Symptoms and Syndromes

19 Coagulopathy and haemorrhage

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The leakage of blood from the blood vessels is referred to as **haemorrhage**. Its causes include: (*1.*) increased permeability of the vascular walls, (*2.*) pathological blood vessel condition, and (*3.*) injury to a blood vessel. • Generally, a haemorrhage may become considerably more severe in the presence of **coagulopathy**, i.e. clotting disorder. It is also possible for a coagulation defect to arise as a separate disorder even without existing tissue damage.

1 Coagulopathy

1.1 Forms of haemostasis

By means of the complex process of **haemostasis**, the organism seeks to protect itself directly from bleeding and the corresponding loss of blood. • **Three components** are available for achieving this end: (*1.*) blood vessels themselves (= vascular haemostasis), (*2.*) platelets and endothelial cells (= cellular haemostasis), and (*3.*) blood-clotting factors (= plasmic blood coagulation).

1. **Vascular haemostasis** comprises reflex contractions of the arteries, reinforced by the release of vasoconstrictor substances from the vessel walls (e.g. catecholamines, serotonin, thromboxane A_2).

2. **Cellular phases** of the arrest of bleeding commence as so-called **primary haemostasis,** during the course of which thrombocytes, with the aid of von Willebrand's factor, adhere to collagen fragments released from the injured vascular endothelium. The discharge of various factors from the thrombocytes then ensues. The prostaglandin-thromboxane system is directly involved in the subsequent aggregation of thrombocytes.

3. **Plasmic coagulation** is effected by a system of 15 coagulation factors. (s. p. 110) (s. tab. 5.12) So-called **secondary haemostasis** begins with the progressive activation of the plasmic coagulation system. All the coagulation factors involved are proteins and for the most part enzymatic. They are normally present in the plasma in their inactive form, and with the initiation of plasmic coagulation, they become successively activated. The clotting process (= **coagulation**) has the function of converting soluble fibrinogen into stable, insoluble fibrin. *Procoagulation and anticoagulation factors* regulate the process of coagulation.

Exogenous activation is initiated by tissue thromboplastin (= tissue factor) and the activated form of factor XII in the plasma. This complex is enlarged by ionic calcium and platelet factor 3. As a result, the activation of factors IX to IXa and X to Xa is triggered, thus forming a cross-connection between the endogenous and the exogenous system. (s. fig. 19.1)

Endogenous coagulation commences with the activation of factor XII. Factor XIIa then catalyzes the conversion of prokallikrein to kallikrein, plasminogen to plasmin and factor XI to XIa. The presence of factor XV is necessary for the activation of IX to IXa. This creates a complex comprising IXa, VIIIa, calcium and phospholipids, which then activates factor X to Xa. (s. fig. 19.1)

► Depending on the causative mechanism, either the exogenous or the endogenous coagulation system is activated. These progress differently until the activation of factor X, which then allows both pathways to merge into a common final phase of coagulation. • At this point, the activation of **prothrombin II** to thrombin by the Xa/Va/calcium/phospholipid complex represents the final step of both coagulation cascades. The prothrombin complex (factors II, VII, IX and X) does not exist as such − it refers to various proteins, the synthesis of which depends on vitamin K. • Soluble **fibrinogen** (I) is converted by thrombin into insoluble *fibrin*, which infiltrates and thereby solidifies the thrombocytic embolus. Thrombin simultaneously activates factor XIII to XIIIa and protein C to protein C_a. The fibrin network is further strengthened by factor XIIIa. • The most effective **inhibitors** of coagulation are antithrombin III, α_2-macroglobulin, C_1-inactivator and protein C_a as well as fibrinogen-fibrin degradation products.

1.2 Fibrinolysis

The minor coagulation processes constantly taking place in the vascular system (whereby fibrin is deposited) are counteracted by simultaneous fibrinolysis. *Coagulation and fibrinolysis are thus in continuous dynamic balance.* Plasminogen is converted to plasmin by activators such as urokinase PA (isolated from urine) and tissue PA (isolated from tissue). The effect of tissue PA is strongly enhanced by the presence of fibrin. Fibrinolysis is stimulated by protein C, while plasmin activity is maintained in balance by inhibitors (e.g. α_2-antiplasmin, α_2-macroglobulin). (s. fig. 19.1)

1.3 Vasopathies

Vasopathies may arise from direct injuries to the vessel wall, but also from pathological changes in the vessel wall or in the endothelium. It can be expected that vasopathies will occur or become more severe during the course of various liver diseases or with concomitant coagulopathy.

Osler-Rendu-Weber disease (*haemorrhagic telangiectasia*) is the most common congenital vasopathy. It is an autosomally inherited structural defect of the blood vessels with an accompanying decrease in muscular and elastic fibres in the capillaries and venules. Multiple telangiectases are most frequently found in the upper body and in the mucous membranes. Severe bleeding may occur from the nasal and pharyngeal passages as well as from the gastrointestinal tract.

Schoenlein-Henoch disease (*anaphylactoid purpura*) represents the most important acquired vasopathy. It is due to toxic or allergic inflammatory blood-vessel damage accompanied by immunological reactions. Bleeding may be present in the skin, in the form of petechiae or ecchymoses, or in the gastrointestinal mucosa.

1.4 Thrombocytopathies

Thrombocytopathies may arise in the course of a liver disease and during the measures taken to treat it as well

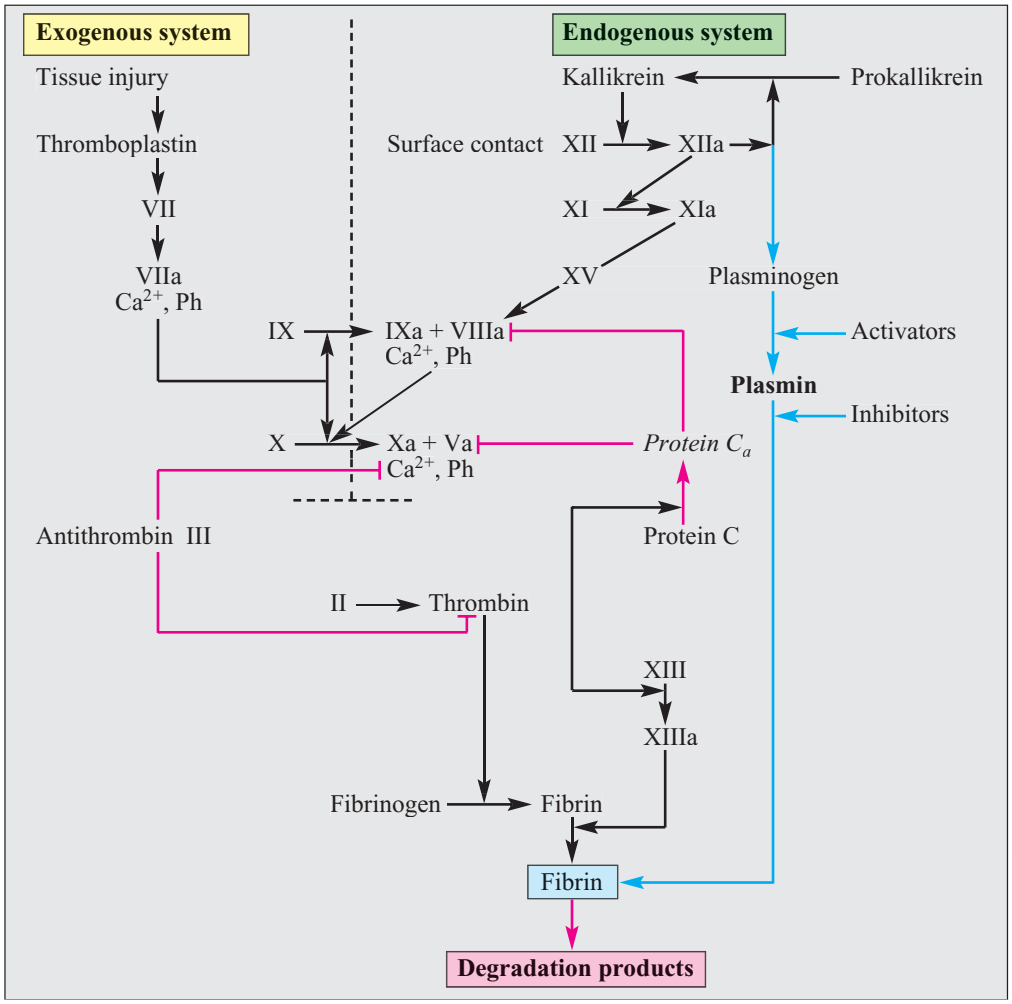

Fig. 19.1: Exogenous and endogenous plasmic coagulation cascade (with inhibition by antithrombin III and protein C_a) and the fibrinolysis pathway through plasminogen-plasmin. Proteolytic plasmin principally hydrolyzes the cross-linked fibrin clot into high molecular weight fragments and D fragment dimers (Ph = phospholipids) (s. tab. 5.12)

as from complications. This condition can lead to serious disturbances in haemostasis. Thrombocytic bleeding is typically observed as punctate or petechial haemorrhaging in mechanically stressed skin areas as well as in mucous membranes. Ecchymosis is found less frequently. • A *leftward shift* in the differential blood count may indicate thrombocytopathy. (17)

1. **Thrombocytopenia** may be caused by various metabolic disturbances: (*1.*) synthesis disorders (e. g. medicaments, alcohol, folic acid deficiency, thrombopoietin deficiency, increase in the platelet inhibitors prostacyclin and NO), (*2.*) replacement disorders (e. g. immunologically derived degradation, consumption coagulopathy, antiplatelet antibodies, loss of blood), and (*3.*) distribution disorders (e. g. increased sequestration in the enlarged spleen, involving up to 90% of the thrombocytes).

2. **Thrombocytosis** is a (generally temporary) rise in the thrombocyte count. Thromboembolic complications may arise. This disorder occurs in hepatocellular carcinoma, for example, following splenectomy or portosystemic anastomosis as well as after haemorrhage or cortisone therapy.

3. **Thrombocyte dysfunction** frequently emerges in the course of liver diseases and their complications, especially in the case of coagulation disorders and elevated fibrinolysis. Thus a decrease in both thrombocyte aggregation and the release of platelet factor 3 may occasionally be observed in cirrhosis. In most cases, this is caused by medication (acetylsalicylic acid, non-steroidal antirheumatic agents, dextran, antibiotics, etc.).

1.5 Plasmic coagulation disorders

Defects in liver function greatly affect the haemostatic system: (*1.*) most coagulation and fibrinolytic factors are synthesized in the liver; (*2.*) many procoagulation and anticoagulation factors must be metabolically converted into their functionally active forms in the liver, and (*3.*) various plasmic coagulation and fibrinolytic factors are removed from the bloodstream by clearance mechanisms in the liver. Thus liver diseases can disrupt the haemostatic system at various stages of coagulation or fibrinolysis and with varying degrees of intensity. It is the severity of the disease which is of decisive importance rather than its acute or chronic character or its aetiology (with the possible exception of liver carcinoma). Appropriate *diagnostic tests* are: thrombocyte count, Quick's value and AT III. Plasmic coagulation defects in liver disease are derived from acquired disorders in the synthesis of coagulation factors or from their accelerated breakdown. (1, 3, 6, 7, 10, 13–17)

In liver disease, procoagulation and anticoagulation factors are generally decreased to the same extent, so that haemostasis is kept in balance, albeit at a pathological level. Thus the clinical significance of haemostatic changes may be less serious than laboratory findings would seem to indicate. This pathological "equilibrium" is, however, extremely vulnerable and may be quickly destroyed by diagnostic or invasive procedures as well as by biochemical or toxic effects.

1.5.1 Synthesis disorders

The synthesis of almost all coagulation factors takes place in the liver. In liver disease, several factors, especially the vitamin K-dependent factors II, VII, IX and X, are affected differently, depending on the severity of the illness. Synthesis of non-functional coagulation factors, particularly fibrinogen (dysfibrinogenaemia), may also occur. Defects in factor activity become clinically manifest quite rapidly due to their short plasma half-life. (s. tab. 5.12) This is where Quick's value, the Colombi index and the AT III value, among others, play their part as accepted clinical parameters of impaired liver function. (s. p. 111) A decrease in fibrinogen is observed only in severe liver damage, in consumptive disease processes or in consumption coagulopathy. Plasminogen and factors XI, XII and XIII are likewise reduced in cases of severe loss of liver function.

1.5.2 Clearance function disorders

The liver has the unique ability to differentiate between inactive and active coagulation factors and to remove the latter, along with plasminogen activators, from the bloodstream. Cirrhosis greatly interferes with the clearance of t-PA. The fibrinogen-fibrin degradation products, which act as thrombin inhibitors, are likewise eliminated by a healthy liver. In severe liver disease, obstructive gall-bladder disorders, cholestasis or biliary cirrhosis, the clearance function of the liver (s. p. 69) as well as the elimination of coagulation factors (especially factor XIII) and fibrin degradation products can be seriously impaired. This disrupts the haemostasis system, and fibrinolysis increases.

1.5.3 Increase in consumption

An increased consumption of coagulation factors is found in extensive disseminated intravascular coagulopathy. Secondary hyperfibrinolysis evolves. Simultaneous activation of the coagulation cascade or fibrinolysis system leads to the consumption of coagulation factors and inhibitors. (17)

Haemostatic disturbances result in *hypocoagulopathy with a bleeding tendency* (= haemorrhagic diathesis) seen as manifest haemorrhage or in *hypercoagulopathy with a tendency to thrombosis* (= thrombophilia) seen as manifest thrombosis. An imbalance in the physiological equilibrium of the procoagulation and anticoagulation factors of the coagulation and fibrinolytic systems is invariably present. (17)

1.6 Consumptive coagulopathy

1.6.1 Definition

Disseminated intravascular coagulation (DIC) is due to enhanced formation of thrombi following an activation disorder in either the extrinsic or intrinsic coagulation cascades. Fibrin clots form in the small blood vessels and capillaries. In response, fibrinolysis increases, thus allowing large amounts of fibrin degradation products to reach the bloodstream. In the case of highly activated coagulation, platelets and coagulation factors are consumed in such large amounts that they cannot be adequately replaced. • *DIC may develop into consumptive coagulopathy.*

This coagulation disorder may occur in the course of a variety of diseases and clinical conditions. Aetiopathological possibilities include infections, toxins, endotoxins, dehydration, acidosis, antigen-antibody complexes or stasis of the blood flow as well as the tumour necrosis factor.

Disseminated intravascular coagulation does not present a clinical picture in its own right, but constitutes a severe pathological manifestation of an **altered haemostasis system.** Blood vessels, thrombocytes and endothelial cells, the coagulation system, fibrinolysis, inhibitors and activators as well as the kallikrein-kininogen system are all involved in this disorder. The haemostasis system is activated either exogenously by the release of tissue thromboplastin and its homologues or endogenously by direct proteolysis of one or several procoagulants. (1, 3, 4, 8, 14, 15, 17)

1.6.2 Clinical aspects

Clinical aspects and laboratory findings vary widely not only from patient to patient, but also during the course of DIC. Depending on the extent to which the coagulation system is activated, either an acute or chronic form develops. Furthermore, DIC may occur merely as an additional complication in an existing illness, without necessarily having serious consequences – or it may culminate in a life-threatening condition.

