Esophageal Varices
Part I – Pathophysiology, Diagnostics, Conservative Treatment and Prevention of Bleeding

Abstract
Prevention of the development of esophageal varices is controversial and not fully documented. At the same time, variceal bleeding is the most dangerous complication of portal hypertension. It appears suddenly and presents as rapid, massive hematemesis and leads to hemovolemic shock if not properly treated. The direct cause is often hard to find. Varix rupture may be caused by local trauma or a sudden increase in portal pressure. Therefore it is critical to introduce proper treatment immediately. Cessation of bleeding and restoration of adequate blood volume is life-saving and prepares the patient for upper digestive tract endoscopy. Endoscopy performed immediately (or after controlling possible hypovolemic shock) allows location of the site of bleeding and rapid introduction of causative treatment (Adv Clin Exp Med 2008, 17, 3, 351–357).

Key words: portal hypertension, complication, treatment, prophylaxis.

Hematemesis and melena are often the first symptoms of bleeding from the upper digestive tract, i.e. the esophagus, stomach, or duodenum. Despite popular beliefs, these are not rare symptoms. Reports from intensive care units inform that they are the primary cause of admission in 10% of all cases [1]. The most common diagnosis is duodenal or stomach ulcer or hemorrhagic gastritis (including portal gastropathy) and esophageal varices (EVs). Non-steroid anti-inflammatory agents, especially when combined with corticosteroids, add additional bleeding risk. Most of these
bleedings do not cause significant medical consequences, but some may be life-threatening. Hematemesis and melena may or may not be present at the same time and do not provide enough information about the location or extent of the bleeding. Hematemesis can be observed even in duodenal bleeding, while the presence of blood in stool samples depends on the amount of blood reaching the small intestine (minimum: 50 ml). If intestinal passage is accelerated, it is even possible to detect fresh blood in the stool. Digestive tract bleeding may be simulated by bleeding from the upper respiratory tract (blood swallowed from the nasopharynx, nasal cavity, or pharynx). Distressed patients usually cannot provide useful information about the volume of vomit, and the blood almost always reaches the small intestine. Lack of symptoms of hypovolemic shock does not exclude the possibility of massive hemorrhage (over 30% of blood loss), and the patient’s condition may be quite good at the beginning. Locating the source of bleeding, assessing its intensity, and introducing appropriate treatment have significant impact on the patient’s life [2].

**Portal Hypertension (PH)**

The celiac system consists of: the superior mesenteric vein, which collects blood from the small intestine and the right part of the colon, the splenic vein, supplied by the inferior mesenteric vein that directs blood from the spleen, left part of the colon, and rectum, and the left gastric vein. These three vessels connect and create the portal vein (or portal system), optionally supplied by pancreatic or vesicular vessels. The portal vein has no valves and it drains blood into the liver, where the blood from the portal vein is mixed with that from the hepatic artery and drains further to the inferior vena cava. The system of these vessels usually differs in architecture. Normal portal pressure varies between 4–8 mm Hg. In case of an obstruction, when natural connections needed to sustain normal flow from the celiac system to the inferior vena cava become insufficient, the portal pressure increases greatly. Smith [3] classified PH into: pre-sinusoidal obstruction: a) extrahepatic (usually portal vein obstruction) and b) intrahepatic (such as schistosomatosis, bilharziosis); sinusoidal obstruction: Wilson’s disease, hepatic cirrhosis; extra-sinusoidal obstruction: a) intrahepatic (post-alcoholic cirrhosis), b) extrahepatic (Budd-Chiari syndrome), c) caused by cardiac dysfunctions (pericarditis, right ventricular insufficiency), d) caused by increased blood flow (arteriovenous fistulas).

The etiology of PH among adults in Europe and in the USA is dominated by chronic liver diseases, usually hepatic cirrhosis, with 90% of cases are caused by intrahepatic block. Over 50 years ago, Ludington [4] stated that in 92% of patients with Laennec’s cirrhosis, chronic (1–7 years) alcoholism was the primary cause. In children, obstruction of the portal vein is more common (pre-sinusoidal obstruction in ca. 10%), while extrahepatic block, which could cause obstruction of the hepatic veins due to thrombosis or external pressure (Budd-Chiari syndrome), is less common [5].

PH is not a separate disease entity, but a complex hemodynamic disorder. When it is present for a prolonged period of time it leads to the development of an extensive network of portosystemic collaterals. One of these collateral systems is through the vessels in the esophageal mucosa that collects blood from the left (coronal) gastric vein. The blood is later drained to theazygos and hemazygos veins and later to the superior vena cava. The submucosal vessels of the esophagus are surrounded by a small amount of perivascular tissue and do not have valves. These factors make them prone to increasing blood pressure, which leads to their dilation, called esophageal varices. The blood flow in the varices is bidirectional and changes with the breathing cycle due to the existence of perforating veins arising from the paraeosophageal veins [6].

