REVIEWS

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Esophageal Varices
Part II – Invasive Methods of Treatment and Prophylaxis of Variceal Bleeding

Żylaki przełyku
Część II – Inwazyjne metody leczenia i zapobiegania krwawieniom

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Abstract

Portal hypertension (PH) is not a distinct disease, but a complex syndrome of hemodynamic disturbances. When hypertension persists for a long period, collateral circulation develops in the area of communication between the portal blood and the drainage basin of the superior or inferior caval vein. One of a dozen or so of the described anastomoses is the way through the submucosal plexus of the esophagus. The overloaded plexus become gradually wider and may transform into irregular varices. In controlling variceal bleeding, two endoscopic methods are usually used. Sclerotherapy (EVS) requires the use of strongly irritating agents, which causes a high risk of local and general complications. The other method, esophageal varix ligation (EVL), was introduced with the hope of achieving similar effectiveness without the mentioned dangers. The classical surgical methods include shunt and non-shunt operations and the transjugular intrahepatic portal-systemic stent-shunt (TIPSS). Total EV eradication is sometimes possible only after liver transplantation (LT) (**Adv Clin Exp Med 2008, 17, 3, 359–367**).

Key words: portal hypertension, complications, endoscopic treatment, surgical treatment.

Streszczenie

Po dłuższym czasie, w następstwie nadciśnienia wrotnego, rozwija się krążenie oboczne. Jednym z wielu połączeń powstających między dorzeczem krwi wrotnej i żyły czczej górnej lub dolnej jest podśluzówkowy splot przełyku, który przeładowany łatwo się rozszerza, tworząc tzw. żylaki. Do opanowywania i zapobiegania krwawieniom z żylaków przełyku najczęściej stosuje się dwie metody endoskopowe. Pierwsza z nich – skleroterapia wymaga użycia silnie drażniących preparatów, co jest obarczone wysokim ryzykiem komplikacji miejscowych i ogólnych. Drugą – podwiązywanie żylaków – wprowadzono w nadziei, że może być równie skuteczna, a pozbawiona tych niebezpieczeństw. W klasycznym postępowaniu chirurgicznym stosuje się najczęściej tzw. zespolenia omijające, operacje nieomijające i zaliczane często do radiologii interwencyjnej przezskórne, przeszyjne wewnątrzwątrobowe zespolenie wrotno-czcze – *transjugular intrahepatic portal-systemic stent–shunt*. Pełną, przyczynową eradykację choroby umożliwia jednak najczęściej dopiero przeszczep wątroby (**Adv Clin Exp Med 2008, 17, 3, 359–367**).

Słowa kluczowe: nadciśnienie wrotne, powikłania, metody endoskopowe, leczenie chirurgiczne.

# Endoscopic Methods for the Prophylaxis and Treatment of EVs

Sclerotherapy was started in 1871 by the American physician Mitchell, who injected carbolic acid (phenol) into hemorrhoid varices. This new, safe, and easy method spread very quickly, especially because the author was selling his secrets even to people without any medical qualifications. A glycerin-based carbolic solution was commonly used until 1928, when Morley used 5% phenol diluted in plantar oil. This date is considered to be

the beginning of modern sclerotherapy. It was quickly adopted in situations where the creation of connective fibrous tissue was especially desired. At the end of the 20th century, sclerotherapy was commonly used also in the treatment of such conditions as hernias, condylomatosis, and the obliteration of esophageal, gastric, and spermatic cord varices. Today, obliterative (sclerosing) agents can be classified into five groups: 1) alcohol, 2) water solutions, such as of morrhuate sodium and sodium linoleate (e.g. Varicocid), 3) synthetic agents, such as sodium tetradecyl sulfate (e.g. Sotradecol), 4) paraffin-based agents (e.g. Dondren), and 5) others (50% dextrose, phenol). Alcohol (inexpensive and commonly available) works by denaturing albumins in the tissue. Other "obliterants" induce inflammatory/necrotic processes or lead to local thrombosis. Despite the wide range and variety of obliterating agents, there is still a strong need to find the most effective substance with the optimal thrombotic properties and minimal induction of inflammation and necrosis [1].

