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Variceal Bleeding from Cirrhosis: A Clinical Review of Causes and Pharmacotherapy Options

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Variceal Bleeding from Cirrhosis: A Clinical Review of Causes and Pharmacotherapy Options

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Goal:

This home-study CPE activity has been developed to educate pharmacists on the prevention and treatment of hemorrhagic esophageal varices resulting from cirrhosis.

Objectives:

At the conclusion of this lesson, successful participants should be able to:

1. Explain which systemic complications are commonly seen in cirrhotic patients
2. Compare the mechanism of action of the medications used to prevent and treat hemorrhagic varices
3. Select an appropriate dose of medication for the prevention and treatment of hemorrhagic varices
4. Formulate an appropriate therapeutic regimen for a patient given the current state of the varices

Introduction:

Epidemiology and Etiology

Cirrhosis is an irreversible, chronic liver disease which affects slightly more than 100,000 individuals and caused 31,000 deaths in 2009.[1] This represents a 30% mortality rate, which is significantly higher than more prevalent disease states. The high rate of death due to cirrhosis indicates the importance of pharmacotherapeutic interventions, which can readily prevent complications and reduce mortality. Educating pharmacists on proper treatment options allows them make recommendations and ensure that patients are receiving optimal therapy based on the most current evidence available.

There are multiple etiologies of cirrhosis, including metabolic diseases, autoimmune diseases, and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. The most common causes, however, are chronic alcohol abuse (defined as two to three drinks per day for women, and three to four drinks per day for men) and chronic infection with Hepatitis B, C or D viruses.[2,3] In addition, certain medications can lead to cirrhosis due to hepatotoxicity, the most commonly used of which is acetaminophen.[4]

Pathophysiology

Cirrhosis is characterized histologically by the presence of fibrotic lesions in the liver. Due to chronic offense to the liver, inflammation and tissue injury persist. Abnormal wound healing leads to the replacement of normal hepatocytes with collagenous scar tissue, which can then be encapsulated by a fibrotic cap. Eventually, the fibrosis accumulates to such a degree that the scar tissue disrupts hepatic vasculature, compromising hepatic circulation and resulting in a reduction of liver function. Once hepatic circulation is compromised and vasculature is damaged, liver fibrosis is classified as cirrhosis. The end result of this excess fibrosis is poor liver function, increased intrahepatic resistance (leading to portal hypertension), and an increased risk for the development of hepatocellular carcinoma.[3,5]

Signs and Symptoms

Signs and symptoms of cirrhosis vary widely, depending on the degree of liver damage that has occurred. Typically, early damage shows few unique signs and symptoms, and as a result goes undetected and undiagnosed. Symptoms of nonspecific liver damage, which may present in the early stage of cirrhosis, include jaundice, bleeding and bruising, fatigue, and nausea.[3,6,7] As cirrhosis progresses, the signs and symptoms become progressively more serious. These systemic complications are often the reason a patient gets evaluated and diagnosed in the first place. Advanced cirrhotic patients present with the hallmark systemic complications described below.

In addition to the described signs and symptoms, certain lab findings are consistent with cirrhosis. In both the early and advanced stages of cirrhosis, a patient may present with elevated liver enzymes (with AST > ALT), elevated bilirubin, hypoalbunemia, thrombocytopenia, and leukopenia.[3,7] As with external signs and symptoms, these laboratory findings progress as the disease progresses, and may not become apparent until a patient has a more advanced case of the disease.

Systemic Complications

Stemming from the vascular changes and the resultant increase in intrahepatic resistance, cirrhosis results in systemic complications. These complications include: portal hypertension, esophageal varices, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, hepatorenal syndrome, and coagulopathies.

The primary complication, nearly universal among cirrhotic patients, is portal hypertension. It is defined as an increased resistance to hepatic circulation. Due to altered morphology of the liver caused by fibrosis, the liver is unable to efficiently circulate blood through the portal vein, hepatic sinusoids, and in hepatic venous outflow. Quantitatively, portal hypertension is defined as a pressure gradient between the portal and central veins of more than 5mmHg. This gradient is called the hepatic venous pressure gradient (HVPG).[3,5]

A primary consequence of portal hypertension is the development of varices. Due to an increase in portal resistance, blood flow backs up into the left gastric vein, which drains much of the blood leaving the esophagus. As a result of back-up, the left gastic vein and its tributaries become dilated. These swollen esophageal veins are called varices, which are prone to twisting and rupture, leading to internal hemorrhage. Qualitatively, hemorrhagic varices typically present as hematemesis and abdominal pain. Quantitatively, varices develop when the HVPG rises to 8 - 10mmHg. When the HVPG further rises to >12mmHg, these varices can rupture, resulting in variceal bleeding into the abdomen. Variceal bleeding occurs in up to 40% of cirrhotic patients, and has a 33% fatality rate.[3,5]