Esophageal varices (EVs) are visible in endoscopic examination just under the esophageal mucosa and present as columns of various size and shape. They are usually purple-blue and may look like small lumps or long folds. Varices can usually be found in the lower parts of the esophagus, just above the cardia, but may reach to the aortic arch. The advancement of vascular changes can be classified by various scales describing the stages from the dilatation of “flat” vessels to large varices closing the lumen of the esophagus, covered by thinned mucosa with visible dilated submucosal veins (cherry-red spots) [7]. For simplification, the 40-year-old Conn classification is still used in publications concerning EVs [8]:

1. **Grade I** – visible only during one phase of respiration/performance of the Valsalva maneuver.
2. **Grade II** – visible during both phases of respiration.
3. **Grade III** – 3–6 mm.
4. **Grade IV** – varices – > 6 mm.

Every classification is used to monitor the results of introduced therapy. Since the effects of treatment are strongly dependent on liver functions, the Child-Pugh score (CPS) is very popular [9]. Despite many modifications, it always classifies the patients into one of three groups with low (I), medium (II), of high (III) perioperative mor-
tality risk. Group I describes patients who do not have significant liver dysfunctions and may not present any clinical symptoms. Group II classifies patients with clinically visible but not advanced hepatic insufficiency that usually increases during bleeding, infections, operative stress, or trauma. Group III consists of patients with persistent, significant, and heavy hepatic insufficiency and short life expectancy. CPS takes into account total level of bilirubin and serum albumins, the presence of hepatic encephalopathy, and ascites, most serious complications of chronic hepatic insufficiency besides bleeding from the EVs.

Encephalopathy is a neuropsychiatric group of symptoms of various extent. It may present as mild personality disorders or changes in the sleep/wake cycle to a coma or severe mental/intellectual disorders. Encephalopathy develops because some of the blood does not pass through the liver due to the presence of porto-systemic fistulas. This leads to insufficient detoxication of the blood from nitrous substances (ammonia) and its toxic influence on neural tissues [10]. The primary source of ammonia is the digestive process (bacterial digestion), occurring mostly in the colon. Many treatments were thus based on diminishing the amount of protein in the diet, use of antibiotics (neomycine) or laxatives, or changing the pH of the digestive system with lactulose [11].

Ascites, which develops in 50% of patients with portal hypertension in hepatic cirrhosis within 10 years, is caused of the decompensation of liver functions. The clinical condition of patients with ascites is usually poor and only half of them have a life expectancies of over two years [12]. High pressure in the sinusoids and low oncotic pressure caused by the loss of serum albumins allow the fluids to enter the perisinusoidal space (Disse’s spaces), between the hepatocyte and a sinusoid. The overproduction of lymph in the liver makes its drainage through the thoracic duct impossible. The excessive fluid leaks through the liver capsule and accumulates in the peritoneal cavity. In most cases, ascites can be treated with diuretics; the drug of choice is usually spironolactonum (Spironol, Aldacton). If pharmacological treatment is not sufficient, repeated paracentesis or persistent peritoneovenous drainage with Le Venn’s shunt is applied. As these procedures lead to significant loss of albumins and may create a risk of infection, they are less commonly used [13].

Besides primary disorders and ulceration of the duodenal and gastric mucosa, the most common cause of digestive tract bleeding are EVs. They develop in about 50% of patients with hepatic cirrhosis, and 30% of them present with bleeding within two years from the time of diagnosis. One in seven incidents of bleeding ends in the patient’s death, and 50% of untreated adults die within one year after the first bleeding episode [14, 15]. It is necessary to add that only 10% of bleedings from EVs occur in patients with a healthy liver [16]. For 70% of the patients the first bleeding is not the last, and it returns in a couple of months.

In children, where half of the patients present with normal liver structure and function, the risk of bleeding is associated mostly with PH and varies between 22% (hepatic cirrhosis) to 80% (portal vein occlusion). It also seems that children tolerate bleeding better than adults. Massive, life-threatening bleeding occurs less often, and only about 8% of children die within six weeks from the first incident [17]. Significantly less common than EVs are varices penetrating the stomach. The locations of the esophageal and gastric varices (GVs) in the wall of the digestive tract is the main difference between them. GVs are located more deeply, under thicker mucosa. This may explain why bleeding from GVs occurs less frequently, but when it happens it is usually more dangerous and harder to stop [18].