In the **initial stage** of DIC, the haemostasis system is activated via the exogenous and/or endogenous cascade. This stage is characterized by a state of hypercoagulability. There is consumption of thrombocytes and coagulation factors as well as of procoagulants and anticoagulants, with simultaneous intravascular release of thrombin. The fibrinolysis system undergoes secondary activation. (s. fig. 19.2) (s. tabs. 5.12, 5.13)

In the **second stage,** the intravascularly released thrombin begins to have an effect at various points in the pathological process. Thus (*1.*) fibrinogen and fibrin are converted into degradation products, (*2.*) factor XIII is activated, (*3.*) factors V and VIII are altered to more highly active forms with a fall in factor VIIIc, and (*4.*) aggregation of thrombin and thrombocytes occurs. The amount of monomeric fibrin rises, while the clearance capacity of the RES becomes progressively strained at the same time. Fibrin D fragments increase, as do fibrin-fibrinogen X, Y and E fragments. The monomers disintegrate into aggregates and, together with the thrombocytes, begin to form microthrombi and fibrin clots in the terminal vessels. Circulatory disorders arise with blood stasis, hypoxia and acidosis. These result in endothelial damage, involving cell destruction to the point of organ failure. Further consumption of coagulation factors leads to a state of *hypocoagulability* with a tendency towards bleeding, which is dramatically intensified by reactive *hyperfibrinolysis* and a growing AT III deficit – a consequence of the irreversible binding to thrombin as well as to factors IXa, Xa, XIa and XIIa. (2, 4, 5, 6, 9, 10, 11, 12–15, 17–19) (s. fig. 19.2) (s. tab. 5.13)

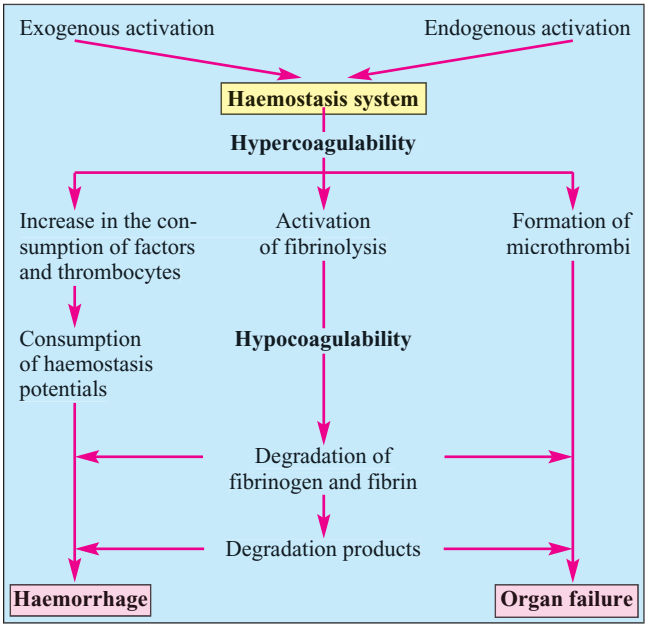

Fig. 19.2: Schematic course of consumptive coagulopathy

Latent and compensated forms of consumptive coagulopathy frequently occur in the course of severe acute or chronic liver disease. In 80–85% of cirrhosis patients, the values of at least one basic test (thrombocytes, Quick's value, fibrinogen, AT III, bleeding time) are pathological. In 15–30% of cases, clinically relevant haemorrhagic diathesis evolves.

Differential diagnosis, which is necessary for distinguishing consumptive coagulopathy from DIC in a short time, is often extremely difficult to draw up. It is only possible by implementing a closely woven series of laboratory tests. Plasma thrombin time or reptilase time (in the event of concurrent heparin therapy) are appropriate parameters to determine the transition into reactive hyperfibrinolysis. (s. tab. 19.1) • The diagnosis is complicated by the fact that laboratory values typical for disseminated intravascular coagulopathy might also be due to the reduced synthesis of blood-clotting factors. Likewise, evidence of fibrinogen-fibrin degradation products is not necessarily conclusive, since the diminished clearance capacity associated with the underlying liver malfunction often precludes an adequate elimination of these substances. *It may thus prove difficult in individual cases to distinguish between a synthesis disorder and the consumption of coagulation factors as possible causes of haemorrhagic diathesis or haemorrhage.*

	Normal range	Compensated/decompensated DIC
Thrombocytes Bleeding time	150,000–380,000 2–5 min	↓–↓↓ ↑–↑↑
Quick's value (% TPT) Fibrinogen (clottable) Antithrombin III (AT III) Partial thromboplastin time (PTT) Plasma thrombin time (TT) Factor XIII	70–120% 1.8–3.5 g/l 70–120% 28–40 sec 17–22 sec 70–120%	↓–↓↓ ↓–↓↓ ↓–↓↓ ↑–↑↑ ↑–↑↑ ↓–↓↓
Fibrin monomers (soluble) (= *hypercoagulability*)	< 15 mg/l	↑–↑↑
Fibrinogen degradation products (serum) D-dimer (= *hyperfibrinolysis*)	< 1 mg/l 20–400 µg/l	↑–↑↑ ↑–↑↑
Thrombin-antithrombin-III complex (TAT) (= *chronic DIC*)	1–4.1 µg/l	↑–↑↑

Tab. 19.1: Haemostasis parameters showing the normal range and corresponding changes in the course of hepatogenic consumption coagulopathy up to decompensation (s. tab. 5.12)

An accurate evaluation of the dynamics of clotting disorders or the development of disseminated intravascular coagulation as well as the further course of disease is only possible by monitoring the changes in the various laboratory parameters. Frequently repeated controls are far more important than determining each and every variable. (s. tab. 19.1)

The threshold between an inactive and an active coagulation system may be overcome abruptly at times by small stimuli, and haemostasis can then break down quite unexpectedly.

1.7 Therapy of haemostatic disorders

It is only possible to treat haemostatic disorders in liver disease *symptomatically*. In most cases, therapy also has to be adjusted to the individual patient. A causative effect on the haemostatic disorder can only be expected in the long term once liver function has begun to improve.

1.7.1 Prophylactic measures

Basic laboratory parameters concerning the haemostatic status should exceed a minimum level before any diagnostic or therapeutic procedure is initiated. The following values may be taken as a guideline (although in certain instances, some values may lie below those given): thrombocytes > 80,000, Quick's value > 40%, fibrinogen > 1.5 g/l, AT III > 40%, normal bleeding time.

Prevention of haemorrhage is always of particular importance. In view of the highly unstable nature of the haemostasis system, which − even though still in equilibrium − has a generally reduced factor level, the *insertion of catheters* (e. g. stomach probe, urinary bladder) is only carried out if particularly stringent indications are given. (7) Likewise, the administration of any medication which might affect the haemostatic system (e. g. acetylsalicylic acid, certain antibiotics, antihistamines, antirheumatic agents, clofibrate, dextran, diuretics, glucocorticoids, cardiac and psychotropic drugs, nitrofurantoin and radiological contrast medium) should be carefully evaluated. Even traces of acetylsalicylic acid, which may be "hidden" in some medicaments, can severely disrupt haemostasis and precipitate the collapse of the painstakingly maintained equilibrium. Application of *H_2-receptor antagonists* or *omeprazole* may prove to be a helpful preventive measure in controlling gastrointestinal haemorrhaging. *Infection-limiting measures* can also serve to prevent haemorrhage. *Intestinal cleansing* (purgation) using poorly absorbable antibiotics (e. g. neomycin, paromomycin) and/or lactulose to suppress gram-negative flora and diminish the danger from endotoxins is of vital importance. (s. pp 285, 286, 288)

If no haemorrhagic diathesis is present or when no invasive measures or techniques which might possibly distress the patient are planned, coagulation disorders generally **require no treatment.** *The equilibrium between haemostasis and fibrinolysis, which is based on lower clotting factor levels, is indeed somewhat unstable, yet it does not normally lead to spontaneous haemorrhaging.*

Should **substitution** of haemostatic factors be needed prior or subsequent to invasive procedures, *fresh plasma* is the agent of choice, since it contains not only a balanced mixture of procoagulant and anticoagulant factors, but also fibronectin, which serves to reinforce RES clearance. However, relatively large quantities of fresh plasma are required, and it is important that individual volume limits are adhered to for haemodynamic reasons. Preventive administration of *vitamin K* (10 mg/week), subcutaneously injected if oral application is deemed inefficient or an intramuscular injection appears too risky, is recommended in suspected vitamin K deficiency. This measure can also be used prior to treatment with cephalosporins, in particular β-lactam antibiotics, or if the intestinal flora is in some way affected.

1.7.2 Pharmacological therapy

The **treatment** of haemostasis disorders is indicated in acute liver failure or when a necrotic episode occurs during the course of cirrhosis, even without haemorrhagic complications. There are *two reasons* for this: (*1.*) an elevated risk of haemorrhage must be anticipated in the event of acute liver dysfunction, and (*2.*) extensive liver necrosis leads to the release of thromboplastic compounds, accompanied by a deterioration in the microcirculation and additional haemostatic disturbances. In this situation, an early and optimized correction of coagulation and fibrinolysis parameters is thus essential. (1, 4, 10, 12, 16) (s. tab. 19.2)

Haemorrhage-related lethality of 20−30% (and more) has to be expected in the event that acute liver failure leads to **acute haemostasis disorders.** The following courses of treatment are recommended:

(*1.*) *Fresh frozen plasma* (FFP)*: 250 ml at six-hour intervals (10−20 ml/kg BW = 1,000−1,500 ml/day). Administration of 10 ml/kg BW (about 600−1,200 ml) serves to elevate the concentration of coagulation factors and inhibitors by 15−20%. The half-life of factor VII is only 6 hours, which is why dosage intervals of 6 to 12 hours must be maintained. IgA deficiency is a known contraindication. Adverse transfusion reactions may occur with a frequency of 1−5% of cases. Improvement in coagulopathy generally lasts one or two days. • Caution is called for, since accentuated coagulation entails the danger of thrombosis (if necessary, AT III replacement of up to 60−80%), and an overload of the intravascular volume must be avoided (monitoring of CVP!). (20) (s. tab. 19.2)

(2.) *Antithrombin III concentrate**: 1,000–2,000 U/day until the plasma AT III value exceeds 70%.

(3.) *Desmopressin acetate**: This vasopressin derivative (DDAVP) acts as an antidiuretic and antihaemorrhagic agent. It increases the turnover of factors VII, VIII, IX and XII and also shortens the bleeding time. The recommended dosage is 0.3–0.4 µg/kg BW as an i.v. infusion. This substance is contraindicated in the case of a thrombotic status. Further contraindications include ischaemic heart disease, cardiac arrhythmias and seizure disorders.

(4.) *Vitamin K**: 10 mg, subcutaneous administration, to be repeated for 3 to 7 days until the prothrombin time has been corrected. Be careful when using the intravenous route due to the risk of anaphylaxis and hypotension. Onset of action is within 6–12 hours, full impact is at 24 hours, subsequently lasting up to 7 days. An overdose should be avoided as it can cause a (sudden and dangerous) drop in Quick's value resulting from the formation of vitamin K oxide (s. tab. 19.2).

(5.) *PPSB**: Should Quick's value remain below 20% after treatment with fresh plasma, administration of 1,000–3,000 U/day is indicated (1 unit PPSB activates coagulation by 1–2%). This treatment should always be carried out in combination with fresh plasma and AT III concentrate to avoid the danger of thrombosis or the manifestation of DIC. It must also be borne in mind that PPSB (prothrombin [II]/proconvertin [VII]/Stuart-Prower factor [VIII]/antihaemophilic globulin B) may induce an increase in intravascular consumption in the presence of hypercoagulability, and indeed trigger haemorrhaging.

(6.) *Thrombocyte concentrates**: Administration of thrombocyte concentrates may be advisable when values lower than 30,000/µl are present, but this must be specifically indicated (e.g. thrombocyte deficit due to sequestration in the spleen, increase in consumptive coagulopathy, potential antibody formation).

(7.) *Fibrinogen**: Doses of 2–4 g (i.v.) at six to eight-hour intervals are recommended. Where haemorrhaging occurs, simultaneous administration of even small amounts of heparin is strongly contraindicated, particularly as the patient's heparin sensitivity may be highly elevated in this condition as well as after the administration of AT III. The use of heparin in such a situation thus involves very high risks. (s. tab. 19.2)

(8.) *Factor XIII**: The administration of *factor XIII* for fibrin stabilization (1,250 U, i.v. until cessation of bleeding) is worthy of consideration.

(9.) *Heparin**: Heparin was recommended as early as 1963 for the *prevention* of consumptive coagulopathy in cirrhosis patients. The interruption of intravascular thrombin coagulation by heparin has been confirmed in animal experiments. Soluble, circulating fibrin aggregates into microthrombi (within a few hours of the coagulation system being activated); heparin, however, cannot prevent this. The efficacy of heparin is dependent on normal AT III values. • *Heparin is no longer recommended as a prophylactic or therapeutic agent for DIC.*

*) The manufacturer's recommendations regarding application and dosage must be followed.

Treatment of **haemorrhagic complications** in acute or chronic liver disease initially focuses on the site of bleeding, i.e. in the upper or lower gastrointestinal tract. Mechanical, thermal and sclerotic measures are of prime importance. • Systemic clotting dysfunction is a potential contributory factor in more than 30% of cirrhotic patients with gastrointestinal bleeding. The seriousness of the haemorrhage depends to a great extent on the severity of the haemostatic disorder. Localized treatment must therefore be supplemented by additional corrective therapeutic measures, especially since a deterioration of the haemostatic potential in a haemorrhagic patient may occur rapidly and with serious consequences. The preparations listed above are also of value here, depending on the respective individual findings. (s. tab. 19.2)

1. **Local measures to arrest the bleeding**
2. **Correction of haemostasis disorders*** – antithrombin III concentrate – desmopressin acetate – factor XIII (factor rVII) – fibrinogen – fresh plasma/fresh blood – PPSB – thrombocyte or erythrocyte concentrate – vitamin K

Tab. 19.2: Therapy of haemostasis disorders

It is not possible to draw up a "treatment schedule", since each individual case, including the financial status, calls for careful and critical evaluation of the respective measures. • The potentially deleterious countereffects produced by the haemostatic and fibrinolytic systems must be considered before any medication is administered.

2 Upper gastrointestinal haemorrhage

2.1 Definition

Upper (non-variceal) gastrointestinal (GI) haemorrhages comprise any bleeding occurring between the nasopharynx and the duodenojejunal fold (Treitz's arch), i.e. proximal to the duodenojejunal flexure. • *Such haemorrhages are especially problematic in cases where liver disease is also present.*

2.2 Forms

Acute gastrointestinal haemorrhage is the most frequent life-threatening emergency situation in gastroenterology. Incidence is as high as 50–100/100,000 population. In 85–90% of cases, upper gastrointestinal bleeding is involved. Differentiation can be made by applying various criteria relating to the haemorrhage, such as its course, extent, type and localization, as well as by classifying the bleeding activity. (s. tab. 19.3)

1. **Course of haemorrhage**
   - acute or chronic
2. **Extent of haemorrhage**
   - severe or slight bleeding
   - seeping bleeding
3. **Type of haemorrhage**
   - arterial, venous or capillary
4. **Source of haemorrhage**
   - petechiae, bleeding erosions, mucosal fissures, ulcer, variceal bleeding

5. **Classification of the bleeding activity of an ulcer** (J. A. H. Forrest et al., 1974)

I	lesions with active bleeding
Ia	spurting arterial bleeding
Ib	seeping bleeding
II	lesions with signs that bleeding has occurred
IIa	visible vascular stump
IIb	blood clot formation
IIc	haematin at the bottom of the ulcer
III	lesions without the above criteria, but with positive bleeding anamnesis

Tab. 19.3: Forms and classification of upper gastrointestinal haemorrhage, including the classification according to Forrest

2.3 Causes

Gastroduodenal ulcers account for 45–55% of cases of upper gastrointestinal bleeding, gastric or duodenal erosions for 25–35%, and oesophageal or fundus varices for the remaining 15–25%. Portal hypertensive gastropathy is frequently found together with portal hypertension. (22, 30, 37–39, 41, 46–48) Extensive haemorrhaging can often be observed in cases where a clotting dysfunction occurs simultaneously. • The spectrum of possible causes is exceptionally wide, particularly since manifest bleeding may originate from a combination of various (subthreshold) factors in individual cases. • Actually, approximately 5% of all cases of upper gastrointestinal haemorrhage remain aetiologically unresolved. (s. figs. 19.3–19.5) (s. tab. 19.4)

2.4 Diagnostics

Upper gastrointestinal bleeding may be either chronic or acute. It becomes manifest as severe or slight haemorrhages of arterial, venous or capillary origin. (s. tab. 19.3) Elimination of the blood is effected by vomiting or in the stool.