Endoscopic Variceal Sclerotherapy (EVS)

EVS was first introduced by Crafoord and Frenckner in 1939 [2]. A series of intravariceal injections of quinine-urethane compound was the result of a long search for the simplest and minimally invasive procedure that would provide efficient termination of bleeding. The new method of treating bleeding from EVs became very popular in the 1940s and '50s [3]. The poor quality of endoscopes at that time meant that therapeutic results were not immediately promising. The procedure was carried out by injecting into the dilated varices, or in their close proximity, irritating agents that worked as a tamponade by stopping blood flow in the esophageal veins [4]. Autopsies of patients who died during or after EVS led to the conclusion that this method can also be performed in prophylaxis of recurrent bleeding. After the injection of obliterative agents, a connective tissue was formed in the esophageal walls and perivascular fibrosis together with thickening of the internal mucosa reduced the risk of variceal perforation (either from trauma or increased blood pressure). Cicathrical changes led to the creation of secondary collateral vascularization which bypassed the esophageal veins and could possibly permanently prevent recurrent bleedings. The injection of the obliterating substance not directly into the varix but in its proximity resulted in inflammation followed by thickening of the variceal walls and fibrous changes in adjacent varices, thus increasing the risk of ulceration. Based on these observa-
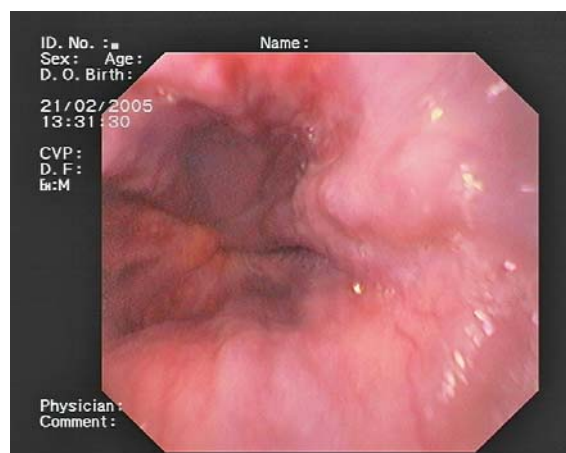
Fig 1. Columns of varices visible in the lumen of a flexible fiberoscope

Ryc. 1. Kolumny żylaków widoczne w świetle giętkiego gastrofiberoskopu

tions, EVS was accepted at the end of the 1970s as the eradicative treatment [5]. A mixed technique (combined application of obliterating substance into the variceal lumen and in proximal tissues) is now the most popular [6].

Twenty years later the idea arose that if EVS protects patients from a recurrence of EV bleeding, it might prevent the first one as well. Many endoscopists could not accept the "watch and wait" strategy. In addition, establishing control groups with a placebo seemed unethical in life-threatening situations. Prophylactic EVS was introduced in various groups of patients in different stages of the disease, without taking into account the side effects of the obliterants. Assessment of its efficacy is therefore not easily measurable. A three-year observation by Miyoshi et al. [7] showed that it is actually possible to reduce the risk of bleeding and decrease mortality of patients with EVs significantly. The possibility to prevent the first bleeding episode was also confirmed by Goncalves et al. [8]; EVS allowed eradication of 94% of EVs. In 36 months only 6% of patients developed EV bleeding in comparison with 42% in the control group. EVS was initially performed with the use of a rigid esophagoscope; later, fiber optics came into use. Rigid endoscopes allowed using stronger suction instruments and compressing bleeding sites with the steel pipe. At the other hand, the risk of esophageal perforation was higher. General anesthesia was also often necessary. Using flexible fiber optics is technically easier and allows better visualization of the operating field. Rigid endoscopy was advised for stopping unexpected sudden bleedings, and flexible endoscopes were recommended for planned operations. Nowadays, flexible endoscopy is the method of choice in every case of EV bleeding.

The maximum dose of obliterant used in one sessions of EVS is not precisely defined. It usually does not exceed 20 ml in adults and 10 ml in children when injected into the variceal lumen. Smaller amounts are usually used when injecting obliterants into submucosal layers since ulceration develops more easily in the perivariceal spaces. EVS can be also performed when the bleeding site cannot be visualized. For total obliteration it is usually necessary to do 3–5 injections, maintaining a 2–3 week break between them. If the break between sessions is shorter, the operator often finds open ulcerations. A longer break increases the risk of recurrent bleeding. Results of research show that it is not necessary to perform multiple injections of the same vessel [9]. After EV eradication, the patient should be observed on an outpatient basis every 3–6 months after the EVS and later once a year. Every confirmation of EV recurrence requires surgical treatment.

