misuse among patients with ulcerative colitis (UC) have not been studied extensively, and it is unknown whether functional gastrointestinal disorder (FGID) affects these rates. The aims of this study were to evaluate rates of opioid use and misuse in UC and determine whether these rates were affected by concomitant FGID. Patients with FGID and UC were 4.5 times more likely to be using chronic opioids and 5 times more likely to be misusing opioids. This highlights the potential risks of opioid use in the management of UC, particularly in those patients with concomitant FGID.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory gastrointestinal condition which can manifest with recurrent bouts of abdominal pain, rectal bleeding, and diarrhea. During disease flares, opioid medications may be prescribed in the acute setting for the treatment of pain, but carry significant negative consequences including worsening intestinal dysmotility and visceral hyperalgesia, along with the potential risk for medication dependency and addiction^[1,2].

Rates of opioid addiction, diversion, and overdose have risen dramatically in the United States over the past two decades^[3,4] and are currently at epidemic levels. State-run prescription monitoring programs (PMPs) have been established to combat this issue and make it possible to identify patients who have behaviors suggesting opioid misuse, such as “doctor shopping,” obtaining prescriptions from multiple prescribers, using multiple pharmacies, using multiple opioids simultaneously, and obtaining early refills of medications. While there is no standard definition for opioid misuse, Katz *et al*^[5] defined the use of greater than or equal to four pharmacies and greater than or equal to four prescribers of schedule II medications within a 12-mo period as “questionable activity” which is consistent with opioid misuse.

Functional gastrointestinal disorders (FGID) have been shown to be prevalent among patients with inflammatory bowel disease (IBD)^[6]. Simrén *et al*^[6] demonstrated that irritable bowel syndrome-like symptoms were two to three-fold more prevalent in patients with IBD in remission than in the general population, and patients with these symptoms also exhibited increased levels of depression and anxiety. FGID has been shown to be a significant risk factor for chronic opioid use and misuse among patients with Crohn’s disease^[7], representing a two-fold and three-fold increased risk of chronic opioid use and misuse, respectively. While the prevalence of opioid use has been previously reported in UC^[1,8], to our knowledge, the prevalence of opioid misuse has not been specifically studied in this population. The primary aim of this study

was to determine whether patients with UC and concurrent FGID had higher rates of chronic opioid use, and to determine the prevalence and risk factors for prescription opioid misuse in this patient population.

MATERIALS AND METHODS

Patients

A retrospective chart review was performed on patients with UC treated at the University of Virginia Digestive Health outpatient clinic from 2006 to 2011. Patient demographics were obtained from the electronic medical record (Epic Hyperspace, Verona, WI) including patient age, sex, race, insurance status, geographic area of residence, tobacco use, and alcohol use. Medical, surgical and psychiatric histories were recorded for each patient; including the diagnosis of any co-existing FGID. The Rome III criteria and diagnoses served as the basis for our inclusion of FGIDs in this study, and all patients with a FGID, regardless of whether their FGID related to upper or lower gastrointestinal symptoms, were marked as having FGID. Patients with symptoms of FGID without an existing diagnosis made by a clinician were not recorded as having FGID. Medication history was obtained from the electronic medical record including IBD-related therapy and non-IBD medications. Information on opioid use was also collected using electronic prescription monitoring program databases from Virginia and West Virginia (<https://virginia.pmpaware.net>). To access the PMP database, patient name, date of birth, and date of initial clinic visit were entered into the database, and information regarding the type and number of opioid prescriptions, as well as the number of different prescribers and pharmacies, were recorded. Prescription data was collected for a one-year period following the date of the initial office visit, and thus patients had an established diagnosis of UC at the time at which prescription data collection began.

Chronic opioid use was defined as having three consecutive prescriptions for opioids filled or having two or more opioid prescriptions filled within a six-month period. Opioid misuse was defined as a patient meeting the “4 + 4 criteria” of having opioid prescriptions given by four or more prescribing physicians and using four or more pharmacies in a 12-mo period^[5]. Post-operative pain medication prescriptions that were limited to one prescription were not counted toward the analysis.