In addition to causing varices, portal hypertension results in ascites, which is the accumulation of fluid within the peritoneal cavity. Ascites occurs in approximately 50% of cirrhotic patients. It is a result of three factors: persistent water retention (due to a drop in arterial blood pressure), increased splanchnic vascular permeability (due to persistent

vasodilation as a result of intrahepatic resistance) and lymph leakage into the peritoneum.[3,5]

Another common, and often fatal, complication of cirrhosis is spontaneous bacterial peritonitis (SBP). In cirrhotic patients, enteric bacteria undergo bacterial translocation into abdominal lymph nodes. When cirrhotic patients become ascitic, these bacteria move along with lymphatic fluid into the peritoneum, resulting in SBP.[8] In the presence of ascites, patients are often treated prophylactically to prevent SBP. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend treating patients prophylactically for SBP when they present with hemorrhagic varices, as studies have shown that this reduces infectious complications and reduces mortality.[9,10]

Hepatic encephalopathy (HE) is the result of the liver's inability to process nitrogenous wastes, resulting in an increased ammonia load in the blood. These wastes can enter the CNS, altering neurotransmission and resulting in an altered mental status, typically confusion. While HE does not correlate directly with a specific blood ammonia level, treatments focus on removal of ammonia from the blood.[3]

As a result of splanchnic vasodilation, there is decreased renal blood flow, and thus, a decreased glomerular filtration rate. These factors present as hepatorenal syndrome, which is functional renal failure in the absence of renal disease. Hepatorenal syndrome occurs in about 20% of patients within 1 year of being diagnosed, and approximately 40% of patients after 5 years.[11]

The last commonly seen systemic complication of cirrhosis is a set of coagulopathies. Due to the fact that the liver is responsible for producing the proteins responsible for hemostasis, damage to the liver disrupts this delicate balance. Hemostatic substances, such as clotting factors and platelets, are decreased in cirrhotic patients. The net result of this hemostatic disruption is the development of bleeding, which results in an elevated prothrombin time.[3]

Classification of Cirrhosis and Varices

The Child-Pugh scoring system is a numerical measurement of the severity of a patient's cirrhosis. It takes into account whether the patient has ascites, the patient's bilirubin level, serum albumin, prothrombin time, and whether encephalopathy is present. Based on the patient's lab values and the severity of encephalopathy and ascites (if present), point values are assigned to each characteristic. The points are then added up, and the patient is then classified as Child A, B, or C, in order of increasing severity of cirrhosis. See Table 1 for the numerical scores assigned to each characteristic.[12] A Child A patient has a 100% 1-year survival rate, whereas a Child C patient only has a 40% 1-year survival rate.[3]

Table 1 – Child-Pugh Classification of Cirrhosis[10]

	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Tense (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.3-3.5	<2.8
PT (sec prolonged) or INR	<4	4-6	>6
	<1.7	1.7-2.3	>2.3

*5-6 points: Child A; 7-9 points: Child B; 10-15 points: Child C.

Table 2 – Primary Prophylaxis of Variceal Bleeding

	Child-Pugh Class A	Child-Pugh Class B or C
Small Varices	Annual upper endoscopy	Initiate NSBB therapy
Medium or Large Varices	N/A	Initiate NSBB therapy or treat with endoscopic ligation (EBL/EVL)

Varices are categorized based on their appearance and size. Per AASLD guidelines, varices should be classified into one of two categories: small or large. Small varices are those that are <5mm in diameter, while large varices are those that are >5mm in diameter. Some institutions utilize a three category classification based on morphological assessment. In these institutions, small varices are minimally elevated above the lumen, medium varices are torutous veins occupying less than one-third of the esophageal lumen, and large varices occupy more than one-third of the esophageal lumen. AASLD guidelines recommend treating medium varices the same as large varices.[10]

A combination of the Child-Pugh score and variceal categorization is used to determine the treatment for varices, as described below.