1. **Oesophageal, gastric and duodenal varices** (18–25%)
2. Angiodysplasia (1%) (s. fig. 19.5)
3. Boerhaave's syndrome
4. Bouveret's syndrome (31)
5. Clotting defects (s. fig. 19.4)
6. Dieulafoy's bleeding
7. Duodenal ulcer (25–30%)
8. Erosions (10–15%) (s. fig. 19.3)
9. Gastric ulcer (20–25%)
10. Haemobilia
11. Malignancies (3–5%)
12. Mallory-Weiss syndrome (5–8%)
13. Oesophagitis/reflux oesophagitis (8–10%)
14. Osler-Rendu-Weber's disease
15. Peptic jejunal ulcer
16. Portal hypertensive gastropathy or gastric antral vascular ectasia (GAVE) (22)
17. Watermelon stomach (36)

Tab. 19.4: Causes of upper gastrointestinal bleeding (with some references and frequencies)

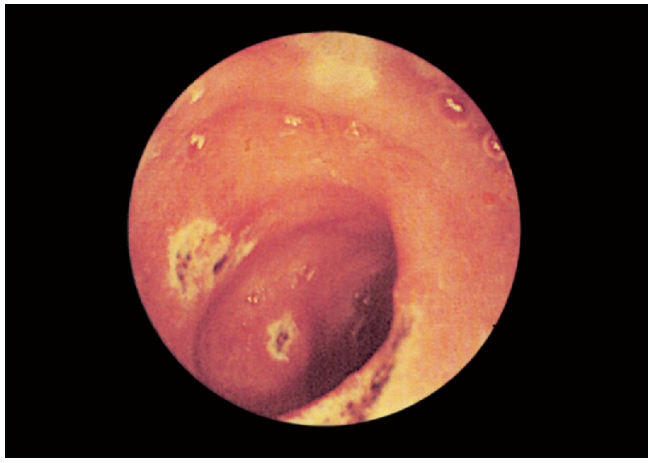

Fig. 19.3: Haemorrhagic erosions in the stomach as the cause of bleeding

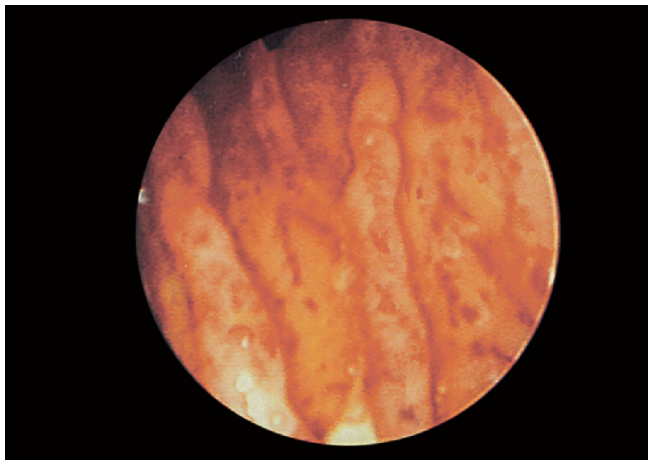

Fig. 19.4: Haemorrhagic gastritis in thrombopenia

Haematemesis: If bloody vomiting occurs immediately upon the onset of bleeding or if there is a deficiency of gastric hydrochloric acid or insufficient time for the formation of haematin, the vomited blood appears

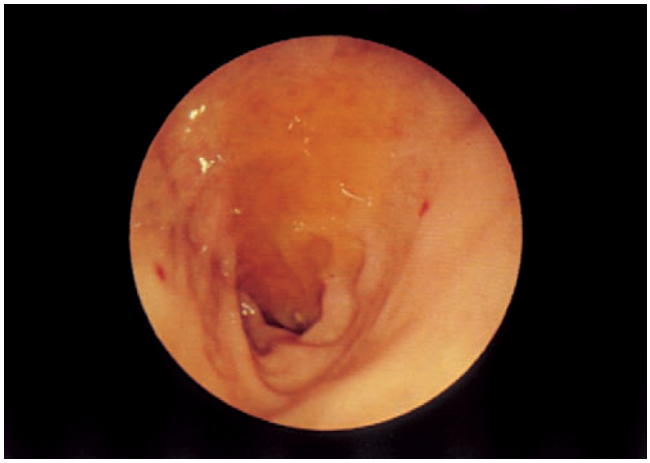

Fig. 19.5: Angiodysplasia in the duodenum

bright red and is not foamy. After somewhat longer periods in the stomach, the blood becomes dark red to brown or black (= *coffee-ground vomiting*).

Melaena: A recognizable elimination of blood from the intestine normally takes place when more than 60−70 ml have accumulated in the lower intestine. As a result of bacterial and chemical action (lasting several hours), the stool becomes black in colour, so that a so-called *tarry stool* is observed. As a rule, the source of bleeding lies above the duodenojejunal flexure (ca. 90%). Melaena (s. p. 372) may, however, also arise from bleeding in the ileum or right colon − as could be demonstrated by the collection of blood in the caecum during appendectomy. The presence of larger amounts of blood in the intestine leads to an accelerated passage with diarrhoeal elimination.

Occult blood: Blood volumes of < 50 ml are not generally recognizable by discolouration of the stool, but must be demonstrated by special testing (e. g. test strips). (s. p. 372)

Diagnostic goals: The diagnostic procedure for upper gastrointestinal bleeding is largely standardized and has three main aims:

1. Estimation of the haemorrhagic activity
2. Quantification of the blood loss
3. Identification of the source of bleeding

Circulatory parameters: The determination of circulatory parameters allows a rough calculation of the amount of blood already lost as well as optimizing the subsequent diagnostic and therapeutic measures. Loss of more than 800−900 ml blood (or less in older patients and in cases of anaemia) causes *circulatory symptoms:* tachycardia, fall in blood pressure, decrease in both cardiac output and venous return to the heart. A central venous pressure (CVP) of < 5 cm H_2O suggests an unfavourable prognosis. The *Allgoewer-Burri index* has proved to be a useful, objective parameter:

Allgoewer-Burri index

heart rate : *systolic RR = index*

index: 0.5 = normal; 1.0 to 1.5 = impending shock with circulating blood decreased by about 30%; exceeding 1.5 = circulating blood decreased by about 50%

Venous entries: Venous access points (one or possibly two) must be created as quickly as possible and kept open. Circulatory stabilization by means of *volume substitution*, at best with monitoring of the central venous pressure, is crucial. Diagnostic or therapeutic endoscopy is only possible once the circulation has been stabilized and any necessary *fresh blood* has been administered.

Loss of blood: Blood loss must be quantified by repeated determination of the *haemoglobin* and *haematocrit values*, because − depending on the severity of the bleeding − significant changes in these (and other) values only become evident after two to four hours due to the gradual flow of tissue fluid into the circulatory system.

Laboratory parameters: Once the initial blood sample has been taken to assess the blood loss, the following values must be determined immediately: *blood group, thrombocyte count, Quick's value, electrolyte profile* and *creatinine* as well as *fibrinogen* and *AT III levels.*

Endoscopy: It is essential that an endoscopic examination of the oesophagus, stomach and duodenum is carried out *as quickly as possible* under intensive care conditions with monitoring and pulsoximetry. The term "emergency endoscopy" is in fact misleading because upper gastrointestinal bleeding always constitutes an emergency and calls for immediate hospitalization and rapid diagnostic clarification.

► The **primary objectives** of initial endoscopy are: (*1.*) accurate identification of the location of the bleeding, (*2.*) evaluation of the bleeding activity, (*3.*) assessment of the danger of recurrent bleeding, and (*4.*) collection of coexisting findings. Endoscopy is 90−95% reliable in clarifying these questions (if necessary, repeated within a period of 12 to 24 hours). • The **secondary objective** is to decide on the therapeutic consequences, such as conservative and/or local treatment, or surgical intervention. To this end, the use of endoscopy with the possibility of simultaneous therapy is the method of choice, for which there is no viable alternative.

The grounds for the **primary use of endoscopy** to clarify upper (and lower) gastrointestinal bleeding are: (*1.*) endoscopy is acknowledged as the procedure which reveals the most conclusive information; (*2.*) this diagnostic procedure also provides the opportunity of using various endoscopic techniques to effect local haemostasis; (*3.*) endoscopic techniques are more likely to be readily available than scintigraphy or selective angiography; (*4.*) endoscopy is significantly more economical in terms of time and cost than scintigraphy or arteriography; (*5.*) endoscopy is less stressful for the patient and less invasive than angiography.

Complications cannot be attributed to endoscopy itself, but to the pre-existing conditions: localized perforations, risks associated with aspiration, cardiac problems, low blood pressure, etc. Premedication may be inappropriate in individual cases, and endotracheal intubation or endotracheal anaesthesia is then indicated.

Stomach tube: Use of a double-lumen stomach tube may be justified by several factors: (*1.*) detection of blood in the stomach, (*2.*) assessment of haemostasis, (*3.*) irrigation of the stomach to improve visibility during subsequent endoscopy, and (*4.*) permanent drip for clearing blood residues from the intestine to prevent the development of hepatic encephalopathy. (s. p. 285)

Scintillation scanning: In intermittent haemorrhagic lesions or subacute bleeding, valuable diagnostic data are yielded within a period of 24−36 hours by the use of scintillation scanning, employing ^{99m}technetium-labelled erythrocytes. The sensitivity of detection of bleeding is 93%, the specificity 95%, with an overall accuracy of 94%. Verification of bleeding is thus not only more reliable than arteriography, but is also far less invasive. (21)

Angiography: Selective angiography (coeliac artery, superior mesenteric artery) may be attempted if the haemorrhage site could not be localized by means of endoscopy and scintillation scanning. Angiography is also of intraoperative benefit. However, it is only possible to draw diagnostic conclusions with bleeding rates exceeding 0.5 ml/min. In individual cases, the administration of vasoconstrictor substances or an attempt at therapeutic embolization are rendered possible by using an in-situ angiography catheter.

2.5 Prognosis

Spontaneous haemostasis: Some 60−80% of all upper gastrointestinal haemorrhages cease spontaneously. Early diagnosis with simultaneous stabilization of the circulation facilitates such spontaneous haemostasis without further therapeutic measures being called for. In 10−15% of cases, the bleeding persists.

Risk factors: Several risk factors have a decisively negative influence on the prognosis. High-risk patients require particularly close observation. The necessity for surgical intervention may arise rapidly and often unexpectedly in such patients. Treatment is thus also directed at maintaining the patient in a permanent condition of operability. A new endoscopic index might possibly predict first bleeding from the upper gastrointestinal tract in patients with cirrhosis. (49) There is an almost linear correlation between the risk factors (s. tab. 19.5) and a negative prognosis or lethality. Larger vascular stumps at the base of ulcers (Forrest IIa, IIb) also show a tendency towards recurrent bleeding within 48 hours in 50% of cases. The risk remaining subsequent to the cessation of bleeding drops to less than 5% after three days and less than 1% after seven days. (28, 33, 42, 49)

Surgical measures: Surgical intervention is necessary in 5−25% of cases.

Lethality: Figures for lethality rates vary between 5−8% (and up to 30%). When no blood transfusion is necessary, the rate lies below 4%; when more than six units of blood have to be transfused, it can rise to 50%.

Prognosis: Decisive factors influencing the prognosis of acute GI bleeding include: (*1.*) immediate stabilization of circulation, (*2.*) prevention of aspiration, (*3.*) type of bleeding (varicose, arterial, diffuse), (*4.*) intensity of bleeding and blood loss, (*5.*) age and possible comorbidity of the patient, (*6.*) success of the treatment, and (*7.*) recurrent bleeding. (s. tab. 19.5)

1. State of shock in the hospitalized patient
2. Initial Hb value < 7 g/dl or haematocrit < 30%
3. Forrest state Ib/II
4. Insufficient circulatory stabilization despite optimal volume replacement
5. Consumption of > 6 units of blood per 24 hours
6. Advanced age of patient, depending on biological aging
7. Concomitant illness: chronic liver, cardiac, pulmonary or kidney disease; diabetes mellitus; *etc.*
8. Short-term recurrence of bleeding
9. Ulcer patients after unsuccessful conservative therapy, possibly over an extensive period of time, and now requiring subsequent surgery

Tab. 19.5: Significant negative prognostic risk factors in upper gastrointestinal bleeding

In extensive bleeding from the larger arteries (e. g. gastroduodenal artery), surgery should be carried out immediately as opposed to losing valuable time with pointless endoscopic treatment.

2.6 Therapy

With coexisting liver disease, upper gastrointestinal bleeding poses special problems due to haemorrhagic complications or haemostatic disorders. Therapy is initially determined by the *form, location* and *classification* of the bleeding. (s. tab. 19.3) The *causes* of bleeding have a substantial influence on the therapy to be implemented − depending on the respective underlying disorder. (s. tab. 19.4) *Risk factors* that have a negative effect on the prognosis have to be considered in any decision regarding therapy, which is why the therapeutic procedures vary in individual cases. A bacterial infection is another important risk factor, so that the administration of antibiotics (e.g. norfloxacin) is recommended. (s. tab. 19.5) (s. fig. 19.12)

2.6.1 Basic therapy

Volume replacement: Adequate volume replacement, when possible through *two venous entry points*, is initially of utmost importance. A central vein entry point is strongly recommended to facilitate the constant monitoring of changes in CVP.

(*1.*) *Crystalloid i.v. solutions*, e.g. Ringer's solution, should only be used if the blood loss is relatively small (< 1 litre), since only 25−30% of the crystalloid i.v. solution has an effect on the volume. If administered in excessive amounts, this can lead to an undesired decrease in the colloidal pressure of the plasma. Crystalloid i.v. solutions, often with *glucose* as a principal energy source, also serve as carriers for any medicaments which have to be added to the drip infusion. HES

is an acceptable plasma substitute. • *The use of fructose, xylose and lipid solutions, high concentration glucose (= rise in portal pressure) or dextran products (= inhibition of thrombocyte aggregation) is not advisable.*

(*2.*) *Human albumin solution* has proved extremely reliable, especially when used in conjunction with crystalloid infusions. (Synthetic iso-oncotic colloids should be avoided as far as possible because of their negative effects on coagulation and kidney function.)

(*3.*) *Packed red blood cells* are indicated when the blood loss is >25% (Hb < 7−8 g/dl). In this event, at least three or four units of blood should be readily available, and sufficient reserves must be on hand. An Hb value of 10−11 g/dl is seen as an adequate transfusion target. Degradation of the citrate normally present in conserved blood is delayed in the case of cirrhosis, so that a substitution of 10 ml calcium per four units of erythrocyte concentrate is advisable. In order to avoid transfusion acidosis (pH < 7.2), 40 mval bicarbonate are administered for every four or five transfusions.

(*4.*) *Frozen fresh plasma* is used in cases of high blood loss (>50%), or even earlier if necessary (e.g. in the presence of concomitant coagulation defects). (s. p. 352)

Oxygen supply: Supplementary oxygen supply via a nasal tube is recommended. The air passages must be kept unobstructed, if necessary by intubation.