Statistical analysis

Statistical analysis was performed by a biomedical statistician (Northup PG) using SAS 9.2 (SAS Institute Inc., Cary, NC). Comparisons of categorical variables were made using Chi-squared tests, odds ratios and 95%CI were used to assess the interaction between chronic opioid use and opioid misuse and the following variables: age, sex, alcohol use, cigarette smoking, Medicaid/disability insurance status, anxiety, depression, and FGID. Similar interactions were assessed between FGID and the following variables: age, sex, alcohol use, cigarette smoking, Medicaid/disability insurance status, anxiety, depression, chronic opioid use, and chronic opioid misuse. Univariate and multivariate logistic regression analyses were conducted to identify potential variables affecting rates of chronic opioid use and misuse. Approval for the study was obtained through the Institutional Review Board for Health Sciences Research at the University of Virginia.

RESULTS

A total of 497 patients with UC seen at the University of Virginia Digestive Health Clinic from 2006 to 2011 were included in the study cohort (Table 1). Of these, 39 (7.8%) patients were identified as having concurrent FGID. In addition, 103 (20.7%) patients had concomitant psychiatric disease including 68 patients with depression, 22 with anxiety, and 13 with an alternative psychiatric diagnosis. Forty-three (8.7%) patients were current tobacco users.

Patients with UC and FGID were no different in age than patients with UC without FGID (49.5 years *vs* 51.2 years, $P = 0.463$). Patients with FGID were more likely to be female (74% with FGID *vs* 48% without FGID, $P = 0.010$). There was a trend toward FGID and anxiety (23% with FGID *vs* 3% without FGID, $P = 0.055$). FGID was not significantly associated with depression, alcohol use, tobacco use, insurance or disability status in this patient cohort.

Of the 497 patients, 56 (11.3%) were identified as using chronic prescription opioids. The proportion of patients on chronic opioids was significantly greater among those with FGID than those without FGID (36% *vs* 9%, $P < 0.0001$, Figure 1).

Table 1 Patient characteristics n (%)

	FGID patients (n = 39)	Non-FGID patients (n = 458)	Total (n = 497)
Mean age (yr)	51.2	53.0	52.9
Sex (Female)	29 (74.4)	220 (48.0)	249 (50.1)
Disability/Medicaid status	4 (10.3)	14 (3.1)	18 (3.6)
Tobacco use	7 (17.9)	36 (7.9)	43 (8.7)
Alcohol use	12 (30.8)	185 (40.4)	197 (39.6)
History of depression	9 (23.1)	59 (12.9)	68 (13.7)
History of anxiety	9 (23.1)	13 (2.8)	22 (4.4)
Disease extent			
Proctitis	6 (15.4)	39 (8.5)	45 (9.1)
Left sided	12 (30.8)	153 (33.4)	165 (33.2)
Extensive	20 (51.3)	227 (49.6)	247 (49.7)
Average disease duration (yr)	8.2	7.5	7.6

Among the patient characteristics analyzed, only female sex was associated with functional gastrointestinal disease (FGID) in comparison to the non-FGID cohort. FGID: Functional gastrointestinal disease.

Anxiety ($P = 0.035$) and tobacco use ($P = 0.038$) were associated with significantly higher rates of chronic opioid use. Using the PMP to review prescription data, there was evidence of opioid misuse in 11 (2.2%) patients using the 4 + 4 criteria. Of these, 5 of 39 patients (12.8%) with FGID were identified as misusing prescription opioids, compared with 6 of 458 patients (1.3%) without FGID ($P < 0.001$, [Figure 1](#)).

Multivariate logistic regression analysis demonstrated a significant association of chronic opioid use and FGID. Patients with UC and FGID had a 4.5-fold higher risk of chronic opioid use than those patients without FGID (OR = 4.50; 95%CI: 1.91-10.59). There was also an association of FGID and opioid misuse, with a five-fold increase in the risk of opioid misuse in FGID patients (OR = 5.19; 95%CI: 1.04-25.76). Tobacco use (OR = 2.53; 95%CI: 1.06-6.08) and anxiety (OR = 3.17; 95%CI: 1.08-9.26) were also associated with higher risk of chronic narcotic use, whereas patient gender, alcohol use, depression, and disability status were not ([Table 2](#)).