Variceal Management:

There are three main components to management of variceal hemorrhages: prevention of first incident of bleeding, treatment of acute variceal hemorrhages, and prevention of rebleeding. It is recommended that all patients undergo esophagogastroduodenoscopy (EGD) regularly to screen for the presences of varices. The AASLD guidelines recommends an EGD every three years if no diagnosis of varices is made upon initial examination. After a diagnosis of varices is made, preventive measures of variceal hemorrhages are dependent on the patient's Child-Pugh Score.[13]

Prevention of Variceal Hemmorhages

Patients with Small Varices

AASLD guidelines state that patients with small varices that have not bled who have a Child-Pugh score of B/C should use nonselective β-blockers (NSBB), such as propranolol or nadolol, for the prevention of a first variceal bleeding event. These agents can also be used for patients with no increased risk of bleeding but benefits are inconclusive.[13] NSBB can significantly reduce the risk of bleeding by reducing portal pressure by two mechanisms. These medications can decrease cardiac output by blocking adrenergic β1 receptors and reduce portal blood flow through splanchnic vasoconstriction by blocking adrenergic β2 receptors. For this reason, NSBB must be used over selective beta-blockers in the case of primary prophylaxis. According to the AASLD guidelines, propranolol 20 mg orally twice daily or nadolol 40 mg orally once daily can be given. Doses of these agents are titrated to decrease the heart rate 25% from baseline. However,

reducing heart rate has not been found to reduce HVPG so maximal tolerated doses are commonly used.[13,14] Heart rate and blood pressure should be monitored in patients on this medication. Patients should be cautioned against the side effects of NSBB which include, but are not limited to syncope, fatigue, dizziness and impotence.[15,16] Although direct comparison trials have not been completed with propranolol and nadolol, propranolol showed higher rates of side effects[13]. If patients are to discontinue their use of NSBB, the medication must be tapered over 2 weeks to avoid hypertension, acute tachycardia and/or ischemia.[15,16] Patients receiving beta-blockers do not require an EGD but those who are not should obtain an EGD every 2 years.[13]

Patients with Medium/Large Varices

AASLD guidelines state that patients with medium/large varices that have not bled (Child-Pugh score of B/C) should receive NSBB. The same recommendations can be considered in patients who are not at a high risk of bleeding. Propranolol 20mg orally twice daily or nadolol 40 mg orally once daily can also be given to patients who fall under this category. Monitoring parameters for safety and efficacy for these medications follow those described previously.[13] Endoscopic variceal ligation (EVL) can also be used for patients with medium/large varices and has showed a small, significant lower incidence of bleeding in comparison to NSBB use.[14] EVL involves the use of rubber bands attached to varices. After 48 - 72 hours, the varix will slough off and leave a mucosal ulceration that will heal. The procedure is repeated every 1 - 2 weeks until complete resolution of the varices.[17] Repeat examinations are also recommended in 1 - 3 months, then every 6 - 12 months. AASLD guidelines do not recommend the use of nitrates in the prevention of first event variceal hemorrhage. Nitrates, such as isosorbide mononitrate, are effective in comparison to NSBB but were found to increase mortality rates in a long-term follow up study. In addition, shunt therapy or sclerotherapy is also not recommended for use in primary prevention.[13]

Treatment of Variceal Hemmorhages

The treatment of cirrhosis includes resolving acute complications that arise from the condition and preventing further ones from occurring. Variceal hemorrhage is a dangerous complication of cirrhosis that warrants immediate treatment requiring general stabilization of the patient and controlling the bleeding.[3] According to the AASLD guidelines, the treatment of variceal hemorrhage include pharmacotherapy and endoscopic intervention. Drug therapy typically includes a vasoactive agent to assist in the reduction of bleeding and an antibiotic to prevent SBP. Endoscopic treatments such as sclerotherapy and variceal band litigation is also necessary to inhibit bleeding.[13]

Acute Management of Variceal Bleeding

Variceal hemorrhage requires intensive care and hemodynamic stability of airway, breathing and circulation of the patient. Goals of treatment include systolic blood pressure of 90-100 mmHg, heart rate less than 100 beats per minute, and a stabilization of blood volume for a target hemoglobin level of 7-8 g/dL. In addition, a transfusion of fresh frozen plasma and platelets can be given for severe coagulopathy or thrombocytopenia Excessive fluids are typically avoided to prevent complications of ascites. Recombinant factor VIIa is also not recommended.[3, 14]