Gastrolavage using a double-lumen tube is of both diagnostic and therapeutic value in upper gastrointestinal haemorrhage. • Endobronchial intubation is recommended for disturbances of consciousness.

Bowel purgation: In gastrointestinal haemorrhage, large quantities of plasma proteins infiltrate the intestine. This results in an abundance of protein degradation products, which may cause **hepatic encephalopathy** in the presence of sustained failure regarding the detoxification function of the liver. In addition, the breakdown of intestinal blood releases a large amount of ammonia stored in the erythrocytes for systemic transport, thereby considerably accentuating the danger of HE. • *Any blood must therefore be removed as rapidly as possible from the gastrointestinal tract!* To this end, a gastric tube is used (during endoscopy) to aspirate blood from the stomach. A swift and thorough intestinal purge is achieved by administering a 10% *mannitol solution* or *Golytely solution* through nasal intubation until a state of haemostasis is assured. Residual blood may also be flushed from the lower colon by additional *high enemas* with 300 ml lactulose (plus 700 ml water). This intestinal purgation is followed by further treatment with lactulose. An additional infusion of *ornithine-aspartate concentrate* may be advisable for the prevention or treatment of HE. (s. p. 287)

In severe bleeding of portal hypertensive gastropathy, treatment with **thalidomide**, a potent inhibitor of angiogenesis, may be indicated. (32)

2.6.2 Endoscopic haemostasis

Spontaneous haemostasis, which is found without active therapy in about half the cases of upper gastrointestinal bleeding, should never encourage the assumption of a passive approach with the postponement of suitable therapeutic procedures. There is an enormous danger of massive renewed haemorrhage as well as of the development of complications within a few hours following spontaneous haemostasis. (s. fig. 19.15)

The development of effective procedures for endoscopic haemostasis − as well as the use of TIPS (45) − has significantly broadened the spectrum of treatment in cases of non-varicose, upper gastrointestinal bleeding. Endobronchial intubation is strongly recommended for disturbances of consciousness. In patients with acute upper GI bleeding, infusion of erythromycin (3 mg/kg BW over 30 minutes) before endoscopy improves the removal of blood and water from the stomach. Erythromycin is a motilin agonist and, as such, produces this favourable gastrokinetic effect. (27) These procedures have also improved the results achieved in differential therapy. In Forrest I and IIa, endoscopy is of prime importance. Three groups of **endoscopic methods** are available: (*1.*) topical procedures, (*2.*) thermal methods, and (*3.*) local injection techniques.

1. Topical procedures: Various compounds may be applied under endoscopic observation to the site of non-varicose bleeding or bleeding ulcerations following sclerotization. • The experience obtained with **adhesive fibrin** or **thrombin** is encouraging. This is also true of their application in *hypertensive gastropathy* and in *gastric antral vascular ectasia (GAVE)*. **Argon-plasma coagulation** (and possibly **laser** procedures) may also be used. Angiodysplasia is best managed using heat treatment, especially in the case of argon plasma coagulation.

2. Thermal methods: Various thermal methods may be employed successfully in clearly defined instances of non-varicose bleeding of the upper gastrointestinal tract:

(*1.*) The **heater technique** (R.L. Protell et al., 1978) involves the use of a plastic-coated metal probe, the tip of which is heated by means of a wire. Definitive haemostasis may be attained in 90−95% of cases. The heater probe has proved easy to operate and is free of complications. (25, 35)

Whereas the heat of the heater probe is directly transferred to the site of bleeding, in the following types of probes, the electrical energy is transferred by high frequency diathermy.

(*2.*) The **monopolar probe** (C.R. Youmans et al., 1970) has a small differential electrode inside a catheter, which may be routed to the site of bleeding through the endoscope. At the same time, the non-differential electrode surface is fastened to one of the patient's extremities. Highly concentrated electrical energy is emitted from the probe and effects deep tissue coagulation. Primary haemostasis was achieved in 79−91% of the reported cases; recurrent bleeding only occurred in 6−8%. (28)

(*3.*) The **bipolar probe** (D.C. Auth et al., 1980) has no non-differential electrode, both electrodes being built into the tip. In the most widely used BICAP (= bipolar circumactive probe), a circular arrangement of several adjacent electrode pairs is incorporated

into the probe tip. This limits the depth to which the electrical pulse penetrates the tissue. (28, 34, 43)

(*4.*) The **electrohydrothermoprobe** (EHT) (W. Matek et al., 1983) is a refinement of the monopolar probe. It allows a stream of water to be directed through the probe: the site of bleeding can thus be irrigated and rendered more easily visible, and, at the same time, charring of the tissue in contact with the probe is prevented. In 92% of reported cases, definitive haemostasis was achieved, with recurrent bleeding in 11% of patients.

(*5.*) The high energy **neodymium YAG laser** (yttrium-aluminium garnet) has been used to treat bleeding gastrointestinal lesions (G. Nath et al., 1976). This method ensures deep tissue penetration of the energy, yet entails the disadvantage of a greater risk of perforation or ulceration. As with the monopolar probe, the tangential approach to the site of bleeding raises technical problems. On average, primary haemostasis was achieved in 90% (87−100%) of patients, and definitive haemostasis in 43−90%. Complication rates of up to 4% have been reported. (40, 43)

Analysis of the literature reveals no significant differences between electrocoagulation and (expensive) laser treatment procedures in terms of primary or definitive haemostasis. With laser therapy, the complication rate (0−4%) lies above that of electrocoagulation (0%). Heat and bipolar probes are regarded as the most "tissue-friendly", an inference supported by the results of animal experiments, while laser and monopolar probe methods are more "aggressive". The electrohydrothermal probe offers a compromise. In addition, electrocoagulation and EHT procedures are technically uncomplicated, locally applicable and lower in cost compared to laser methods.

3. Local injection techniques: Differentiation must be made between the use of local injections in the therapy of non-varicose bleeding in the upper gastrointestinal tract and the treatment of bleeding oesophageal varices. (24, 28, 40, 44)

Local injection treatment methods for non-varicose bleeding have proved uncomplicated, quick to carry out, independent of location, extremely reasonable in terms of cost and also very successful. • Absolute alcohol, adrenaline, polidocanol and hypertonic sodium solution are among the **active substances** used. A combination of suprarenin and polidocanol has meanwhile been established as first choice: adrenaline (0.005−0.01%) is injected into the mucous membrane surrounding the lesion in order to induce vasoconstriction. Directly afterwards, polidocanol (1%) or a hypertonic NaCl solution may be injected at the edges of the lesion, resulting in local oedema with vascular compression and thrombosis. The reported effectiveness of this method for primary haemostasis is 83−100%, and definitive haemostasis is attained in 91−94% of cases. The *complication rate* is < 1%.

If a blood clot is found at the bleeding site, it should be removed straight away with the help of a probe or loop. This is followed by endoscopic therapy. In this way, the risk of rebleeding can be markedly reduced.

The spectrum of local injection treatment in gastrointestinal bleeding has been expanded and the results improved by the introduction of **N-butyl-2-cyanoacrylate** (J.P. Gotlib et al., 1981). This "fluid tissue glue" polymerizes instantly on contact with blood and rapidly forms an embolus-like occlusion at the site of bleeding. (s. p. 362) • In addition, *fundus* and *stomach* as well as *duodenal varices* (K. Ota et al., 1998), which cannot be adequately assessed using standard sclerotization techniques, have become easier to treat. Tissue glue is still a possible therapy option.

4. Haemoclips: Using clips for bleeding ulcers can be problematic, since precise application is often unsuccessful in the presence of severe bleeding or when the ulcer has undergone deformation through scarring. Nevertheless, clips are nowadays regarded as the first-choice alternative if other forms of therapy fail. • Good results have meanwhile been achieved using haemoclips: recurrent bleeding was reduced to < 10%. When this technique was combined with subcutaneous injection of hypertonic sodium solution or adrenaline, the rate of recurrent bleeding dropped to < 3%. (29) The clips do not destroy the tissue, and the ulcer healing process is not impaired. If the ulcer base is too firm, it becomes more difficult to attach the clips and it may not be possible to use them at all. They are particularly suitable for dealing with Mallory-Weiss bleeding and Dieulafoy's ulcer. It should be mentioned that such clips are still relatively expensive. (24, 25, 29, 35)

2.6.3 Drug-controlled haemostasis

The use of particular substances may be considered in concordance with the existing haemorrhage situation. (s. tabs. 19.3−19.5) These may constitute either an adjuvant therapy to endoscopic haemostasis or be used when endoscopic or surgical measures are not indicated or not possible. (23, 26, 27, 38, 41, 48)

► Application of **pharmacological substances** in existing portal hypertension is aimed at reducing both the portal pressure and the hyperdynamic circulatory status as well as improving the microcirculation in the gastrointestinal mucosa. • Such substances are also used to correct the secretory and motor function status of the gastrointestinal tract, thus diminishing the overall vulnerability of the gastric mucosa. • The instability of the clotting system is controlled by the administration of fresh plasma. All these measures improve primary and definitive haemostasis as well as reducing the probability of any complications or recurrence of bleeding:

- **Proton pump inhibitors**
- **H. pylori eradication**

- **Propranolol derivatives**
- **Vasopressin derivatives**
- **Somatostatin or octreotide**
- **Fresh plasma**
- **Thalidomide**
- **Sucralfate, antacids**

3 Bleeding oesophageal varices

3.1 Oesophageal varices as collateral circulation

A serious **consequence of portal hypertension** is the formation of *collateral circulatory systems* with characteristic *haemodynamic circulation*. (s. p. 261) An awareness of these possibilities makes it easier to understand typical complications and provides grounds for the application of medicinal or invasive therapy for portal hypertension in the presence or absence of a haemorrhage. Enhanced inflow of blood from the splanchnic area into the portal vein or decreased resistance in the arterial splanchnic circulation (e.g. due to glucagon) increases portal hypertension. (s. tab. 14.8) (s. fig. 14.6)

► **Oesophageal varices,** like **cardia varices** and **fundus varices,** arise from a regional stasis of submucosal perioesophageal and paraoesophageal veins. • These varices are supplied by the left gastric vein and posterior gastric vein, while stomach varices are additionally served by the branches of the splenic vein and short gastric veins. Fundus varices may also receive a direct supply via a.v. shunts in the stomach wall. Neither the formation nor the presence of oesophageal varices shows any clinical signs. The development of Cruveilhier-von Baumgarten syndrome may protect cirrhotic patients from the risk of oesophageal varices forming and bleeding. (70) • *Elevated portal pressure is usually responsible for the formation of oesophageal varices.* (s. figs. 14.8−14.10)

3.2 Frequency and risks

Some 60−80% of all patients with portal hypertension develop oesophageal varices at some stage of their lives, half of them within two years and up to 90% within ten years of the initial diagnosis. Retrogression or spontaneous disappearance of oesophageal varices has been observed in less than 1% of patients within one year, mostly in the wake of extended and strict abstinence in cases of alcoholic cirrhosis. In 90−95% of cases, the varices are localized in the middle and lower third of the oesophagus (= "junction zone", i.e. in the area 2−6 cm above the oesophagogastric junction), and in 5−10% of cases, they are found in the area of the stomach fundus. Approximately 15% of patients have both oesophageal and stomach varices; these patients are particularly at risk with regard to haemorrhaging.

About 30−50% of oesophageal varix patients suffer from variceal bleeding during the course of their lives. • The risk of *initial haemorrhage* in a control group of untreated cirrhosis patients is approx. 20% per year (about 30% within three years). Most episodes of bleeding occur within the first year; altogether 70−90% occur within the first two years of observation. Some 20−30% cease spontaneously. The rate of *recurrent bleeding* (without prophylactic measures) is about 70% after the initial haemorrhage; the probability of a relapse is highest during the first week (75%), but is still relatively high after three months (30%). The prognosis is very poor in the event of early recurrent bleeding (more than twice within two days). (153)

Primary oesophageal bleeding proves fatal in 30−40% of cases despite adequate conservative treatment or emergency intervention. In general, 60−80% of patients survive longer than one year. Some 20−25% of all cirrhosis patients die as a direct result of bleeding oesophageal varices. • The lethality rate for each haemorrhage episode varies among the Child groups (A = 10%, B = 30−40%, C > 70%).

3.3 Predictive haemorrhagic factors

The *timing, degree of severity* and *frequency* of haemorrhage depend on numerous predisposing factors, which cannot, however, be used as sole criteria or in individual cases to predict the respective risk of bleeding. Full awareness of such established risk factors (s. tab. 19.6) is an important aid in defining previously non-haemorrhaging risk groups, giving the possibility of primary prophylactic measures. Severe splenomegaly and thrombopenia are also seen as risk factors. This aim has not become reality as yet. (125, 133, 134, 151)

Three pathogenetic mechanisms can trigger bleeding oesophageal varices: (*1.*) critical pressure increase in the varices, especially when it is sudden (= *explosion hypothesis*), (*2.*) flow turbulences with bidirectional blood flow in the varices (= *circulation hypothesis*), and (*3.*) inflammatory lesion at the varix surface with the formation of thin spots (= *erosion hypothesis*).

3.3.1 Increase in pressure

Oesophageal varices do not occur when the portal pressure lies below 10−12 mm Hg. It has been established that the risk of bleeding increases significantly in accordance with (*1.*) *size of the portohepatic pressure gradient*, (*2.*) *rise in the oesophageal varix pressure* (58, 135), and (*3.*) *subsequent growth in size of the varices.* The danger of recurrent bleeding also rises in relation to the variceal radius. A temporary elevation of the intravaricose pressure and the resulting increase in vessel wall tension may derive from one of several factors: the circadian rhythms (increase in nocturnal/early morning pressure), food intake, intra-abdominal pressure increase (from coughing, lifting heavy loads, choking, etc.) and even deep breathing as well as forceful respiratory movement. These may cause a sudden variceal rupture in isolated cases. (88, 131, 145, 149, 172) • An *upright posture* helps to limit the blood flow to oesophageal varices and hence reduces the risk of haemorrhage (101).

► The **pressure gradient** (HVPG) between the portal vein and the inferior vena cava (measured as the difference between WHVP and FHVP) is regarded as a more meaningful criterion than the simple portal pressure, which may be influenced by a variety of factors. (Portal vein pressure [P] = portal blood flow rate [F] x transhepatic vascular resistance [R]) (78) • Measurement of the blood flow in the **azygous vein** by means of thermodilution reveals a strong correlation between the oesophageal varix pressure and the varix size, but no correlation with the risk of bleeding. • The verification of a **hepatofugal blood flow** in the portal vein, splenic vein or superior mesenteric vein by duplex sonography predicts a limited risk of haemorrhage. The sonographic determination of a **hepatopetal blood flow** in the coronary veins correlates with a decreased tendency towards haemorrhaging. (192)

3.3.2 Endoscopic evaluation

In view of the methodological difficulties involved in the (direct or indirect) identification of relevant indicator levels, endoscopy is the only proven method available

for identifying meaningful parameters concerning varices and hence for estimating the risk of haemorrhage. • The **various criteria** to be assessed in each endoscopy may also be of individual relevance for prognosis:

1. **Size of varices:** The determination of the size of varices is of fundamental significance in assessing the haemorrhage risk. This is done according to different criteria: *grade I* = 1−3 mm (small), visible or visible under strain; *grade II* = 3−5 mm (medium-sized), visible twisted, solitary or corkscrew-like; *grade III* = 6−10 mm (large), lumen-occluding; *grade IV* = >10 mm (very large), lumen-occluding, red patches, thin spots.

2. **Localization of varices:** The localization of varices may likewise be useful for evaluation purposes: those in the lower oesophagus and in the cardia area are more likely to rupture. The simultaneous presence of *oesophageal* and *fundus varices* (10−15%) carries an increased risk of haemorrhage.