DISCUSSION

Within this UC patient cohort, chronic opioid use was identified in 11.3% of patients overall. UC patients with concomitant FGID were over four-fold more likely to be using chronic opioids than those UC patients without FGID. Prescription monitoring program data identified 2% of the total UC patient cohort to be misusing prescription opioids. Patients with UC and concurrent FGID had a 5-fold increased risk of opioid misuse, with 13% of patients in this group showing evidence of opioid misuse based on PMP data. The rates of chronic use and misuse of opioids are significant given the negative impacts that opioids have on disease outcomes in UC and FGID^[1,2], in addition to the potential risks of opioid dependency and addiction in this population.

Our study also found an increased risk of opioid misuse in patients with UC and FGID (OR = 5.19, 95%CI: 1.04-25.76); however the overall number of patients identified with opioid misuse was small, and larger numbers of patients would be needed to confirm this association. Tobacco use and anxiety were also associated with an increased risk of chronic narcotic use, associations which have been identified in prior studies^[9-11] and are also identified in our population to be risk factors for opioid misuse.

Given this was a retrospective study at a single tertiary care center, these results may not be generalizable to the UC population in the United States as a whole. The majority of our patient cohort resides in Virginia and West Virginia, and the opioid prescription information was limited to the PMPs from these two states. It is possible that some patients obtained opioid medications from other neighboring states and thus were not identified in the PMP data search, and this model does not account for patients using opioids that they have obtained outside of a provider's prescription. This model also assumes that all patients who filled opioid prescriptions took the medications themselves, and does not account for diversion of opioid medications. Another limitation of this study was that it was not possible in all instances to know the circumstances for which patients were using opioids (*e.g.*, flaring disease,

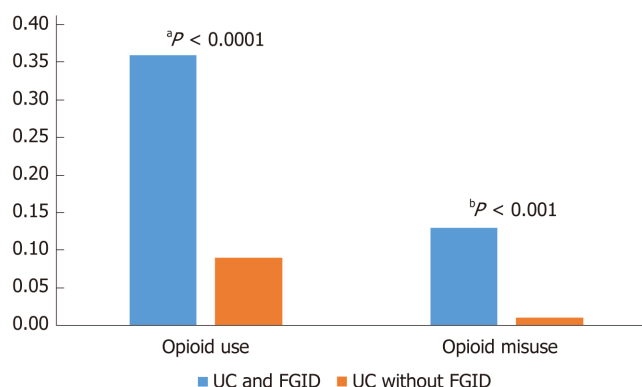


Figure 1 Rates of opioid use and misuse. Patients with ulcerative colitis and concomitant functional gastrointestinal disease had higher rates of prescription opioid use (36% vs 9%; $^aP < 0.0001$) and opioid misuse (13% vs 1%; $^bP < 0.001$). UC: Ulcerative colitis; FGID: Functional gastrointestinal disease.

abdominal pain in the absence of active UC). Thus it was not possible to stratify patients according to disease activity or severity, as patients often sought care in places other than our institution, such as from a local gastroenterologist, primary care provider, urgent care, or local emergency room.

Despite these limitations, this is the first study to our knowledge that assesses the risk of prescription opioid misuse in the UC population and identifies a subgroup of patients with concomitant FGID to be at particular risk for chronic opioid use and misuse. This has important implications in managing patients with UC and FGID as a particularly “at risk” group for opioid misuse and a population to be monitored for early intervention if this is occurring.

In conclusion, patients with UC and concomitant FGID have a 4.5-fold increased risk of chronic opioid use. Patients with UC and FGID are also at risk for opioid misuse, based on prescription monitoring program data. There is significant risk for development of opioid-related complications including opioid dependency and misuse in this population.

Table 2 Predictors of chronic narcotic use in patients with ulcerative colitis

Variables	Odds ratio estimates (Point estimates with 95% Wald confidence limits)	P value
FGID	4.50 (1.91-10.59)	< 0.001
Female sex	0.76 (0.41-1.42)	0.390
Tobacco use	2.53 (1.06-6.08)	0.038
Alcohol use	0.53 (0.27-1.04)	0.065
Anxiety	3.17 (1.08-9.26)	0.035
Depression	1.36 (0.59-3.11)	0.468
Disability/Medicaid insurance status	1.77 (0.49-6.38)	0.382

Among the risk factors included in the multivariate analysis, only functional gastrointestinal disease, tobacco use, and anxiety increased the risk for chronic narcotic use in ulcerative colitis. FGID: Functional gastrointestinal disease.