While the mechanism of EV development is well described, the direct cause of the bleeding is often hard to find. Pressure in the portal vein is not the only factor. Tripathi et al. [19] observed recently that 8% of patients with EV bleeding had low (< 12 mm Hg) pressure in the portal vein. One can risk the statement that if esophageal venous vessels (the most critical factor in the whole pathology of portal hypertension) were located deeply enough, the problem of EV bleeding would not exist. Of the many factors that cause the rupture of EVs, the most often mentioned are trauma to the varices by food particles, inflammation caused by gastro-esophageal reflux, and a sudden increase in pressure in the vessels (coughing, vomiting, defecation, physical exercise). EV bleeding usually occurs suddenly and presents as sudden hematemesis and leads to hypovolemic shock if untreated [18]. Thus all patients with suspected EV bleeding must be hospitalized, preferably in intensive care units. Treatment should be provided in specialized hospitals with access to various treatment methods. Since every EV bleeding event is a life-threatening situation, treatment must be introduced as soon as possible and should cover three basic steps: 1) treatment of hypovolemia, 2) localization and termination of bleeding, and 3) preventing recurrence of bleeding.

### Diagnostic Methods and Nonsurgical Treatment

The first part of treating EV bleeding is providing typical life support procedures: blood transfusions or blood substitutes, substitution of elec-
trolytes, and recovery of acid-base homeostasis. Securing the airways often requires intubation. Most patients with EV bleeding also present with hepatic cirrhosis and require intensive treatment of coagulation disorders, substitution of proteins, and hepatic encephalopathy prophylaxis. It is often necessary to provide plasma coagulation factors (V, VIII, IX, X). As the amount of replaced blood or blood-based products increases (greater number of donors) the risk of post-transfusion complications increases. The symptoms often do not correlate with the extent and/or duration of the bleeding. Unmonitored transfusion may lead to increased portal pressure and induce secondary bleedings [20]. Pharmacotherapy provides a chance to reduce the amount of blood and blood-based product transfusions. The optimal moment for endoscopy is when the hypovolemic shock has been brought under control. Diagnostic endoscopy of the esophagus, stomach, and duodenum is mandatory in every single incident of upper digestive tract bleeding. It is the fastest diagnostic tool that provides information about the location of the bleeding, it is well tolerated by patients, and provides over 90% of correct diagnoses. The risk of the patients’ life is low (0.59%) [18]. Before endoscopy became a routine evaluation, almost 50% of bleeding sites were not properly identified and almost 30% of patients with PH bleed occasionally from other sources. Removing the blood in the stomach not only increases visibility, but also reduces the risk of developing encephalopathy in patients with hepatic cirrhosis [21]. During diagnostic endoscopy, endoscopic treatment should also be implemented. If the bleeding is unexpected and extensive, and the patient’s condition is poor, the diagnostic and therapeutic possibilities are sometimes limited. Even an experienced endoscopist may have difficulty in localizing the bleeding spots or determining its cause.

When assessing the risk of bleeding, two other diagnostic tools play an important role: Doppler ultrasonography and echoendoscopy. Color Doppler ultrasound (CDU) allows one to determine the diameter, speed, and direction of blood flow in the portal vein and also determines the presence of occlusive material (thrombus) in the portal system. CDU can also be used to determine the direction of blood flow in the left gastric vein; when reversed, it is often accompanied by varices of the gastric fundus [22]. In only ca. 5% of all cases can varices of the gastric fundus be found alone, without accompanying EVs (usually caused by portal thrombosis secondary to pancreatic disorders). In these cases the flow in the left gastric vein is not reversed and the bleeding risk is low. It has been demonstrated that a speed of reverse blood flow in the left gastric vein greater than 15 cm/s is associated with large EVs and a higher risk of bleeding. The sensitivity of classic endoscopic ultrasound sonography (EUS) in diagnosing varices of the gastric fundus is twice as high as that of endoscopic evaluation, but only half as sensitive in diagnosing EVs. The lower sensitivity of EUS in the detection of EVs is due to two factors. First, the frequency used in classic US varies between 7.5–12 MHz and their focus falls past the varices. Second, filling the balloon with water compresses the varices and results in their disappearance or severe diminishment [23]. High-resolution ultrasound (20 MHz) introduced thorough the nose or a gastroscope allows the visualization of varices without the necessity of filling the balloon. This method proved to be more sensitive and additionally allows one to access the size, diameter, and thickness of the varix walls as well as calculate their cross-sectional area [24].

Three methods are available for measuring the pressure inside the varices; their value is a sensitive indicator of bleeding risk. The first method is based on measuring intraesophageal pressure during relaxation and after filling a balloon and compressing the varices. The difference usually correlates with intravariceal pressure. The second method is a modification on the first, but the balloon is filled under EUS control until the flow in the varices stops. The third method measures the pressure inside the varices during the formation of the peristaltic wave caused by swallowing water, and the pressure is measured at the moment of their depression [23]. Another way to assess bleeding risk is to determine the total cross-sectional area of the varices in the distal parts of the esophagus. Miller et al. [25] concluded that an increase in variceal cross-sectional area of 1 cm² increases the risk of bleeding 75 times in one year. An advantage of echoendoscopy is the possibility to visualize periesophageal varices. These are present in almost all patients with PH and are joined with perforating veins. The presence of large periesophageal varices correlates with the risk of recurrent EV bleeding after endoscopic treatment (sclerotherapy and ligation). EUS combined with CDU during treatment may be used to control the efficacy of therapy by confirming diminished flow in the varices and perforating vessels. It may reduce the number of planned and performed procedures.