3. **Surface of varices:** An assessment of the appearance of the variceal surface provides valuable criteria. The colour may be classified on a scale from (connective tissue-like) white to (blood clot-like) blue. Occasionally, there may be circumscribed red patches or stripes, corresponding to blocked and dilated vessels in the mucosa or submucosa. These are accompanied by an abnormal elevation of oesophageal varix pressure. They may be classified as small, *cherry-red spots* (A.E. Dagradi et al., 1966), *red wall markings* in the form of stripes or *haemocystic spots* of over 4 mm in size resembling blood-filled blisters (K. Beppu et al., 1981). *Diffuse red areas* may signify thin patches on the variceal wall. • *With elevated pressure in the varices, the growing increase in wall tension and decrease in wall thickness culminate in the formation of so-called* **thin spots,** *which are significant indicators of the risk of haemorrhage.* Varices with red-coloured signs are subject on average to about 40% more pressure than those without such signs, and haemorrhage occurs two or three times more frequently in such cases. (s. fig. 19.6)

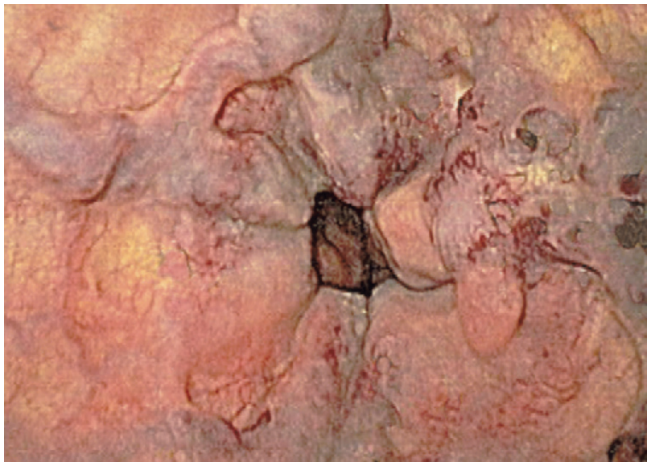

Fig. 19.6: Oesophageal varices with red wall signs

The **site of bleeding** can be located with precision in about 90% of cases. Haemorrhage may occur as seeping bleeding or as bright-red, spurting bleeding; there is often "pulsation", synchronous with respiration. An inactive haemorrhage site may occasionally be observed in the form of a coagulate or as a whitish thrombocytic embolus located at the point of rupture.

White nipple sign: No confirmation could be given of the findings reported by R.S. Chung et al. (1984) that a white nipple sign (= fibrin embolus) on a varicose node (= *Mount St. Helen's sign*) pointed to an unfavourable prognosis and recurrent haemorrhage. (171)

3.3.3 Sonographic evaluation

Endosonography may be regarded as a diagnostic improvement over sonography. (134, 139, 149, 162) (s. fig. 19.7) The recognition, diagnosis and sclerosing of varices is more reliably achieved by endosonography than by conventional endoscopy. (201) • A better evaluation of the risk of recurrent haemorrhage is also afforded by *duplex sonography.* (164)

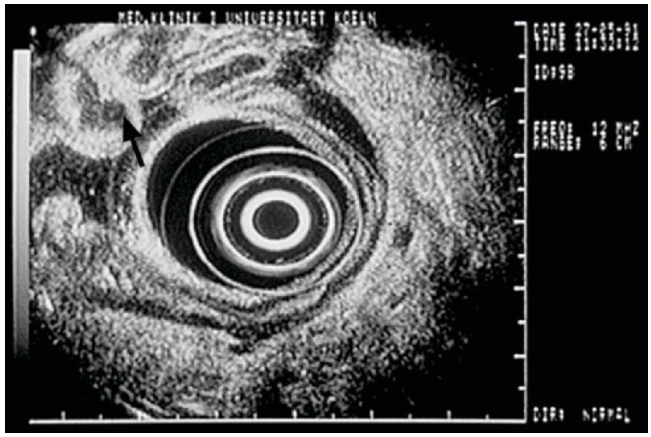

Fig. 19.7: Endosonographic detection of fundus varices (↑)

3.3.4 Child-Pugh criteria

Child-Pugh stage C (ascites, icterus, encephalopathy, albumin deficiency, drop in Quick's value) and regular alcohol abuse increase the frequency of haemorrhage and worsen the prognosis. *Coagulopathy* and *hyperfibrinolysis* are also considered to be additional risk factors, especially since higher fibrinolytic activity has been demonstrated in the mucosa of oesophageal varices. A correlation between the appearance of large *spider naevi* (>15 mm in diameter) on the skin surface and the onset of bleeding oesophageal varices was established by B. Varela Funtes et al. (1950). • A change in body position (e.g. bending over, lying down), cardia insufficiency, oesophagitis and gastro-oesophageal reflux have *no influence* on the tendency towards variceal bleeding.

3.3.5 CT and MRI

It is helpful to use CT with gastric varices (161, 197) and MRI with oesophageal varices (127), portal biliopathy (72) and bleeding of gall-bladder varices. (73)

3.4 Clinical aspects

Haematemesis: Oesophageal bleeding usually begins unexpectedly and without any characteristic preliminary signs. The onset is frequently in the evening, during the night or in the morning – possibly relating to the circadian rhythm of the portal pressure increase, vascular tone or clotting factors. (88, 131, 172) The haemorrhage often presents as surging haematemesis, and volumes of 500–1,000 ml of blood are vomited. The renewed accumulation of blood in the stomach may give rise to further surging haematemesis after a certain "pause in bleeding".

Endoscopic findings: An endoscopic diagnosis of the haemorrhaging should be undertaken as a matter of priority as quickly as possible after the circulation has been sufficiently stabilized. This has *three objectives*: (*1.*) exact localization of the source of bleeding, (*2.*) determination of the haemorrhage criteria, and (*3.*) assessment of coexistent findings. Additional, nonvariceal sources of haemorrhage occur in up to 30% of cases in the presence (and even absence) of varices. (s. fig. 19.8)

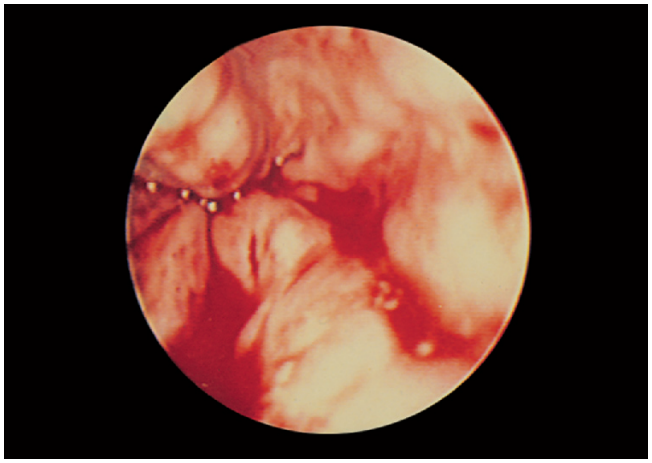

Fig. 19.8: Fresh bleeding of the oesophageal varices (first bleeding)

Circulatory disturbance: There is great variation in the effects of oesophageal bleeding on the circulation, depending on individual circumstances. Sometimes, only slight tachycardia and hypotension are presented despite extensive bleeding, whereas in other cases, a critical state of shock is rapidly induced, often leading to death. Sudden, unexpected transitions from an apparently compensated circulatory condition to a deleterious haemorrhagic shock must always be anticipated. The monitoring and evaluation of *circulatory parameters* are thus of utmost importance. (s. p. 355)

In the evaluation of the various **risk factors** hitherto discussed, which have also been expressed as quantifiable *scores* (NIEC score, München score), a simplified and practicable scheme may prove useful. (s. tab. 19.6)

Parameter	Low risk / I	High risk / III
1. Varix size	**small (3–5 mm)**	**large (> 6 mm)**
2. Fundus varices	**absent**	**present**
3. Red-coloured signs	**slight**	**strong**
4. Variceal pressure	**< 15 mm Hg**	**> 16 mm Hg**
5. Localization	**mid-oesophagus**	**lower oesophagus**
6. Alcohol	**abstinent**	**habitual user**
7. Hyperfibrinolysis	**no**	**yes**
8. Thrombopenia	**no / slight**	**strong**
9. Splenomegaly	**slight**	**strong**
10. Child-Pugh stage	**A ⟶ B**	**C**

Tab. 19.6: Relevant parameters as distinct risk factors for assessing the haemorrhagic tendency of oesophageal varices

Complications: The possible outcome of oesophageal haemorrhage can take the following forms: (*1.*) haemorrhagic shock, (*2.*) acute liver or kidney failure, (*3.*) hepatic encephalopathy (culminating in hepatic coma), (*4.*) consumptive coagulopathy, and (*5.*) aspiration pneumonia.

3.5 Conservative therapy

3.5.1 Basic therapy

Basic therapy of bleeding oesophageal varices is carried out under intensive care conditions. It essentially corresponds to the procedures for upper gastrointestinal haemorrhage (s. p. 356) and has **three main objectives:**

1. *Volume replacement* for circulatory stabilization
2. *Gastrointestinal irrigation* to prevent hepatic encephalopathy
3. *Monitoring of haemostasis* to prevent coagulopathy

Volume replacement should not increase CVP beyond 4–5 cm H_2O or the haematocrit beyond 35%, since there is a danger of recurrent bleeding from the oesophageal varices in the event of overcompensation. *Haemostasis parameters* (e. g. thrombocyte count, Quick's value, fibrinogen, AT III) must be continually monitored, so that any need for volume replacement is recognized immediately. • A *torsade de pointes* (special form of ventricular tachycardia) may arise in the case of an electrolyte imbalance combined with vasopressin and neuroleptics. (84) (s. fig. 19.9)

3.5.2 Sclerotherapy

► The sclerosing of bleeding oesophageal varices was first carried out by C. Crafoord et al. (1939). They injected the agent quinine-uretan (used at that time to sclerose haemorrhoids) into the varices via an oesophagoscope applying their own customized needle. This

method was taken up by E. Wodak in 1958 and subsequently recommended for the periodic treatment of bleeding oesophageal varices. Positive clinical results employing a paravaricose sclerosing technique were likewise reported by H. Denk (1963).

Primary haemostasis: According to many publications, sclerotherapy has a success rate of 80−90% (60−100%) for establishing primary haemostasis.

Definitive haemostasis: Definitive haemostasis can only be considered as "certain" after the complete sclerosing of oesophageal varices carried out during four to six days of treatment in a period of six to eight weeks. • The sclerosing of oesophageal varices has meanwhile become standardized procedure.

Methods: Many technical modifications in the field of sclerotherapy have been reported and evaluated in a variety of publications. Variations in method include the range of instruments, injection technique, amount and concentration of the sclerosant per puncture as well as over the whole treatment period, needle gauge and time lapse between treatments. The results achieved are nonetheless largely identical. The method selected ultimately depends on the experience of the physician involved and, in individual cases, on the particular clinical picture. (174)

Rigid oesophagoscope: Endoscopic sclerosing is normally carried out under i.v. sedation, employing flexible instruments with a wide suction channel. General anaesthesia is recommended in difficult cases of severe bleeding. • The use of a rigid oesophagoscope may be advantageous for endotracheal anaesthesia in special circumstances (compression of strongly bleeding varices, localized focusing on varicose nodes within the endoscope aperture, improved aspiration of blood). Such a technique is, however, in itself more difficult. *Adequate experience in "rigid" methods is without doubt extremely advantageous in intensive care situations.*

Injection technique: Intravascular, paravascular (submucosal) or combined injection techniques may be employed. • An *intravaricose injection* results in immediate thrombosis and subsequent fibrosis of the varices. • The *paravaricose technique* facilitates first the compression of the haemorrhaging varices and then the (submucosal) formation of coarse scar tissue, which prevents variceal rupture and maintains the collateral integrity of the venous lumen at the same time. Replacement of the entire oesophageal mucosa by a connective tissue lining may be necessary to eradicate the varices completely. Paravascular injection often results in the sclerosing of varices. No significant differences between the efficacy of the two methods have been shown. Moreover, the "free-hand" nature of clinical treatment renders any strict differentiation between intra- and paravascular methods difficult. • Preference is thus given to the *combined injection technique* (N. Soehendra et al., 1981), since the sclerosing of varices is more rapidly achieved in this way and rebleedings or the appearance of new varices are more seldom. • It is important for successful treatment that sclerosing begins at the gastro-oesophageal junction and proceeds proximally.

Sclerosants: The following sclerosants are generally applied: polidocanol (0.5%−3.0%), ethanolamine oleate (5%), sodium morrhuate (2.5−5.0%), aqueous phenol solution (3%), sodium tetradecylsulphate (1−3%), ceplacolin (95%), phenolic almond oil (5%) and ethyl alcohol (45%). • **Polidocanol** (hydroxypolyethoxydodecane) is the most frequently used. The higher the concentration and the quantity of the sclerosing agent, the more common side effects are. However, the sclerosing impact is far more reliable, including the "desired" local inflammation with scar formation. • The most effective sclerosant (within ca. 20 seconds) is **N-butyl-2-cyanoacrylate** (0.5 ml + 0.7 ml lipiodol), which may only be injected into the varicose vein! It is already used widely as a method of choice. Technically speaking, an endoscopic operation is time-consuming and calls for perfect teamwork if tissue damage and clogging of the instrument are to be avoided. Risks for the patient include mediastinitis, local ulcerations and systemic embolisms. (81, 85, 122, 136, 179) • The combined use of butylcyanoacrylate and ethanolamine oleate has also been reported. (181)

Injection volumes of 1−2 ml per paravascular technique and 3−5 ml per intravascular technique are recommended, with a maximum of 30 ml per day. A total of ten injections may be required for each treatment session.

Injection interval: A one-week interval between treatment sessions (three to seven days for paravascular injection, at least seven days for intravascular injection) has proved to be effective for the obliteration of varices by means of repeated sclerosing (usually a total of five to six sessions).

Advantages: There are obvious advantages in using sclerotherapy: (*1*.) high effectiveness, (*2*.) low complication rate, (*3*.) no deleterious effects on haemodynamics or liver function, (*4*.) simplicity of use, (*5*.) patient acceptance, and (*6*.) well-balanced cost-benefit ratio.

Side effects: Side effects such as erosions, superficial ulceration or mucosal necrosis can be expected in >80% of cases. Sucralfate, cimetidine, ranitidine and omeprazole as well as fibrin adhesive have been used both for prevention and to promote healing. From a morphological viewpoint, these inflammatory tissue reactions are to a certain extent necessary to induce thrombosis and angiofibrosis. Fever, leucocytosis, chest pain and tension occur as frequent, yet usually insignificant concomitant reactions. Dysphagia or dysfunction of the oesophagus are of no clinical significance. The development of a gastro-oesophageal reflux is the subject of some controversy.