ARTICLE HIGHLIGHTS

Research background

Opioid use in the inflammatory bowel disease (IBD) population is common, given that symptoms of disease activity often include abdominal pain. While opioids may provide temporary relief, they carry long-term risks such as narcotic bowel syndrome and the potential for dependence and addiction. However, little is known about the specific rates of opioid use and misuse in the ulcerative colitis (UC) population. Functional gastrointestinal diseases often overlap with symptoms of IBD, and abdominal pain or functional symptoms in patients with UC with a concomitant diagnosis of functional gastrointestinal disorders (FGID) may be easily mistaken as a manifestation of active UC during periods of disease remission. In a previous study, we showed that rates of chronic opioid use and misuse among patients with Crohn's disease (CD) and concomitant FGID were two-fold and three-fold higher, respectively, than in patients with CD without a diagnosis of FGID.

Research motivation

Identification of risk factors for opioid abuse in the IBD population, specifically in UC patients, is key in prevention of complications of these medications. Patients at risk for chronic opioid use and misuse can be identified, and prescribers can be better informed, thereby preventing many of the adverse effects – physical, mental and psychosocial – associated with long-term opioid therapy in this vulnerable population.

Research objectives

The purpose of this study was to characterize rates of chronic opioid use and misuse in the UC population, as these have not been studied extensively. One of the objectives of this study was to investigate whether FGID was a risk factor for chronic opioid use and misuse in UC patients, as has been demonstrated in patients with CD and FGID.

Research methods

Following approval through the institutional review board, a retrospective chart review was conducted at the University of Virginia Digestive Health Center including all patients who had been evaluated for ulcerative colitis between 2006 and 2011. Patient demographics and selected variables (tobacco use, alcohol use, *etc.*), medical, surgical and psychiatric histories, and concomitant diagnoses of FGID (as outlined by Rome III criteria) were collected from the electronic medical record. Data on opioid use was collected from the electronic prescription monitoring program databases for the states of Virginia and West Virginia (<https://virginia.pmpaware.net>). Statistical analysis was conducted by a biomedical statistician and both univariate and multivariate regression analyses were performed.

Research results

This study cohort consisted of 497 patients with UC, who were seen at the University of Virginia from 2006 to 2011. Of these patients, 7.8% had a concurrent diagnosis of FGID as defined by Rome III criteria, 20.7% had concomitant psychiatric disease, and 8.7% were current tobacco users. Patients with UC and FGID were more likely to be female ($P = 0.010$), but no other risk factors were found to be associated with FGID in the UC cohort. A greater proportion of patients with FGID and UC were on chronic opioid therapy than patients with UC without FGID (36% *vs* 9%, $P < 0.0001$), and a greater proportion of patients with FGID and UC met criteria for opioid misuse (12.8% *vs* 1.3%, $P < 0.001$). In the multivariate logistic regression analysis, patients with FGID and UC had a 4.5-fold increased risk for chronic opioid use and 5-fold increased risk for opioid misuse in comparison to their UC counterparts without FGID. Tobacco use and anxiety also conferred higher risks for chronic narcotic use.

Research conclusions

To our knowledge, this is the first study which assesses the rates of and risk factors for both

chronic opioid use and misuse in the UC population. This study sheds light on the need for careful prescription practices among providers who have patients with UC, particularly those with concomitant diagnoses of FGID. As we hypothesized, FGID increased the risk for both chronic opioid use and misuse in our cohort of UC patients, which is a novel finding and may set the foundation for future studies. Tobacco use and anxiety also conferred an increased risk for chronic narcotic use in UC patients, as demonstrated in prior studies, but were not variables associated with FGID. While FGID did increase the risk for opioid misuse five-fold in our UC cohort, our numbers of patients meeting the definition of opioid misuse was small, and thus more associations may not have reached statistical significance.