Vasoactive Drug Therapy

Common vasoactive medications used for the treatment of variceal hemorrhages include octreotide and vasopressin.[3] Octreotide is a splachnic vasoconstrictor that assists in the reduction of portal blood flow and pressure. This agent works by inhibiting vasodilatory agents in the body with effects localized to the splanchnic vasculature, causing fewer side effects than vasopressin. Although octreotide is available as subcutaneous and intravenous injections, it is recommended to be used intravenously for this treatment. The recommended dose for the use of octreotide is a 50 mcg bolus followed by 50 mcg/hr continuous infusion. The guidelines recommend continuing the use of octreotide for 5 days after an incident of variceal hemorrhaging to prevent the reoccurrence of bleeding, since this complication commonly occurs 3 - 5 days after an initial incident.[13,14] Patients on octreotide should be monitored for safety for dyspnea, hypothyroidism, cardiovascular issues, GI disturbances and CNS changes. It should also be used in caution with patients currently on insulin therapy for hyper/hypoglycemia. Patients should also be educated on side effects of dyspepsia, flatulence, nausea, and headache.[18]

Vasopressin (also known as antidiuretic hormone) can also be used for the treatment of acute variceal hemorrhages. This agent is also a splachnic vasoconstrictor that causes a reduction of portal blood flow and pressure, however, unlike octreotide, vasopressin is a nonselective agent so its effects are not localized to the splanchnic vasculature bed. Because of its systemic effects, vasopressin can cause a reduction of cardiac output, heart rate and coronary blood flow which can cause further complications of myocardial infarction, arrthymias and other cardiovascular effects. The recommended dose for vasopressin is a 0.2 - 0.4 unit/minute (maximum of 0.8 unit/minute) by continuous infusion for a maximum of 24 hours. It must be administered along with intravenous nitroglycerin (40 – 400 mcg/minute adjusted to maintain SBP of over 90 mmHg) to reduce the risk of adverse events.[3,13,14] Serum and urine sodium, serum and urine osmolality, fluid input and output, blood pressure and heart rate should be monitored for safety in the use of vasopressin.[19] Common side effects of vasopressin include nausea, vomiting, vertigo and chest pains. The use of vasopressin is undesirable in comparison to octreotide due to its systemic side effects and risk for complications. Because of this, octreotide has been more commonly used for the treatment of acute variceal hemorrhage than vasopressin.[13]

Terlipressin, a common agent used in Europe, is a synthetic analogue of vasopressin. Although it is quite similar to vasopressin, it has a longer duration of action. More importantly, terlipressin has fewer side effects compared to vasopressin and has a lower risk for serious complications.[3]

Spontaneous bacterial peritonitis (SBP) is a serious complication that can arise due to an acute variceal hemorrhage. Active bleeding in patients can increase the risk of bacterial infections such as SBP. As described previously, enteric bacteria undergo bacterial translocation into abdominal lymph nodes which can lead to SBP. According to AASLD guidelines, all patients should receive

a short course of antibiotic therapy to reduce these risks. Antibiotic therapy can also prevent bleeding reoccurrences and decrease mortality in cirrhosis patients. Common pathogens of SBP include Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae, and Enterococcus species. Over 90% of these cases are monomicrobrial and most are caused by E. coli and Klebsiella sp.[3, 13, 20, 21] Norfloxacin 400mg BID can be used for oral administration of antibiotic prophylaxis to cover E. coli, K pneumonia, S. pneumonia over a course of 7 days maximum. Norfloxacin should be taken on an empty stomach either one hour before or two hours after meal. Adequate hydration is also recommended in norfloxacin use. Patients should be informed of common side effects including dizziness, lightheadedness, headache, nausea, vomiting and photosensitivity. Patients on norfloxacin should also be monitored for tendon inflammation or pain.[21] For prolonged therapy, CBC, renal and hepatic function must be monitored. If oral administration is contraindicated, ceftriaxone 1g/day or ciprofloxacin IV can be used.

Endoscopic Interventions

Endoscopy should be performed as soon as possible to inhibit active variceal bleeding. Although endoscopy is used to diagnose the variceal bleeding, it can also be used to assist in the inhibition of active hemorrhaging. EVL, as described above, can be completed in the event of active variceal hemorrhage and the procedure is repeated in 7 - 10 days to ensure complete resolution of the varices. Repeat examinations are also recommended in one month, then every three months, after the procedure.[13, 17]

Endoscopic sclerotherapy involves the injection of a sclerosing agent to cause thrombosis of varices and subsequently inhibit blood flow. There are many sclerosing agents that can be used and none have been proven to be superior over another agent. Commonly, 1 - 2 mL of 5% sodium morrhuate per injection for a total of 12 - 20 mL per session has been used. Ethanolamine is an alternative sclerosing agent using the same dosing regimen. In regard to endoscopic interventions, sclerotherapy has shown inferiority over EVL and should be used in the treatment of variceal hemorrhages. In comparison to EVL, endoscopic sclerotherapy can result in less control of the hemorrhage, higher risks of adverse events and higher risks for rebleeding occurrences.[3,13]