Complications: The frequency of complications fluctuates considerably, and thought must be given to the great differences between haemorrhage patients. Complicative developments can be anticipated in 10−20% of cases (when flexible instruments are used). Serious complications occur in 1−3% of cases. Lethality has been reduced to 1%. (56, 107) • Approximately *forty different types of complications* have been reported: radiologically demonstrable thoracic findings (80−85%) (166), oesophageal strictures (10−15%) (117), thrombosis of the subclavian vein, bleeding from sclerosing ulceration (5−10%) (165, 199), perforation of the oesophagus (1−2%), broncho-oesophageal fistula, mediastinitis, infection or bacteraemia (155) including pyogenic meningitis and cerebral abscess (195), formation of haematoma (159), gastro-oesophageal reflux (111), pleural effusion in 10−20% of cases (55, 109), chylothorax (68) and other pleuropulmonary complications (166), pericarditis or pericardial effusion (114), arrhythmias and myocardial ischaemia, peritonitis (178), ascites, thrombosis of the portal vein (119), development of squamous cell carcinoma (64, 91, 104, 118), etc. • The use of polidocanol can lead to considerable cardiodepressive effects. The potential danger of embolism, particularly of cerebral embolism, has been mentioned in connection with butylcyanoacrylate application. Disseminated coagulopathy has been described

following repeated injections of ethanolamine oleate. • Life-threatening ventricular arrhythmias, so-called **torsade de pointes**, have been observed subsequent to the application of neuroleptics or vasopressin as well as in the case of electrolyte imbalances. (84) (s. fig. 19.9)

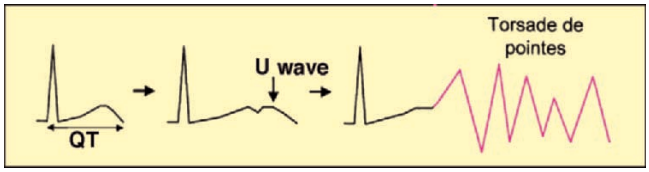

Fig. 19.9: *Torsade de pointes:* The QT interval represents the phase of myocardial spread of stimulus and repolarization. Excessive QT lengthening may be caused by certain drugs or electrolyte imbalance. In addition, a U wave can occur, whereby its amplitude exceeds the T wave in V_4-V_6. Subsequently, a potential life-threatening arrhythmia of type torsade de pointes may develop. Clinical symptoms include vertigo and syncopes. This arrhythmia can spontaneously disappear, but also pass into ventricular fibrillation and thus end fatally

Indications: The use of sclerosing therapy − *which has been widely replaced by banding therapy!* − is based on three indications:

1. in acute bleeding of oesophageal varices
2. for preventing the recurrence of bleeding
3. as a preventive measure against primary haemorrhage

Primary haemostasis: *Acute sclerosing* is generally performed during the first endoscopic examination. The rate of haemostasis is 70−95(−100)%. Frequency of (early and late) recurrent bleeding has been reduced to 30−50%, most effectively after several months, when all varices have been obliterated. Nevertheless, an annual risk of recurrent bleeding of 10−20% remains due to newly formed varices, especially in the stomach fundus. Inpatient mortality is about 20%. However, more ways are being found to improve life expectancy. • If acute sclerosing is not possible or has failed due to massive haemorrhaging, the *balloon tamponade* may be used to provide temporary relief until the circulation has stabilized sufficiently. (s. p. 364) However, this is only effective for a limited period of time and in about 80% of patients. • Adjuvant *medicinal therapy* to reduce portal pressure is helpful. (s. p. 366) • At this stage, *elective sclerosing* can generally be performed with better visibility and circulatory conditions. In approx. 70% of cases, primary haemostasis can be achieved by means of acute or elective sclerosing. It is seldom necessary to perform portal vein surgery. (54, 57, 61, 73, 85, 86, 89, 90, 95, 106, 113, 126, 146, 168, 170, 174−176, 180, 181, 183, 184, 189, 190, 194)

The sclerosing of acutely bleeding fundus or stomach varices is more difficult from a technical point of view. (110, 161, 197) In this respect, the use of **butylcyanoacrylate** is a genuine step forward. (79, 81, 85, 122, 136) More effective haemostasis and a lower rate of late recurrent bleeding (about 8%) may also be achieved in sclerosing oesophageal varices using this substance, which is only administered intravascularly! Adverse effects include delayed rejection of the plastic-like plugs (after 6 to 8 weeks) and protracted healing of the defect. (s. p. 362) • *Pregnancy* does not preclude successful sclerotherapy. (102, 116) • *Nutrition* has no influence on the complication rate of sclerotherapy.

Interval sclerosing: There is *recurrence of bleeding* in 30−40% of patients within the first five or six days. Preventing a relapse is the most important consideration in the weeks following the successful treatment of primary haemorrhage. This *secondary prophylactic measure* helped to reduce the rate of potentially fatal recurrent bleeding from 70−80% to 30−40% over an observation period of one to four years as compared with a control group. The importance of acute sclerosing for primary haemostasis and of interval sclerosing for the prevention of relapses as well as in a long-term prophylactic strategy is undisputed. • The next sclerosing step is performed within the first three to seven days and repeated at weekly intervals until the varices are fully obliterated. Interval sclerosing, each time lasting one or two days, is undertaken during hospitalization. Endoscopic follow-up is carried out at two to three-month intervals, with further sclerosing in the event of any recurrence of varices. • During the **bleeding interval,** the following procedures are available: (*1.*) programmed *sclerosing* or *ligature treatment*, (*2.*) supplementary *drug therapy*, and (*3.*) portosystemic *shunting*. These procedures must be in accordance with the specific conditions of each case.

Prognosis: The *renewed formation* of collateral varicose lesions appears in 40−60% of patients within two years following the eradication of varices, although these patients tend to suffer fewer relapses of bleeding than those without new shunts. Fundus varices are found in 2−7% of cases. The question of a prognosis *quoad vitam* cannot be resolved simply in terms of the technical success of sclerosing, but is also substantially influenced by the prevailing liver function and by portal hypertension. In the first year, the survival rate in the Child A group proved to be significantly higher (80−95%) than in the Child C group (40%). Meta-analyses confirm the superiority of acute and interval sclerosing over non-endoscopic procedures not only with respect to primary haemostasis and the prevention of bleeding, but also regarding the improvement of survival time. Repeated sclerotherapy resulted in a five-year survival rate of 26%. (120) The prognosis for fundus varices, which are physically less accessible to therapeutic measures, is generally not so favourable. (71, 93, 120, 158, 176, 197)

Gastric varices are found in the fundus or in the region of the cardia. They have a lower rate of bleeding than oesophageal varices (5−10% of all acute variceal bleeding), but a higher lethality. Due to their deeper location

in the submucosa in comparison to oesophageal varices, sclerotherapy or banding is generally ineffective and may even aggravate the bleeding. Isolated gastric varices are mainly found in splenic vein thrombosis. Therapy is based on direct injection of N-butyl-2-cyanoacrylate into the varices (52, 79, 81, 110, 112, 122, 136, 161, 167, 177), balloon tamponade (140) or balloon-occluded retrograde transvenous obliteration. (s. fig. 19.10)

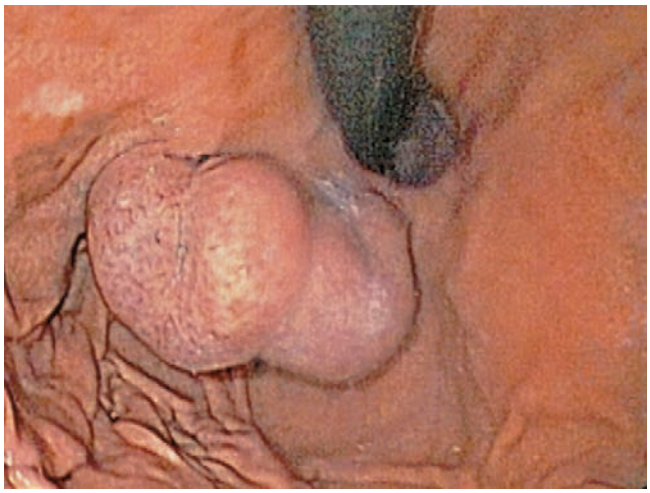

Fig. 19.10: Large varix in the gastric cardia

Duodenal varices are rare. Consequently, their frequency is poorly documented. They are present predominantly in patients with prehepatic portal hypertension. Therapy options include banding and medication (terlipressin, octreotide, later on β-blockers, etc.) or TIPS (provided there is no portal thrombosis). (59)

3.5.3 Endoscopic variceal ligation

► Following the propagation of rubber band ligation for haemorrhoids by J. Barron (1963), oesophageal varix ligation was later introduced by G. Van Stiegmann et al. in 1986.

Method: After sucking a varicose cord into a chamber at the tip of the endoscope, a rubber ring is applied around the respective varix in order to strangulate the bleeding varicose nodule. Between six and ten varices can be ligated during one session with the help of a speedband. Such an application set is available for clinical use. The multiligator top can carry as many as six to eight rings. As a rule, four or five sessions are held at weekly intervals. • A special *complication*, with lethal outcome in one case, is oesophageal perforation. This event can presumably be attributed to the entrapment of the oesophageal mucosa in the 6 mm aperture between endoscope and conductor, with subsequent rupturing upon further penetration of the piloting tube. Another rare complication is cerebral artery air embolism. (s. figs. 19.11, 19.12)

The reported **advantages** over sclerotherapy are (*1.*) lower rate of complications (2% vs. 22%), (*2.*) reduced occurrence of strictures or oesophageal dysphagia, (*3.*) swift and efficacious placement, (*4.*) lower frequency of recurrent bleeding (36% vs. 48%), (*5.*) ligation-related ulcerations are flatter and their healing is more rapid,

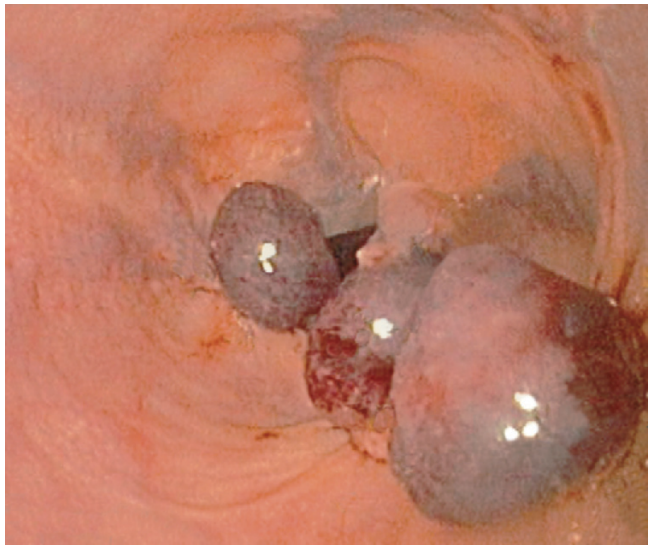

Fig. 19.11: Pronounced oesophageal varicosis: indication for ligation

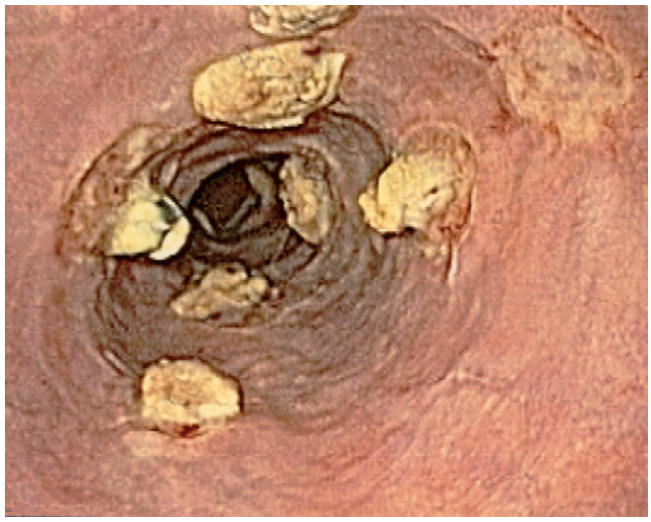

Fig. 19.12: Pronounced oesophageal varicosis: condition after ligation

(*6.*) fewer sessions are required, and (*7.*) mortality rate is lower (28% vs. 45%). The prerequisite is that the method is applied in such a way as to ensure precise placement. *This form of therapy has proved successful and even superior to sclerotherapy.* The ligation set, however, reduces the field of vision by about 30%, and aspiration of blood is hence rendered more difficult. At the Child A stage, this method is very efficient; in Child B, it is only indicated under certain conditions. This applies both to the treatment of acute variceal bleeding and secondary prophylactic strategy. In severe bleeding, a combination of ligation with somatostatin was more effective than sclerotherapy alone or drugs. • *After many years of experience, rubber-ring ligation has become the method of choice.* However, an initial rubber-ring ligature followed by sclerotherapy is also recommended. Mean success rate is 90−92%. (90, 122, 123, 126, 143, 145, 157, 160, 163, 170, 177, 179, 191, 198, 199)

3.5.4 Balloon tamponade

Massive bleeding can be effectively controlled by mechanical compression of bleeding oesophageal or fundus varices, yet only for a limited period of time. Unless the bleeding is life-threatening, it is necessary to carry out a preliminary endoscopic examination in order to localize the source of bleeding for ensuring accuracy in the selection and placement of the tube. (s. fig. 19.13)

The use of balloon tamponades in the form of the *Sengstaken-Blakemore tube* or *Linton-Nachlas tube* constitutes rapid and highly effective **emergency treatment**; this technique is initially necessary in some 10–15% of cases of acute bleeding. It guarantees primary haemostasis in about 80% (75–100%) of cases. Care should be taken in choosing a suitable balloon tube for each individual case. This method is indicated in cases of massive bleeding where no specific sclerotherapy or rubber-ring ligation is feasible because of greatly impaired visibility. The balloon tube may also be indicated in massive bleeding to bridge the time span until the circulation has been stabilized and the planned measures can be applied (even during transportation of the patient). It should also be possible to insert a balloon tamponade under intensive care conditions as and when required. As regards other causes of upper gastrointestinal bleeding, the balloon tamponade method is not appropriate, except under special circumstances. (87, 105, 140)

The **Sengstaken-Blakemore tube** (s. fig. 19.13) is the most widely used type. It comprises *four channels*: gastric tube, gastric balloon tube, oesophageal balloon tube, and tube for aspiration from the oesophagus via the tamponade. The tube is lubricated (using glycerine or liquid paraffin) and introduced through the nose (or, if necessary, through the mouth). The correct position of the tube in the stomach can be checked by auscultation (when air is blown through the lumen) or by X-ray. The gastric balloon is inflated with 150–250 ml air (secured with two clamps) and carefully fixed to the nose (or the mouth). It is not recommendable to weight down the tube. After the balloon has been positioned in the fundus, the oesophageal tube is inflated under manometric control to a pressure of about 40 mm Hg (generally, the oesophageal varix pressure does not exceed 30 mm Hg). At intervals of approximately two hours, the tube should be unblocked for 10 to 15 minutes to maintain the mucosal blood flow. It is imperative to keep the patient and the endoscopic technique under constant surveillance. Should the aspiration controls via the gastric and oesophageal tubes indicate a satisfactory degree of haemostasis, the oesophageal balloon is deflated, while leaving the gastric balloon inflated in the same position. After a further six to eight hours without recurrence of bleeding, the gastric balloon is likewise unblocked and the Sengstaken tube removed. The patient is kept in a head-up position throughout the whole procedure. • A different model, known as the **Minnesota tube**, is equipped with an additional feature to allow aspiration of the oesophageal contents above the balloon.