When considering EVS, it is necessary to mention the possible complications of this method, i.e. superficial ulceration of the esophageal mucosa (93% of all cases, currently considered more as a side-effect than a complication), a slight increase in body temperature, dysphagia and retrosternal pain. Bacteremia has been observed in patients after EVS. Bacterial infections develop within two days of the bleeding in over 20% of patients and are a poor prognostic factor. The risk of infection is greatly decreased when EVS is performed under antibiotic cover [10]. Dysphagia is caused by scars forming on the esophageal walls in 30% of all patients and may be eliminated by their careful dilatation. Severe complications (with the possibility of patient's death) include deep ulcerations of the esophageal walls; constriction, necrosis, or perforation of the esophageal walls (with impaired peristaltics) or the trachea; mediastinitis, pneumonia, or pleuritis; esophageal cancer; and pulmonary or brain abscess [11]. The number of these complications correlates with the large amounts of obliterative agents used during EVS. Therefore their number can be controlled by limiting the use of obliterants to the absolutely necessary amounts. Their penetration can be controlled by adding radiological contrast medium or fluorescent markers [12]. The risk of hemorrhagic gastritis was observed and 10–15% of patients who develop gastric varices (GVs) (which are rarely diagnosed as an isolated disease) [13]. EV eradication can shift increased portal pressure to submucosal gastric veins. Therapy should be considered, but introduced six months later, if GVs are still present. EVS may cause the obliteration of GVs due to the flow of obliterants to gastric vessels [14]. Complications related to the introduction of obliterative agents are not very common and they never limit indications for EVS. Patient mortality never exceeded 5% when using this method [15]. Terblanche et al. [16] defined unsuccessful EVS as recurrence of bleeding after two sessions during the same hospitalization. In 30% of cases, bleeding may recur after completion of treatment. Long-term clinical observations allowed defining the most common causes of failure, i.e. large varices, failure to cease alcohol consumption by patients, unrepeated sessions of EVS, and simultaneous treatment with non-steroid anti-inflammatory agents.

Endoscopic Variceal Ligation (EVL)

For over 50 years, EVS was the only low-invasive method of controlling bleeding and managing EVs. In 1985, Swain et al. [17] described a new procedure based on an animal model involving the use of rubber bands placed on the varices. This technique had been previously successfully introduced in the treatment of hemorrhoid varices. EVL was used in the treatment of EVs with the hope that it would be equally effective and would lack the side effects of EVS. Alternatively to rubber bands, metal mini-loops and clips are used for varices larger than 2 cm in diameter [18]. Varices which have been retracted and isolated from the columns by the mechanical bands are prone to necrosis and separate "automatically". Bleeding is insignificant and the ulceration is shallower and cures faster in comparison to EVS. Newly formed scars strengthen the esophageal walls as well. Less traumatization and the limited area of cicatrisation mean that minor, temporary side effects, such as retrosternal pain dysphagia, are rarely observed. Bacteremia is also much less common compared with EVS. Esophageal functions are almost never impaired and life-threatening complications of EVL now occur in less than 1% of cases.

After the introduction of this technique it was believed that the device used for ligation at the end of the endoscope and the previously applied bands may limit the field of view and make the localization of bleeding sites more difficult or impossible. These fears were overrated; applying several bands in the cardia reduces blood flow and actually makes applying more bands easier and more precise without the threat of removing those previously placed. At the beginning, mechanical ligation was believed to be more complicated and more traumatizing to the esophageal walls. This was because of the necessity to introduce the esophagoscope repeatedly to place each band. In the next few years Japanese and American authors found a solution to this problem. The construction of new devices that allowed applying several

bands during one induction of the esophagoscope made the mechanical method much easier, faster, and safer [19].

Long-term clinical observations confirmed the value and advantages of EVL over EVS. Full eradication of EVs requires fewer procedures and the patient survival rate is significantly higher. Lo et al. [20] compared the results of both methods in stopping EV bleeding in 71 patients. Full hemostasis was achieved in 97% of cases treated with EVL and 76% with EVS. Recurrent bleeding in the 4-week period was observed in 17% and 33%, respectively. EVL is believed to be the method of choice since it seems to be more effective than EVS when treating the first episode of bleeding. Nowadays, indications for EVS are limited to certain circumstances: 1) there is no access to EVL, 2) there is no possibility to introduce the banding device past the first esophageal isthmus (usually in children below 2 years of age), 3) varices are still present after several sessions of EVL, but are too small to be sucked into the banding device with adjacent mucosa, and 4) theoretically, the obliteration of perforating veins may prevent recurrent bleeding.