Research perspectives

The insights gained from this study may provide the basis for practitioners to monitor opioid use in their UC cohorts, and potentially intervene when chronic opioid use and misuse are suspected. Furthermore, this study emphasizes that PMP databases are useful tools not only in the general population, but also in specific populations such as the IBD population. While this study was conducted at a tertiary referral center in the United States and a large number of patients were included, the results may not be generalizable to the US and worldwide, as this was a single-center study and the opioid epidemic has disproportionately affected some of the geographic areas (*e.g.*, Southwest Virginia) in which our patients reside. Future studies with a similar design and the inclusion of multiple sites may help to further define risk factors for chronic opioid use and misuse in the UC cohort. The data obtained from this study may, in the near future, also serve as a basis for quality improvement studies in which at-risk UC patients are identified and treated with alternatives for opioids in the appropriate situations.

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Ipilimumab and Nivolumab induced steroid-refractory colitis treated with infliximab: A case report

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Abstract

BACKGROUND

A variety of immune-modulating drugs are becoming increasingly used for various cancers. Despite increasing indications and improved efficacy, they are often associated with a wide variety of immune mediated adverse events including colitis that may be refractory to conventional therapy. Although these drugs are being more commonly used by Hematologists and Oncologists, there are still many gastroenterologists who are not familiar with the incidence and natural history of gastrointestinal immune-mediated side effects, as well as the role of infliximab in the management of this condition.

CASE SUMMARY

We report a case of a 63-year-old male with a history of metastatic renal cell carcinoma who presented to our hospital with severe diarrhea. The patient had received his third combination infusion of the anti-CTLA-4 monoclonal antibody Ipilimumab and the immune checkpoint inhibitor Nivolumab and developed severe watery non-bloody diarrhea the same day. He presented to the hospital where he was found to be severely dehydrated and in acute renal failure. An extensive workup was negative for infectious etiologies and he was initiated on high dose intravenous steroids. However, he continued to worsen. A colonoscopy was performed and revealed no endoscopic evidence of inflammation. Random biopsies for histology were obtained which showed mild colitis, and were negative for Cytomegalovirus and Herpes Simplex Virus. He was diagnosed with severe steroid-refractory colitis induced by Ipilimumab and

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Nivolumab and was initiated on Infliximab. He responded promptly to it and his diarrhea resolved the next day with progressive resolution of his renal impairment. On follow up his gastrointestinal side symptoms did not recur.

CONCLUSION

Given the increasing use of immune therapy in a variety of cancers, it is important for gastroenterologists to be familiar with their gastrointestinal side effects and comfortable with their management, including prescribing infliximab.

Key words: Colitis; Infliximab; Biologics; Immune mediated adverse events; Ipilimumab; Nivolumab; Case report

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Core tip: A variety of immune-modulating drugs are becoming increasingly used for various cancers. Despite increasing indications and improved efficacy, they are often associated with a wide variety of immune mediated adverse events. We report the first case of metastatic renal cell cancer treated with the anti-CTLA-4 monoclonal antibody Ipilimumab and the immune checkpoint inhibitor Nivolumab to develop severe steroid-refractory colitis, and describe its resolution after treatment with Infliximab.

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INTRODUCTION

A variety of immune-modulating drugs are becoming increasingly used for various cancers. Despite increasing indications and improved efficacy, they are often associated with a wide variety of immune mediated adverse events (IMAE), including gastrointestinal symptoms such as diarrhea, nausea and vomiting. We report a case of severe steroid-refractory colitis induced by the anti-CTLA-4 monoclonal antibody Ipilimumab and the immune checkpoint inhibitor Nivolumab in a patient with metastatic renal cell carcinoma, and its resolution after treatment with Infliximab.

CASE PRESENTATION

Chief complaints

A 63 year male diagnosed with metastatic renal cell carcinoma presents to the hospital with a several day history of diarrhea and fatigue.

History of present illness

The patient had received his third combination infusion of Ipilimumab and Nivolumab and developed severe watery non-bloody diarrhea the same day. He continued to have upwards of 10 watery bowel movements over the next week and ultimately presented to the hospital.

History of past illness

Past medical history included metastatic renal cell carcinoma, deep vein thrombosis of the lower extremity and hypertension.

Personal and family history

He had no significant family history of cancer or inflammatory bowel disease, and did not have a personal history of alcohol, tobacco, drug use or foreign travel.