The **Linton-Nachlas tube** (s. fig. 19.14) has *three channels*: gastric tube with several lateral openings, tube for the pear-shaped gastric balloon, and oesophageal tube with lateral openings for aspiration. The gastric balloon is inflated with 350–500 ml air (depending on the physical stature of the patient) and drawn into the fundus and cardia area as well as into the lower oesophageal section by weight traction (500–750 g). This ensures good compression of the varices. As a rule, the tamponade can be maintained for 36 hours, with no intermittent unblocking. After this period of time, the

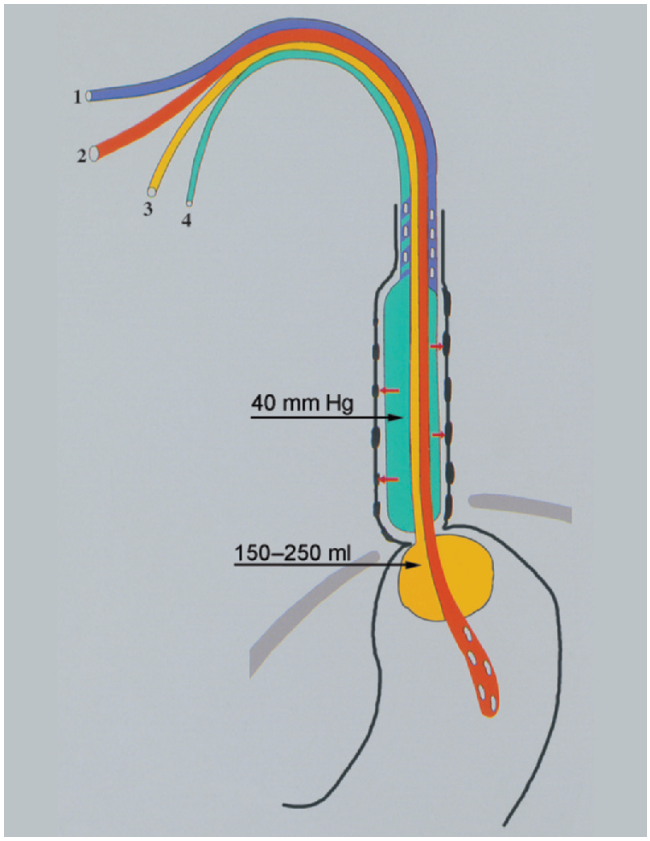

Fig. 19.13: Sengstaken-Blakemore tube (R. W. Sengstaken, A. H. Blakemore, 1950): 1. oesophageal tube, 2. gastric tube, 3. gastric balloon tube, 4. oesophageal balloon tube

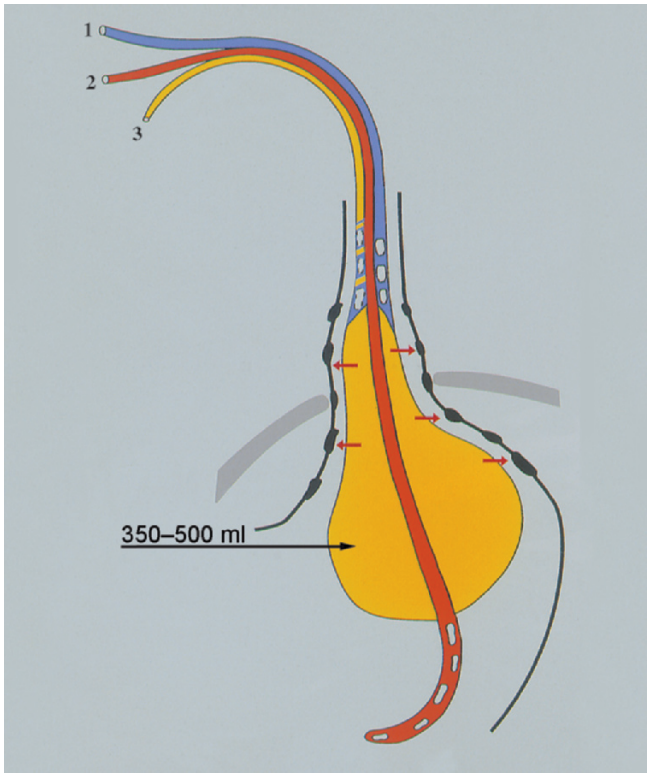

Fig. 19.14: Linton-Nachlas tube (R. R. Linton, 1953; M. M. Nachlas, 1955; L. Bertrand, H. Michel, 1969): 1. oesophageal tube, 2. gastric tube, 3. balloon tube

weight for traction is removed, yet the position of the tube remains unchanged for a further period of 12 hours. Hourly lavage and aspiration yield reliable information on the therapeutic results. In order to prevent nasal ulcers, pressure and rubbing should be avoided as far as possible. It is imperative for the patient to maintain a supine position with the head raised and secured by means of sandbags. • *The tube currently in use was developed by L. BERTRAND and H. MICHEL (1969).*

Complications: In 15−20% of patients, aspiration pneumonia, ulceration, oesophageal rupture or asphyxia occur due to dislocation of the tube. Therefore, the *range of indications for endotracheal intubation* must be limited. Overall duration should not exceed 6 to 12 (to 24) hours. The use of the tube is in itself rather unpleasant. Care of the patient and medicotechnical measures are rendered difficult by the indwelling tubes. After the balloon tube has been removed, **recurrent bleeding** can be expected in 30−50% of cases. This may necessitate another tamponade; alternatively, endoscopic procedures or medication for haemostasis can be employed. • *In cases of inadequate therapeutic success, further measures for a definitive haemostasis of bleeding oesophageal varices must be initiated without delay.*

Self-expandable metal stent: A new type of stent with special introducers allowed correct placement without radiographic assistance in massive bleeding. Bleeding ceased immediately after implantation. The stent was left in position for 2−14 days. This method was safe and effictive. (97)

3.5.5 Prevention of primary bleeding

K.J. PAQUET (1982) suggested the **sclerosing of varices** as a preventive measure and put forward a system of grading to assess risk patients for primary prophylactic procedures. Even though the size of the varix (degrees III and IV) generally correlates with the risk of bleeding, the *compiling of a prognostic index* proved unreliable, since it is virtually impossible to estimate the danger of haemorrhaging in the individual. This applies especially to the risk associated with prophylactic sclerotherapy and shunt operations. The results made available in the meantime have proved variable and controversial, for which reason primary sclerosing is not recommended as a preventive measure. Nevertheless, according to a meta-analysis, primary prophylactic measures using polidocanol were far more effective in improving the survival time when compared to a reference group, particularly in patients with a greater risk of bleeding. (50, 124, 150, 156, 160, 187, 188) • Preventive **variceal ligation** is also effective and safe in Child-Pugh A and B, especially in combination with nadolol, and offers a greater chance of survival than do β-blockers. (99)

Prophylactic medication consists of *β-blocking agents* (propranolol, timolol, nadolol). (s. p. 267) The risk of primary bleeding could be reduced by about 50%. (65, 74, 132, 147, 156) • Parallel treatment with *isosorbide mononitrate, molsidomine* and *spironolactone* is recommendable from a pharmacological point of view. Portal venous pressure should be 20−30% lower. • Previous studies have shown that all patients with cirrhosis and oesophageal varices should be given primary prophylactic medication. • Alcohol, acetylsalicylic acid and NSAIDs should be avoided. There is no advantage to be gained from not consuming certain foods (such as spices) or from the long-term intake of H_2 blockers.

3.5.6 Medicinal treatment

In bleeding oesophageal varices, **adjuvant medication therapy** is advisable for reducing portal hypertension. This can be achieved by (*1.*) lowering vascular resistance with the help of vasodilators, (*2.*) cutting down the blood flow into the oesophageal collaterals with the help of substances which restrict the arterial splanchnic circulation, or (*3.*) applying a combination of these two therapeutic procedures. (57, 77, 92, 143)

In 1956 **vasopressin** was recommended for the first time to treat bleeding oesophageal varices (J.H. KEHNE et al.). Acute bleeding is temporarily arrested within a few hours in 50(−70)% of patients (0.4−0.8 U/min, i.v.). In addition to the pressure reduction in the splanchnic vascular bed (20−30%) and in the varices (ca. 15%), there are occurrences of coronary spasms, ventricular arrhythmia (84), hypertension, abdominal pain and ischaemic organ lesions. By combining vasopressin with **glyceryl trinitrate** (0.4 mg, sublingually or i.v.), the frequency of side effects can be reduced (31%) and the elevated portal pressure lowered. Vasopressin has largely been replaced by its synthetic derivative terlipressin.

Terlipressin has been used for bleeding oesophageal varices since 1975 (K.F. ARONSEN et al.). This "prodrug" is converted by enzymatic splitting off of the three glycine residues into active lysovasopressin, which results in an even distribution in the plasma and a prolonged effect (half-life of 3 or 4 hours). Terlipressin is administered at four- to six-hour intervals (1−2 mg in 10 ml isotonic NaCl solution). Following a bolus injection of 2 mg, the intravaricose pressure is reduced by about 30% within 2 minutes, and HVP is significantly reduced over a period of four hours. Haemostasis was achieved in 60−90% of cases. Terlipressin can be successfully combined with a **nitrovasodilator,** whereby the side effects of the vasoconstrictors are decreased. The combination of terlipressin and nitrates is the most beneficial drug regimen for bleeding oesophageal varices. Comparative studies on balloon tamponade, sclerotherapy and somatostatin have also demonstrated the efficacy of terlipressin. (53, 60, 86, 87, 100, 144, 169, 173) (s. p. 892)

Somatostatin has been recommended as medication for bleeding oesophageal varices since 1979 (L. THULIN et al.). It lowers the elevated portal pressure and reduces the blood flow in the azygous vein. The ideal dosage is 250 µg as an i.v. bolus administered immediately after emergency admission, followed by 250 (−500) µg/hour as i.v. infusion. The arterial splanchnic blood flow is decreased by 20−30% with unchanged systemic pressure. This facilitates sclerotherapy and improves therapeutic efficacy. In diabetes mellitus, it is advisable to check blood glucose

levels repeatedly, since there may initially be a reduction and later an increase in blood glucose. Somatostatin probably antagonizes the effect of glucagon. The haemostatic effect of somatostatin is well documented (64% vs. 41%) (67); the drug has proved to be almost equivalent to terlipressin, and superior to vasopressin. Comparative studies with balloon tamponade or sclerotherapy also indicated that the results achieved with somatostatin were virtually identical in terms of primary haemostasis in 80% of cases. (54, 67, 105, 168) Somatostatin may also be indicated as concomitant treatment after sclerotherapy and ligation for five to seven days, since the danger of recurrent bleeding is particularly great during this period. (61, 106, 144) (s. p. 892) • The synthetic derivative **octreotide** shows good effects (reduction in mesenteric perfusion, HVWP, blood supply into the azygous vein and intravaricose pressure) in 80–85% of cases and has a much longer half-life than somatostatin (1–2 hours vs. 2 minutes). A dosage of 25–50 µg/hr is recommended as a continuous i.v. infusion. Octreotide has only few side effects. Recent results favour octreotide over vasopressin/terlipressin. (75)

	Initial bolus	Maintenance dose	Duration of therapy
Terlipressin*)	**2 mg i.v.**	**1–2 mg/4 hr i.v.**	**2 days**
Somatostatin	**250 µg i.v.**	**250 µg/hr i.v.**	**5 days**
Octreotide	**50 µg i.v.**	**25–50 µg/hr i.v.**	**5 days**
*) in combination with glyceryl trinitrate (20 mg/24 hr transdermally or 40–70 µg/min i.v.)			

Losartan is an antagonist of angiotensin-II receptor. With oral administration (25 mg/day), portal hypertension could be significantly reduced. Side effects were not observed.

Metoclopramide reduces the intravaricose pressure by restoring the normal tone to the lower oesophageal sphincter. The use of metoclopramide for the prevention and treatment of oesophageal varix bleeding is thus another pharmacological alternative. The haemodynamic effects of portal hypertension are not influenced.

Nitrates were used to produce a favourable effect on portal hypertension: isosorbide dinitrate, isosorbide mononitrate (51, 65, 123, 124, 132) and glyceryl trinitrate (87). *Glyceryl trinitrate* can easily be controlled owing to its short half-life of five minutes. It is also effective upon transdermal application (10 mg/day).

Molsidomine (L. R. Del Arbol et al., 1989) diminished the hepatic venous wedged pressure and the hepatic venous pressure gradient as an acute effect. Furthermore, in long-term oral treatment (3 to 6 months), the variceal pressure decreased by 28% and the hepatic venous pressure gradient by 25%, with a simultaneous reduction in the size of varices of about 17%. (98) A dose of 2 mg proved adequate. Orally applied molsidomine can thus be recommended for long-term prophylactic medication. • In further studies, octreotide or the balloon tamponade were found to be superior to the combined application of nitroglycerin + terlipressin or nitroglycerin + vasopressin. (169) • The combination of *nitrates with β-blockers* has proved more effective than monotherapy in reducing portal hypertension. (190)

Propranolol was used for the first time as a *β-blocking agent* for prophylactic measures with regard to bleeding oesophageal varices (D. Lebrec et al., 1980). • By dilating the splanchnic vessels, it leads to a lower blood flow into the portal vein and thus a decrease in portal hypertension of 20–30%. This effect is only maintained when the intake is regular, although careful monitoring of the cardiac and circulatory function is still necessary, with particular attention being paid to a potential reduction in the cardiac output. In some patients, portal pressure cannot be diminished even with an adequate dosage of propranolol (non-responders). The frequency of *side effects* (such as hypotension, dizziness, Raynaud's syndrome, bradycardia, bronchoconstriction, impotence) is below 20%. • Propranolol can be used successfully as a prophylaxis for both oesophageal and fundus varices. The dosage (twice daily) should be continued until the pulse rate is reduced by approx. 25% of the initial value (generally down to 55–60/min); the blood pressure should not fall below 90 mm Hg. (92) • The risk of primary bleeding is lower when propranolol is applied as a primary prophylactic measure in patients with medium-sized or large varices and "red-coloured signs". (50, 74, 147) • *Long-term treatment* with propranolol may be successful in certain situations as a secondary prophylactic measure in order to prevent recurrent bleeding. (60, 124, 150, 189) This is particularly true of simultaneous interval sclerotherapy. (160, 163) The gastric mucosal blood flow was slowed down in portal hypertensive gastropathy; the serum gastrin level remained unaffected. • A combination of propranolol and molsidomine is considered to be efficient. • **Nadolol** has also been used with success as a β-blocking agent – in combination with nitrate – for the prevention of primary bleeding and relapses. It is only administered once daily; its elimination is predominantly renal. Side effects are markedly fewer (< 5%) than with propranolol. (65, 123, 132, 190, 191)

3.5.7 Bacteraemia

Clinically relevant bacteraemia is seen in 5–15% of patients who undergo emergency sclerosing of oesophageal varices. Prophylactic treatment with poorly absorbable antibiotics led to a reduction in the frequency of bacteraemia and infections. The risk of rebleeding is increased by bacterial infection. *Thus it was possible to reduce cases of rebleeding significantly by administering an antibiotic prophylaxis for a period of three to seven days.* In this connection, the use of norfloxacin (2 × 400 mg/day for 1 week), ofloxacin or ceftriaxone proved beneficial. (63, 148, 155) (s. p. 310)

Synopsis

Primary prophylactic measures, such as administration of propranolol or nadolol (if necessary, combined with isosorbide mononitrate, molsidomine and spironolactone), sclerotherapy (50, 148,187) or banding ligation (99, 124, 160), may be indicated in cirrhosis patients who present *major risk factors* for primary oesophageal bleeding. (s. tab. 19.6)

The various **conservative methods** used in the treatment of bleeding oesophageal varices have been investigated in a number of clinical studies. It might well be difficult to assess the results − often varying and occasionally controversial − since the individual findings within the frequently heterogeneous patient groups rarely permit any comparability between the studies. • Subsequent to the endoscopic confirmation of the diagnosis − which may only be omitted under exceptional circumstances − the decision must not only focus on the treatment procedures to be implemented, but on a flexible, sequentially structured process. This means using suitable, clinically well established procedures which have been selected from the entire scope of conservative treatment.

For **primary haemostasis,** *sclerotherapy* or *varix ligation* are considered to be the methods of choice. • Should sclerotherapy or ligation not be feasible (as yet) for primary haemostasis, *medication therapy* (first priority) with terlipressin and octreotide may be applied as an alternative − with the aim of carrying out subsequent sclerosing or ligation as soon as possible. • Should it be imperative to control massive bleeding without delay, the *balloon tamponade* method can be applied for a limited period of time. Here, too, the aim must be early sclerotherapy or ligation.