Although faster (2–4 sessions) and resulting in fewer complications, the use of EVL has proven to be related to a higher number of recurrences. This is explained by the fact that bands are too superficial to fully obliterate perforating vessels. Therefore a combined (adjuvant) method of scleroligation (EVSL) was introduced. Some authors combined EVL and EVS during the same session, while others used EVS to eliminate remaining varices after EVL. The obliterant was applied into the variceal lumen and in its proximity. A surprisingly small amount of recurrence was observed with EVSL and such treatment proved to be more effective than either of the methods used separately. Recurrent bleeding occurred three times less frequently [20]. Of course, all the complications of both methods were still present.

When all other methods fail, massive life-threatening bleedings from EVs are sometimes controlled with thrombin or special tissue glues [21, 22]. These substances do not induce inflammation or fibrosis of venous walls. Cyanoacrylates (n-butyl-2-cyanoacrylate, Bucrylate) are quickly hardening substances that rapidly polymerize when exposed to blood. After cyanoacrylate injection, ulceration is a natural consequence of compression by the hardened glue. Bleeding of the ulceration from this time may occur only if the varix was not completely closed. Tissue glue has been used together with endoscopic methods. Thaked et al. [23] compared the efficacy of simultaneous treatment with Histoacrylate and etholamine oleate compared with the sclerosing agent alone. Combined treatment resulted in four times less frequent recurrence of bleedings. Binmoeller et al. [24] showed promising results of treatment with combinations of three methods. After EVSL the authors used Histoacrylate injected in gastric fundus varices. The procedure was based on the fact that treatment of EVs increases the risk of bleeding from GVs.

Although it seems that the use of classical EVS in EV treatment is fading, this method is still technically easier to perform and does not require specialized equipment. In situations of life-threatening bleeding it can be used by anyone. even by a not very experienced surgeon. It is also well documented that EVL allows for faster EV eradication, but the recurrence rate after EVL is higher. The injection of small amounts of obliterative substances in the area of the remaining varices after mechanical ligation is easy and does not cause complications, allowing for full EV eradication.

Surgical Treatment

It is necessary to note that classical surgical procedures in the treatment of portal hypertension were used before the era of sclerotherapy. Surgical procedures that seemed to have been eliminated in the 1970s actually never disappeared from surgical wards. Almost 90% efficacy of endoscopic treatment and EV bleeding prophylaxis left a margin where surgical treatment may be necessary. Surgical treatment of EV bleeding was and may still be carried out on several levels at the same time, starting from sudden, life-saving intervention to causative treatment. Surgical treatment may be classified in two groups: bypassing shunts and non-shunt surgery.

Bypassing Shunts

This technique tries to mimic the natural processes of creating collateral circulation. Reduced flow in the portal system is possible with every surgical procedure that creates a connection of the portal system with systemic vessels (portosystemic shunt). These shunts may be performed as end-to-end, end-to-side, or side-to-side techniques. According to the type of junction created, they can be divided into total, selective, and partial shunts, which basically differ in the amount of blood they drain from the portal system. The first experiences with shunts in the treatment of PH appeared over 60 years ago. In 1943 such connections between splenic and renal veins, and later the

hepatical vein and superior vena cava, were made in the USA [25]. In the beginning of portal system surgery it was believed that junctions of vessels smaller than 8–10 mm in diameter (i.e. children younger than 8–10 years of age) do not allow provide sufficient long-term reliability due to their frequent clothing. Thus shunts with time become insufficient and recurrent bleedings occurred. This notion became less important with the development of operative techniques. In 1980, Bismuth et al. [26] reported successful results of the treatment of 90 children (the youngest was only 18 months old). Still the group with the highest risk consists of patients with hepatic cirrhosis and portal thrombosis. Coexistence of those pathologies ("double block") occurs in 10–25% of patients. Recurrent bleeding and mortality in this group is almost three times higher than in patients with a single etiologic factor [27].