In situations where endoscopic examination and treatment cannot be accomplished and locating the bleeding site is not precise, gastroesophageal tubes (Sengstaken-Blakmore, Linton-Nachlas, IA, USA) may have a deciding impact on the patient’s life. Using tubes is considered an emergency method, it does not provide patients...
acceptable comfort, and their placement is technically difficult. Pressure in the balloons should not be higher than 40 mm Hg and should be lowered every 2–4 hours for 10–15 minutes. Using inflated balloons for over 12 hours is considered dangerous. They may cause aspiration pneumonia, cardiorespiratory insufficiency, or ulceration or necrosis of the esophageal mucosa. Long-term complications include paraesophageal hiatal hernia, esophageal constrictions, and adhesion [26].

Celiac blood circulation and pressure levels in the portal system can be controlled with many pharmacological agents: alpha- and beta-blockers (clonidine, propranolol), nitroglycerine, calcium channel blockers (nifedipine), somatostatin and its analogue (octreotide), anti-diuretic hormone (ADH) and its analogues (terlipressin), and prostaglandin inhibitors [27, 28]. The efficacy of balloon tamponade (50–70%) increases with application of ADH by secondary, selective reduction of blood flow in the portal system. Lowering the pressure makes it easier to stop the bleeding. Unfortunately, the therapeutic effect of ADH is sustained for only about 1 hour, and every subsequent dose is less effective than the previous. It also has several side effects, such as ischemia of the extremities, necrosis at the site of drug delivery, and cardiac and CNS ischemia. It is also contraindicated for elderly patients and people with coronary heart disease. To prevent the side effects, ADH is often followed by chloralhydrate, which reduces the hemodynamic effect of ADH, or sodium nitroprusside [29]. The synthetic analogue of ADH (terlipressin) acts faster, has fewer side effects, and can be administered in a single dose [36]. In adults, somatostatin is also commonly used in substitution for ADH (it also reduces celiac blood-flow) [30, 31]. Somatostatin and octreotide reduce pressure in the portal vein [32].

They are safe to use and do not have many side effects. Jenkins et al. [33] compared the efficacy of somatostatin and ADH in controlling EV bleeding (87% and 74% at the beginning, 67% and 68% after 24 hours, and 53% and 58% after 48 hours). It has also been shown that metoclopramide (by causing contraction of the lower esophageal sphincter) may be useful in controlling EV bleeding [34]. It is also recommended to administer antibiotics (i.v.) after confirmation of bleeding from EVs, usually cephalosporin or quinolones, since they reduce the number of associated pneumonia or peritonitis [35].

In 1980, Lebrec showed that in patients with hepatic cirrhosis and advanced EV, non-selective beta-blockers significantly reduce the risk of bleeding [36]. These agents diminish the size of varices, have positive chronotropic and inotropic effect on the heart muscle, and therefore reduce the blood flow in the portal system [37]. Oral dose of 80–160 mg of propranolol after several hours reduces the pressure in the portal vein by 12% and reduces the flow through the collaterals and azygos vein as well as total hepatic blood flow. Therefore, beta-blockers may be used in the chronic reduction of PH, and when introduced early enough are more effective in preventing first episode of bleeding than in recurrent bleedings [36, 38]. This method, although it may require life-long treatment, is cost-effective and safe, especially when well-controlled optimal doses of medication are administered. There is a problem with patients who do not tolerate beta-blockers well enough due to their side effects (hypotension, headaches, vertigo) or with alcoholics who refuse to cooperate. There are also not sufficient data regarding the use of propranolol in children with PH and it is therefore not recommended [39].

The precise dosage of propranolol that reduces the heart rate by 25% is very difficult to determine in children, mostly due to their highly variable physical activity during the day. It is also contraindicated in children with cystic fibrosis. Molsidomine in a single 4-mg dose can also be used. It dilates celiac vessels and slows blood flow in the portal vein by 25% [40]. Chronic therapy with beta-blockers has a strong position in the treatment and prophylaxis of EV bleeding. Medications influencing the hemodynamic of the digestive system are also important factors in the treatment of EV bleeding.

Conservative treatment often saves the
patient’s life, allows for recovery from shock and the localization of the bleeding site, and prepares for invasive treatment. Reduction of bleeding gives enough time to transport the patient to a better-equipped specialized hospital. However, complete eradication of EVs can only be achieved by surgical treatment.

References

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