Examinations

Physical examination revealed an ill-appearing man, with mild generalized

abdominal tenderness and tachycardia. He was found to be severely dehydrated, in acute renal failure (Creatinine 5.5 mg/dL) with a significant leukocytosis (WBC 20.4 $10^3/\mu\text{L}$) (Table 1). An extensive infectious workup for diarrhea was performed which was ultimately negative (Table 2). A computed tomography (CT) scan of the abdomen/pelvis was performed which revealed a moderate amount of liquid stool throughout the colon, greatest within the rectosigmoid colon.

A colonoscopy was obtained and revealed copious amounts of fluid and liquid stool, with over 2 liters of fluid suctioned out, but no endoscopic evidence of inflammation (Figure 1). Random biopsies for histology were obtained, as well as biopsies for cytomegalovirus and herpes simplex virus polymerase chain reaction (PCR) testing. His biopsies came back for mild colitis (Figure 2). His cytomegalovirus and herpes simplex virus PCR were also negative, as was testing for *C. difficile*, tuberculosis and hepatitis B.

FINAL DIAGNOSIS

The patient was diagnosed with immune-mediated colitis secondary to Ipilimumab and Nivolumab.

TREATMENT

On admission, the patient was started on broad spectrum antibiotics, intravenous (IV) fluids and electrolyte replenishment for his metabolic derangements. However given the temporal relationship between the onset of his symptoms and his immune treatment and the negative infectious workup, an immune-mediated colitis was suspected. His antibiotics were discontinued and the patient was started on high dose IV steroids. His renal function and leukocytosis improved but the diarrhea persisted. Ten days after receiving his treatment the gastroenterology service was consulted.

The patient had already been on high-dose steroids, diphenoxylate-atropine (Lomotil®), and loperamide without relief or resolution. He continued to have 5-10 large volume watery bowel movements a day, and was on continuous IV fluids, a bicarbonate drip as well as aggressive electrolyte replenishment. The patient was also initiated on a trial of mesalamine and subcutaneous octreotide injections with no improvement. After the colonoscopy was performed the patient was initiated on Infliximab 5 mg/kg.

OUTCOME AND FOLLOW-UP

After initiation of Infliximab, the patient noted improvement later the same day. The following day the patient had complete resolution of his diarrhea without any bowel movements. Over the next few days his renal function normalized and all medications were gradually discontinued. He was discharged with a steroid taper and instructed to follow up as an outpatient. On follow up in clinic his colitis had resolved, and he remained symptom free at 3 mo follow up.

DISCUSSION

Immune checkpoint inhibitors such as Ipilimumab, the CTLA-4 antibody, and Nivolumab, an anti-PD-1 antibody, have been increasingly used in cancers such as metastatic melanoma and renal cell carcinoma but have been associated with several IMAE, including a high incidence of diarrhea and colitis^[1]. Although more common in Ipilimumab than Nivolumab, the incidence of colitis is highest when these two drugs are used in combination^[2]. These side effects can be severe, and some patients may require the initiation of high dose intravenous steroids such as Methylprednisolone 2 mg/kg per day^[3]. However, up to 40% may not respond^[4], and many have used Infliximab for treatment of immune-mediated colitis in patients unresponsive to steroid therapy^[1-3,5-7]. Infliximab is thought to work in these cases by several mechanisms including opposing the activation of T cells by CTLA-4 antibodies by suppressing the pro-inflammatory cytokines IL-1 and IL-6^[8], enhancing FOXP3+ regulatory T cells^[9], as well as preventing tumor necrosis factor (TNF)-alpha from binding to its receptor, thereby preventing it from recruiting neutrophils to the site of inflammation in the colon^[10]. Abdominal CT imaging usually shows mesenteric vessel engorgement, bowel wall thickening, and fluid-filled colonic distention^[11]. In one