Many bypassing techniques have been developed. The most popular are the end-to-end or end-to-side porto-caval shunt (PC), meso-caval and porto-caval (MC and PC), interpositional shunt with H-grafts, central spleno-renal shunt (with splenectomy, CSRS) and distant spleno-renal shunt (without splenectomy, DSRS, Warren's operation). Every PC shunt may be nonselective (reverse direction of portal blood flow to the systemic circulation), bypassing the liver, or selective (Warren's method, and modifications), draining the varices into the systemic circulation without influencing blood flow though the liver (smaller risk of encephalopathy). From the hemodynamic point of view, total shunts should be performed in cases of reversed portal flow. When the portal blood flow retains its proper direction (to the liver), such methods significantly impair portal flow and increase symptoms of hepatic insufficiency. Therefore, selective shunts are recommended in such cases [28].

It is difficult to compare these solutions because patients' qualification criteria are different as are the possible techniques used by surgeons and as well as postoperative care. Furthermore, the results of the treatment depend on the severity of hepatical dysfunction. However, Warren's operation now has a special place in the surgical treatment of portal hypertension. The first promising results of selective spleno-renal shunts were presented by the author in 1967 [29]. Long-term results of treatment of PH caused by hepatic cirrhosis were also significantly better than those achieved with other techniques. Since splenectomy is not performed in DSRS (Warren's operation), this technique is considered to be a method of choice in cases of unsuccessful endoscopic treatment and in patients not qualified for liver

transplantation (LT). MC shunts with the use of the H-type prosthesis (the selective spleno-renal shunt is performed at a safe distant from the liver) may be easily closed and does not present any additional technical difficulties during transplantation. Neither procedure instantly lowers portal pressure, but leads to its progressive diminishing. Therefore the vanishing of varices is similarly slow.

Multicenter analysis of surgical treatment results clearly shows that shunts significantly reduce variceal bleeding, but the frequency of encephalopathy and mortality rates are high. In the present situation, early surgical prophylaxis is not recommended. Hermann et al. [25] compared the results of surgical treatment of PH in Cleveland. From 1946–1964, 76 surgeries (PC, MC, SR) were performed. Encephalopathy developed in 33% of patients and five-year survival was achieved in 45% of all cases. From 1965–1980, surgery (PC, SR, MC, DSRS) was performed in 188 patients. The results were 22% (encephalopathy) and 54% (five-year survival). In patients treated between 1980 and 1990, encephalopathy was observed in 30% and five-year survival of only 33% was achieved in a group of 38 patients. Advances in qualification, technique, and postoperative care did not have a deciding influence in this case. In adults, mortality varies between 15% (in planned surgical procedures) to 60% (in emergencies).

Non-Shunt Surgery

Before the era of endoscopy, surgical procedures evolved in two directions. Non-shunt techniques were done without performing venous junctions. This group consists of various surgical techniques performed to prevent recurrent bleeding from EVs. Their main purpose is to stop and separate the area of potential or active bleeding (in the lower third of the esophagus) from the portal vein. Non-shunt surgical techniques include procedures that stop the hemorrhage after opening the digestive tract and that block the blood flow in the EV. The most popular (in the past, usually performed with splenectomy) are: 1) the Boerem-Crile operation (direct ligation of varices), 2) creation of new collateral circulation, and 3) separation of the portal system from the esophageal circulation by either a) Tanner's method (separation below the varices) or b) Sugiura's method (external esophageal and gastric devascularization). Non-shunt techniques do not lower the portal pressure and do not impair hepatic flow; therefore they were performed in cases of high risk of or in already existing encephalopathy. Most of these operations are historical. They are no longer

performed due to the high number of complications and poor long-term results. Mortality (in planned and urgent operations) was several percent. In Wanamaker's et al. material [30], 90% of patients had hepatic type C insufficiency (Child), post-operative mortality was as high as 50%, usually due to large blood loss during the surgery and septic complications. Recurrent bleeding in children was observed in 12–50% of all cases. Today, the only remaining non-shunt procedure is gastro-esophageal disconnection [31], performed by cutting the esophagus with a stapler. It is the easiest surgical method to stop EV bleeding. It also causes the highest amount of recurrent bleedings and is often associated with a high number of septic complications, which may delay liver transplantation or even render it impossible.