Alternative Treatments

In the case of failure from previous treatments, balloon tamponade can be used. Although this method can assist in the short-term treatment of variceal hemorrhage, it can lead to further complications and a high risk of rebleeding.[13] The Sengstaken-Blakemore tube, the Minnesota tube, and the Linton-Nachlas tube have been used to stop variceal bleeding. Surgery can also be used to control variceal bleeding in the failure of other treatments. Two types of procedures exist for surgical options: shunt and nonshunt procedures. A common surgical procedure for the treatment of variceal hemorrhage includes a transjugular intrahepatic portosystemic shunt (TIPS) which involves the widening of a portal vein branch and a hepatic vein stent with a cylindrical wire mesh. This allows the blood to bypass high pressure vessels which subsequently decreases pressure in the portal veins.[23]

Prevention of Rebleeding

In addition to treatment of an active variceal hemorrhage, it is also important to prevent bleeding reoccurrences in the future. Rebleeding can occur in 60% of patients within 1 - 2 years after an initial complication and holds a 33% mortality rate. Secondary prophylaxis does not have to be initiated in patients who have undergone shunt surgery for treatment. Patients with a Child-Pugh score equal to or greater than 7 should begin secondary prophylaxis for rebleeding.[3] According to AASLD guidelines, the best option for secondary prophylaxis includes a combination of NSBB and EVL. As in the prevention of first event bleeding, NSBB should be adjusted to a tolerated dose for each patient. Also similar to first prophylaxis, EVL should be repeated every 1 - 2 weeks. If EVL is contraindicated, the combination of NSBB and isosorbide mononitrate has shown slight benefits. Guidelines also state that TIPS can be considered in patients with a Child-Pugh Score of A or B who have experienced an acute variceal hemorrhage on multiple occasions. In the event of extreme situations and the failure of aforementioned treatments, liver transplant should be considered.[13,14]

Role of the Pharmacist and Conclusion:

In a community setting, pharmacists may deal with long-term management of cirrhosis and prevention of exacerbations. While the acute complications, such as variceal hemorrhage, can be fatal, proper long-term management of the disease state is essential to prevent those acute complications from occurring. Patients with cirrhosis may be on many medications concomitantly, and the pharmacist should always screen for drug-drug interactions. It would not be uncommon to see an advanced stage cirrhosis patient on a beta-blocker for variceal management, a loop diuretic for ascites prevention, and warfarin for coagulopathy management. When combined with medications for other disease states, it is easy to see where medication therapy management can have a large impact and optimize outcomes.

In an acute care setting, pharmacists can also have a large impact. The acute management of variceal hemorrhage is a complicated one involving many medications and procedures. The pharmacist can ensure that proper antibiotics are being selected, and assist in the management of adverse effects from the myriad medications that a patient will be on while in the hospital.

Overall, cirrhosis is a dangerous disease state with a high mortality rate. There are a host of systemic complications that can arise as a result, and the acute and chronic management of these complications are essential in improving quality of life and preventing morbidity and mortality. The most commonly seen complication is an acute variceal hemorrhage, which has a complicated, but well-defined treatment protocol involving vasoactive agents, beta-blockers, antimicrobials and surgical procedures. A last line-treatment option when complications cannot be managed is a liver transplant.

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Table 3 – Medication Summary for Cirrhosis Management

Medication	Dose	Monitoring Parameters	Side Effects
Prevention of Variceal Hemorrhage			
Propranolol	20 mg twice daily orally	heart rate, blood pressure	syncope, fatigue, dizziness
Nadolol	40 mg twice daily orally	heart rate, blood pressure	drowsiness, insomnia
Treatment of Variceal Hemorrhage			
Octreotide	50 mcg bolus followed by 50 mcg/hr continuous infusion for 2-5 days	dyspnea, hypothyroidism, cardiovascular issues, GI disturbances and CNS changes	nausea, headache, flatulence, dyspepsia
Vasopressin	0.2 - 0.4 unit/minute (maximum of 0.8 unit/minute) continuous infusion for a maximum of 24 hours	heart rate, blood pressure, serum and urine sodium, serum and urine osmolality, fluid input and output	nausea, vomitting, vertigo, chest pains
Prophylaxis of Spontaneous Bacterial Peritonitis			
Norfloxacin	400 mg twice daily orally	CBC, renal and hepatic function for prolonged therapy	dizziness, lightheadedness, headache, nausea, vomiting and photosensitivity