Table 1 Labs at admission

Items	Data
WBC	$20.39 \times 10^9/L$
Neutrophil	61%
Lymphocytes	6%
Monocytes	6%
Eosinophil	0%
Hemoglobin	9.9 mmol/L
Platelets	$335 \times 10^9/L$
RDW	20%
Sodium	132 mmol/L
Potassium	2.8 mmol/L
Chloride	92 mmol/L
CO ₂	7 mmol/L
Creatinine	486.2 μ mol/L
Calcium	2.3 mmol/L
Anion gap	33 mmol/L
Albumin	0.57 mmol/L
Phosphorous	3 mmol/L
AST	15 IU/L
ALT	26 IU/L
Total bilirubin	6.8 μ mol/L
Alkaline phosphatase	110 IU/L
Magnesium	1.1 mmol/L

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CO₂: Serum carbon dioxide; RDW: Red blood cell distribution width; WBC: White blood cell count.

study, endoscopy of patients who ultimately required Infliximab revealed ulceration in 59%, inflammation in 36% and no endoscopic evidence in 5%. Histological findings included chronic inflammation in 68% and acute inflammation in 27%^[4]. The grade of diarrhea has not been found to be associated with endoscopic or histologic findings^[4,6], and on follow up over a third of patients develop recurrent diarrhea^[4]. The median time of response to Infliximab is 2 d, and some patients may need more than one treatment^[6]. Caucasians and patients with melanoma seem to have a higher incidence of diarrhea and colitis^[5]. Studies have suggested better overall outcomes and survival in patients who develop IMAE^[5,12], and in the case of colitis this is thought to be in part secondary to distinct baseline gut microbiota^[13]. Although the use of Infliximab has become part of the treatment algorithm for immune-mediated colitis, the influence of a TNF-alpha on the progression of metastatic cancer is unclear, and further studies evaluating long-term effects are needed. To our knowledge this is the first case of renal cell carcinoma treated with both Ipilimumab and Nivolumab with resultant steroid refractory colitis that resolved with Infliximab. Given the increasing use of immune therapy in a variety of cancers, it is important for gastroenterologists to be familiar with their gastrointestinal side effects and management.

CONCLUSION

The incidence of immune-mediated colitis is higher when Nivolumab is used with Ipilimumab, and many patients may require high dose intravenous steroids for therapy. However, up to 40% of patients will not respond and will need to be initiated on infliximab. Gastroenterologists should be able to recognize adverse events related to novel immune therapy agents and be comfortable managing them, including prescribing anti-TNF-alpha inhibitors for immune-mediated colitis. Future studies are needed to evaluate the response to alternate biological agents, long term management of recurrent immune mediated colitis, and the role of TNF-alpha administration on the progression of metastatic cancer.

Table 2 Infectious workup

Infectious workup
Clostridium difficile toxin B gene DNA PCR
Salmonella, shigella/enteroinvasive <i>E coli</i> , campylobacter, shiga toxin 1/2 NAAT
Cryptosporidium stool antigen, giardia stool antigen
Ova and parasite
Yersinia enterocolitica culture
Vibrio stool culture
Stool cultures
Influenza/respiratory syncytial virus / rhinovirus/adenovirus/metapneumovirus
Blood and urine cultures
Cytomegalovirus colon biopsy DNA PCR
Herpes simplex virus 1/2 colon biopsy DNA PCR

NAAT: Nucleic acid amplification test; PCR: Polymerase chain reaction.



Figure 1 Colonoscopy revealing copious amounts of fluids and liquid stools in colon without endoscopic evidence of disease after removal.

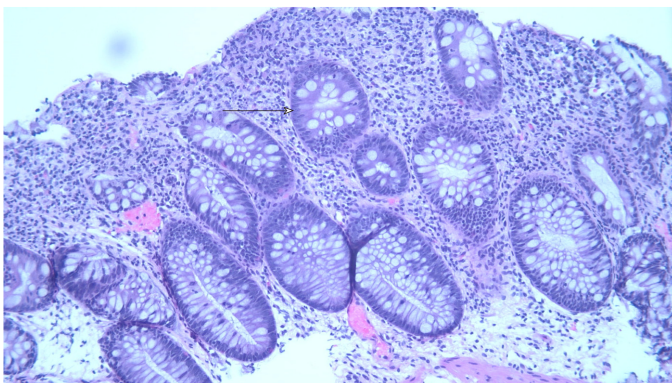


Figure 2 Mild active colitis with increased apoptotic bodies in crypts (arrowhead) and increased plasma cells in lamina propria (HE stain, × 100).

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