Transjugular Intrahepatic Portal-Systemic Stent-Shunt (TIPSS)

TIPSS is defined as an additional connection between the portal system and the systemic circulation in the liver. It is often considered a radiological intervention. Since it creates intrahepatic connection between the portal system and one of the hepatic veins, it may be considered a type of porto-systemic shunt (side-to-side) that lowers hepatic pressure. TIPSS was introduced in the late 1980s after experimental research performed on dogs. Calapinto performed this type of operation on a human being in 1982 in Toronto [32]. Several operations did not result in permanent, promising results. The failures were caused by the lack of a proper intrahepatic stent (prosthesis). Six years later, Richter [33] performed a successful porto-systemic shunt using an approach through the external jugular vein and inserting a metal prosthesis (stent) constructed by Palmaz. At the beginning, indications for TIPSS were very limited. The new procedure developed quickly and shortly became a standard procedure performed in many hepatic diseases. Nowadays, TIPSS is considered a low-invasive method with low perioperative mortality.

TIPSS is indicated in cases of 1) EV bleeding that does not respond to pharmacological treatment, EVS, and EVL, 2) ectopic gastric and intestinal varices, 3) treatment of malignant ascites (ascites not responding to pharmacological treatment), 4) acute episodes of portal vein thrombosis and Budd-Chiari syndrome, and 5) before expected extensive abdominal surgery in patients with portal hypertension (e.g. before LT). During the treatment, portal pressure can be reduced to the

desired level by modifying the stent's diameter. They can be dilated later if necessary. TIPSS allows the prevention of urgent surgical intervention after failure of the endoscopic treatment. TIPSS alone, in terms of efficiency in preventing recurrent EV bleeding, is considered equal to EVS. Just before the operation is finished it is often possible to apply obliterant that quickly stops blood flow to the vessels that drain blood into the portal vein [34]. Since TIPSS is performed intrahepatically, it does not interfere (especially in adults) with planned LT and allows patients waiting for transplantation to recover from bleeding and improve their condition [35].

The absolute contraindications for TIPSS are limited, i.e. terminal hepatic insufficiency, right-ventricle insufficiency (high risk of pulmonary edema or heart failure), and thrombosis or insufficient diameter of the jugular veins. Relative contraindications include left-heart insufficiency, advanced hepatical encephalopathy, and portal vein thrombosis, developing due to slower blood flow in the portal system. Unfortunately, TIPSS does not have a significant influence on the high risk of developing encephalopathy (up to 40%) in patients with hepatic cirrhosis. High mortality in the early postoperative period in patients treated with all the surgical techniques is their main disadvantage in terms of life prolongation when compared with endoscopic techniques. Based on an analysis of almost 2000 cases, Barton et al. [35] assessed the postoperative mortality at 11% in the first month after surgical intervention. Most common failures include hepatic insufficiency, bacteremia, and recurrent EV bleeding.

Liver Transplantation

As mentioned above, LT is a special form of treatment that eliminates the liver disease itself as well as PH. It is necessary to say that the indication for transplantation is determined by the level of hepatic insufficiency, not the severity and size of EV bleeding. The first LT in a human was performed by Starzl in 1963 following over 200 trial transplantations performed on dogs. Unfortunately, the three-year-old boy died during the surgery. The next six attempts of LT in the USA and in France were also fatal. The causes of death were massive bleeding, pulmonary thrombosis, bacteremia, and hepatic insufficiency. None of the six patients survived more than one month after the treatment. The technique of surgical operations continued to develop and the first successful transplantation was performed in 1967, again by Starzl. A one-and-half-year-old boy survived over one year after LT [36]. Two techniques were initially

used in LT. The classical method was done by removing the recipient's liver with part of the inferior vena cava and replacing it with a compatible transplant from a donor. The second technique was to resect the liver leaving the recipient's vena cava intact and performing a side-to-side junction with the inferior vena cava of the donor liver.

The techniques of transplantation in adults and in children differ a lot because almost half of LT indications in children are caused by biliary occlusion. The main biliary duct in children is often narrowed or not present and requires hepato- or choledochojejunostomy to provide appropriate bile drainage. Small patients, weighing less than 30 kg, have a significantly smaller chance of finding a transplant of appropriate size. Most liver donors around the world are adults and youths who suffered fatal injuries in accidents (usually motor vehicle accidents). The above difficulties and the possibility to better utilize transplantation materials has allowed the development of the three most popular procedures: 1) in 1984, Bismuth conducted the first reduced-size transplant, usually done by using 2nd and 3rd or 2nd, 3rd, and 4th liver segment (left lobe), 2) living donor transplantation, performed for the first time in 1988 by Raia et al. and one year later by Strong et al. This technique allows one to find a donor with the best compatibility available. Parents, siblings, and other relatives make good candidates for donors. This procedure is possible because the liver is the only organ critical for the patient's life that has the possibility to regenerate. Both parts (the one left in the donor's body and the one implanted in the receiver) grow to their normal size in a couple of weeks. 3) Split liver transplantation is a development of Bismuth's technique. The donor's liver is separated into two fully functional transplants. Segments 2 and 3 can be implanted in children while the 1st and 4th–8th can be used in adults. The donor may be a person with a dead brain stem and beating heart [37].

The true breakthrough in LT came with the new era of immunosuppression after the introduction of cyclosporine in 1978 [38]. Cyclosporine A is a cyclic, 11-amino-acid peptide obtained from *Tolypocladium inflatum* Gams. Combining cyclosporine and prednisone in the late 1970s dramatically increased the survival rates of patients after LT. The therapy had many side effects, such as hypertension, renal dysfunction, hirsutism, and gingival hypertrophy. Tacrolimus, a macrolide lactone obtained from *Streptomyces tsukubaensis*, proved to be a safer alternative. Tacrolimus hardly ever needs to be combined with steroids, and in recent years has almost completely replaced cyclosporine in LT [36].

Further development of operative techniques, qualification terms, and postoperative care and follow-up have allowed reaching a one-year postoperative survival rate of over 80% in children and adults. Long-term results of PH treatment caused by hepatic cirrhosis are significantly better with LT than with any other method. LT is even sometimes indicated and performed in the treatment of Budd-Chiari syndrome [37]. Contraindications for LT include neoplasms, active extrahepatic infections, active inflammatory process in the portal system, AIDS, active alcoholism, and insufficient mental predisposition of the patient. LT is not usually performed in schistosomatosis and in cases of hyperkinetic hypertension. Although LT is considered to be one of the most difficult operations to perform, it has become very popular. In Europe there are over 100 active LT centers. In the USA alone ca. 5000 LTs were performed in the year 2000, and over 80,000 people around the world are waiting for such intervention. LT is surely not the last word in the treatment of liver diseases and PH. Laboratories are currently conducting research on breeding and transplanting hepatocytes [39].

EVs are still the most dangerous complication of PH. EV bleeding always presents a life-threatening situation. Almost 20% of patients die within six weeks of the first incident. The methods of treatment include possible prophylaxis of the first bleeding, proceeding in urgent situations, monitoring and preventing recurrent bleedings, and possible elimination of the cause of the disease. There is no one perfect method of treatment and all five choices should be considered: pharmacological treatment, endoscopic procedures, classical operations, radiological interventions, and LT. Analysis of the pros and cons of these methods indicates an real need to present an optimal algorithm in the treatment and prevention of bleeding from EVs. During the past 20 years a series of conferences devoted to the methodology, diagnostics, and treatment of PH has been organized in Europe and in the USA. Such workshops have been organized in Italy four times (the last in April 2005) [40]. Especially important was establishing recommended procedures for the treatment of EV in the course of their most common cause in our region, which is hepatic cirrhosis. However, there are no indications for preventing the development of EVs, but consensus was reached in preventing recurrent bleedings and stopping urgent bleedings. During the 4th meeting in Baveno the following conclusions were made: 1) nonselective beta-blockers decrease the risk of a first EV bleeding. Also, EVL provides a similar effect and should be used in the prevention of a first bleeding, especially in patients with medium or large sized varices or in cases of beta-

blocker intolerance. 2) In acute bleeding are recommended treatment of blood loss, prophylactic use of antibiotics, and lactulose in case of present encephalopathy. Balloon tamponade can only be used in cases of massive bleeding for no more than 24 hours, and endoscopy should be performed as soon as possible. EVL is usually recommended, and EVS is allowed when technical difficulties make ligation impossible. When there are no satisfying effects of pharmaco-endoscopical therapy, it should be repeated or TIPSS is recommended. 3) Prevention of recurrent bleeding should be achieved by a combination of pharmacological

treatment and EVL. If the results are not sufficient, TIPSS or a bypassing junction should be made (Warren's operation or 8-mm H-graft). They are efficient in patients in Child's group A/B. In the B/C group, LT provides good long-term results. This algorithm allows making fast and accurate decisions to choose the best possible treatment in specific clinical conditions. This is also true for PH. It is also believed that before the treatment of EVs, every patient should be evaluated for possible LT [16]. These standards are therefore not rigid and unchangeable and will probably evolve with time.

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