As a **secondary prophylactic step** against recurrent bleeding, eradicating sclerotherapy or ligation are the methods of choice. At the same time, β-blocking agents and nitrates may be given both as *adjuvant treatment* and subsequent *long-term therapy.* (200) Furthermore, spironolactone and/or molsidomine are also suitable in such cases.

The question concerning the use of **semi-invasive** or **surgical measures** arises once definitive haemostasis has been achieved. This depends on the liver function in each case and a careful review of the individual risk factors and behaviour as well as an assessment of the indications. • Variceal bleeding that has proved unresponsive to haemostatic efforts over a period of time exceeding two days (with a daily application of more than four units of packed red blood cells) in spite of all conservative measures must be subjected to semi-invasive or surgical therapy. This also applies to an early recurrence of bleeding.

3.6 Semi-invasive treatment

3.6.1 Transhepatic embolization

The transhepatic embolization of bleeding oesophageal varices, which was first used by A. Lunderquist et al. (1974), is only of minor clinical importance today. With this procedure, a vascular catheter is introduced via the percutaneous transhepatic route into the portal system, and the convolute of varices is selectively thrombosed. (83)

3.6.2 TIPS

From a haemodynamic point of view, the transjugular intrahepatic portosystemic stent shunt (TIPS) constitutes a portacaval side-to-side anastomosis in the form of a nonsurgical link between the portal vein and the hepatic vein. The TIPS can be closely compared with the portacaval interposition shunt, because the pressure reduction also depends on the shunt lumen. Stent placement leads to a permanent *decrease in portal pressure*; in 60−70% of cases, it was possible to achieve the desired reduction in pressure to almost 12 mm Hg. In addition, the splanchnic blood pool decreased, the cardiac output increased, the RAAS was deactivated and renal function improved. (66, 128) (s. pp 267, 320, 336, 899) (s. figs. 16.15, 16.16)

This procedure, which is well documented in animal experiments, was introduced into clinical practice by R. F. Colapinto et al. in 1983. A self-expanding *Wall stent* with a width of 8 to 10 mm or a *Palmaz metal stent* (J. C. Palmaz et al., 1985), which can be expanded up to a maximum of 16 mm, is applied. The latter was first used in clinical practice in 1989 (G. M. Richter et al.). • With this method, a catheter is inserted into a right liver vein through the internal jugular vein. The portal vein is punctured near the bifurcation by means of a needle inserted through the catheter, and a guide wire is introduced to an adequate extent into the portal branch. The liver tissue between the liver vein and the portal vein is predilated by means of a balloon catheter via the guide wire, and the Palmaz stent is subsequently inserted. • The problem of stenosis or restenosis of the stent can be largely prevented with the help of a newly developed stent type. (186)

Indications: The indications are: (*1.*) bleeding from oesophageal or gastric varices (acute, non-controllable bleeding, prophylactic measures against rebleeding, variceal embolization) (45, 59, 62, 89, 130, 163, 186), (*2.*) relapsing haemorrhage in hypertensive gastropathy, (*3.*) refractory ascites, (*4.*) Budd-Chiari syndrome, (*5.*) hepatogenic hydrothorax, (*6.*) hepatorenal syndrome, (*7.*) portal thrombosis, and (*8.*) bridging the period of time preceding liver transplantation. (153, 185)

Results: The results of this semi-invasive procedure are convincing: successful insertion of a TIPS by an experienced team could be achieved in 88−100% of cases, with a survival rate of 85% after one year and 78% after two years. The frequency of rebleeding was lowered to about 10%. The functionality of the TIPS could be maintained for 4 years. (130, 185, 196)

Mortality: Mortality during the application of TIPS is 1%, early mortality within the first four weeks amounts to approximately 2%, and in the case of an emergency TIPS, the rate is about 20%.

Complications: The application of a stent rapidly effects the formation of pseudointima. Through increased thrombosis development, this may even culminate in stent occlusion (4−22%), which could cause rebleeding. However, there is the possibility of placing a new stent. The reported frequency of hepatic encephalopathy is 20−30%. Haemobilia was observed in 4−5% and liver haematoma in 4% of cases. In view of such a high rate of hepatic encephalopathy, the subclinical stage should also be diagnosed (s. pp 211, 280) and systematically treated until the time is appropriate for the placement of a TIPS. During the following period, all possible dietary and medicinal measures should be taken to avert the frequent, albeit unexpected occurrence of serious hepatic encephalopathy.

The first **liver transplantations** after the positioning of a TIPS were performed by E.J. Ring et al. (1992). (153) Meanwhile, other good results have been presented. (154) For transplantation purposes, a preceding TIPS is of decisive advantage as compared to a conventional shunt operation, since the extrahepatic vessels and the liver hilus remain intact. Therefore, TIPS is the method of choice when the time period preceding a transplantation has to be bridged for patients with stages Child B and C. (s. fig. 19.12)

3.7 Surgical treatment

As long ago as 1874, G. Banti attempted for the first time to reduce the portal volume by means of splenectomy. In 1894 he developed this procedure further by carrying out the simultaneous resection of the short gastric veins in order to cut off the blood flow into the oesophageal collaterals. During the course of the past 100 years, countless surgical procedures and modifications for the treatment of portal hypertension and bleeding oesophageal varices have been published.

► The **tabular list** presented here consisting of more than 50 surgical procedures cannot be considered as complete or even totally accurate. • *These multiple and ingenious efforts undertaken by surgeons to control the most frequent and most life-threatening bleeding event − bleeding from oesophageal varices with portal hypertension − are worthy of admiration and respect*. • The diversity of the methods might, however, also reflect critical dissatisfaction on the part of the individual surgeon with the clinical results hitherto achieved.

It is very interesting to compare a tabular overview of the surgical treatment of **bleeding oesophageal varices** (s. tab. 19.7) with a list of operative approaches for eliminating **refractory ascites.** (s. tab. 16.18)

3.7.1 Indications

Should it be necessary to consider surgical treatment for acute gastrointestinal bleeding, the decision depends on (*1.*) *cause of bleeding* in each case, (*2.*) *bleeding intensity*, and (*3.*) possibility of surgical elimination of the *source of bleeding*. The decision for operative intervention is taken in line with the following **criteria:**

1. Spurting arterial bleeding *(Forrest Ia)*
2. Volume replacement of >2 litres/day without definitive circulatory stabilization
3. Consumption of >5−6 units of blood/day without definitive haemostasis
4. Unfeasibility and inefficacy of conservative therapeutic measures in bleeding oesophageal varices or in hypertensive gastroenteropathy
5. Elective surgery for eliminating persistent recurrent bleeding from oesophageal and fundus varices (with strict adherence to selection criteria)
6. Ulcer patients with risk factors (initial Hb value <7 g/dl, *Forrest stages Ib/II*, signs of recurrent bleeding)
7. Secondary prophylactic measure at the request of the patient following objective presentation and discussion of the prevailing findings

3.7.2 Surgical methods

Close cooperation with the surgeon is imperative for optimum treatment results in gastrointestinal bleeding. (s. fig. 19.12)

Of the many surgical methods used in the treatment of bleeding oesophageal varices, only two groups are of relevance: (*1.*) block surgery, and (*2.*) pressure-reducing shunt procedures. (76) (s. tab. 19.7)

I. Nonsurgical methods

1. Local haemostatic methods
- Varicosclerosation (Crafoord, C., 1939)
- Tamponade (gauze + thrombin) (Barnett, C.B., 1949)
- Sclerosing of the oesophageal wall (Wodak, E., 1956)
- Transhepatic sclerosing (Lunderquist, A., 1974)

II. Surgical methods

1. Mediastinal tamponade
- upper and lower mediastinal tamponades (Som, 1947)
- gauze tamponade (Harlock, 1950)

2. Varicotomy
- total oesophagogastrectomy (Phemister, D.B., 1949)
- subtotal oesophagogastrectomy (Baranofsky, I.D., 1949)
- total small intestinal interposition (Meredino, K.A., 1950)
- total prosthetic interposition (Nachlas, M.M., 1956)
- total colon interposition (Koop, 1959)

3. Purse-string ligation of varices
- abdom./thorac./subdiaphragmatic (Henschel, C., 1938)
- laparogastroscopic varicosclerosation (Lund, 1939)

- transthoracic/transoesophageal (Boerema, I., 1949)
- transabdominal (Welch, C.S., 1953)
- transthoracic/perioesophageal (Nissen, R., 1954)
- oesophageal dissection ligation (Vossschulte, K., 1957)
- transthoracic/oesophageal (Hartenbach, W., 1963)
- oesophageal dissection ligation (Boerema, I., 1967)

4. Provocation of additional collaterals
- omentopexy (Talma, S., 1898)
- displacement of the spleen into the abdominal wall (Holman, 1950)
- splenopneumopexy (Nylander, E.E., 1950)
- hepatopexy (Rousselot, L.M., 1959)
- transthoracic displacement of the spleen and pole resection (Bourgeon, 1961)

5. Reduction in portal venous volume
- splenectomy (Banti, G., 1874)
- ligation of the left gastric artery and right gastroepiploic artery (Flerow, 1926)
- ligation of the hepatic artery (Berman, E.J., 1950)
- ligation of the splenic artery (Blain, A.W., 1950)
- small intestine resection (Laufmann, 1954)
- thoracic lymph fistula (Dumont, A.E., 1964)
- laterolat. lymphoven. anastomosis (Defni, M., 1965)
- terminolateral cervical lymphovenous anastomosis (Schreiber, H.W., 1968)

6. Interruption of afferent collaterals
- resection of the short gastric veins by splenectomy (Banti, G., 1894)
- ligation and resection of the coronary vein of the stomach (Rowntree, G., 1929)
- subcardia gastric dissection (Tanner, N.C., 1950)
- subtotal oesophageal resection (Cooley, D.H., 1954)
- oesophageal transsection (Walker, R.M., 1960)
- cardia reimplantation (Schmitt, W., 1963)
- submucosal transsection (Stelzner, F., 1963)
- circ. subcard. gastric dissection (Schreiber, H.W., 1964)
- decongestion of the oesophagus and stomach (Hassab, M.A., 1967)
- two-stage oesophageal dissection (Sugiura, M., 1973)
- fundectomy (Hunt, H.A., 1964; Stelzner, F., 1975)
- subcardia staple suture (Rinecker, H., 1975)

7. Shunt operations
- Portacaval anastomosis
  - end-to-side (Vidal, M., 1903; Whipple, A.O., 1945)
  - side-to-side (Rosenstein, P., 1912)
  - crossed (double end-to-side) form (McDermott, W.V., 1960)
  - interposition shunt (Sarfeh, I.J., 1986)
- Splenorenal anastomosis
  - mesentericocaval side-to-end anastomosis (Marion, P., 1953; Valdoni, P., 1954)
  - laterolateral form (Cooley, D.A., 1954)
  - distal form (Warren, W.D., 1967)
  - end-to-end anastomosis (Hivet, M., 1967)
  - proximal (central) form (Linton, R.R., 1974)
- Coronariocaval anastomosis (Gütgemann, A., 1961)
- Renomesent. renosplen. anastomosis (Erlick, D., 1964)
- Saphenoumbilical anastomosis (Piccone, V.A., 1967)
- Mesentericocaval side-to-side anastomosis (Maillard, J.N., 1970; Moreaux, J., 1972)
- Mesentericocaval interposition shunt (Reynolds, T.B., 1951; Drapanas, T., 1972)
- Splenocaval side-to-end shunt (Peiper, H.J., 1973)

Tab. 19.7: Overview of semi-invasive and surgical procedures for bleeding oesophageal varices and portal hypertension in chronological order (1874–1994). For reasons of simplification, only the first authors are named in each case. *(see also tab. 16.18!)*

1. **Block surgery:** This measure stops the venous flow to the bleeding oesophageal collaterals. The **disadvantage** is that portal hypertension is not influenced, so that there is a possibility of the collaterals and varices reforming and hence a danger of recurrent bleeding (40–60%). However, block surgery also has major **advantages:** (*1.*) it ensures rapid haemostasis, (*2.*) the duration of surgery is relatively short, (*3.*) the strain imposed on the patient by surgery is limited, (*4.*) the procedure is technically simple when using a stapler suture, (*5.*) liver perfusion is maintained, and (*6.*) there are no surgical problems with a subsequent shunt operation or liver transplantation. • Consequently, block surgery is performed as an emergency measure, particularly in cases of portal thrombosis. It is sometimes combined with splenectomy. (s. tab. 19.7)

Oesophageal transsection, as with the two-stage technique (Sugiura), and devascularization (Hassab, Paquet) have proved to be most valuable in cases of severe oesophageal bleeding which cannot be controlled by conservative measures. This is particularly true of high-risk patients. Haemostasis is guaranteed, recurrent bleeding is rare, and the frequency of encephalopathy is lower. Block surgery must be followed by systematic prophylactic measures against relapse. The indication for an elective shunt operation should be considered during the bleeding-free interval. Omeprazole and sucralfate have been used successfully in treating postoperative ulceration. (94, 129, 137, 184) (s. p. 900)

2. **Shunt operations:** Anastomoses are created in the portosystemic vascular area by way of this surgical method; they lead to a distinct and persistent reduction in pressure in the portal system. An operative shunt is the most effective method for attaining haemostasis and preventing recurrent bleeding. However, mortality is high: with the selective shunt, surgical lethality is 4–16% and late lethality 21–52%, whereas the respective rates for the total shunt are 4–13% and 18–69%. Before performing a shunt operation, indirect splenoportography and CT portography are the major examination methods. No shunt operation should be performed with a Quick's value of <40%. (108, 138, 141, 142) (s. p. 899)

► The classical form is the **portacaval end-to-side anastomosis** (laterolateral), applied for the first time in a dog by N.W. von Eck in 1877. Nevertheless, this was still a long way from clinical applicability. Not until 1901 was a clinical attempt made by R. Lenoir, yet without success. A renewed attempt to use this (end-to-side) shunt procedure undertaken by M. Vidal (1903) proved satisfactory. The first successful portacaval (side-to-side) anastomosis was reported by P. Rosenstein in 1912. Extensive clinical use of the portacaval shunt was encouraged by the studies of A.O. Whipple and A.H. Blakemore (1945). • The following years saw the development of a large number of varying shunt techniques and their modifications. (s. tab. 19.7)

The **complete shunt** involves a total bypassing of the portosystemic circulation. The liver blood flow is confined to the hepatic artery. This category includes the *portacaval end-to-side shunt*.

The **incomplete shunt** only effects a moderate reduction in pressure in the portal system, but residual mesentericoportal hepatic perfusion is generally maintained, which can be seen as a great advantage. This type of shunt includes: (*1.*) *portacaval side-to-side*, indicated particularly in ascites, (*2.*) *mesentericocaval interpo-*

sition, (*3*.) *portacaval interposition*, (*4*.) *laterolateral (proximal) splenorenal side-to-side*, and (*5*.) *proximal splenorenal end-to-side*, with splenic extirpation.

Deterioration of liver perfusion may possibly be prevented by **arterialization** of the portal vein stump (A. H. Hunt, 1952). Various arterialization techniques, including those which are pressure-adapted, have been tried out (D. Burlui et al., 1968; J. N. Maillard et al., 1970; U. Matzander, 1974; and others). • The technical advantages of a **mesentericocaval anastomosis** can be seen in the simplified access to the superior mesenteric vein and the easier decompensation of the anastomosis in a liver transplantation later on. • **Disadvantages** include the twofold anastomosis and the use of a plastic vascular prosthesis with the associated higher rate of thrombosis of 15−30%.

A selective decrease in pressure coupled with the simultaneous maintenance of portal liver perfusion permits a **distal splenorenal anastomosis** (Warren shunt). Decompression is then selectively limited to the gastrosplenic tract. Yet, this low-pressure area can only be maintained with an extensive surgical uncoupling of the circulation area of the splenic vein from the portal vein. Complete splenopancreatic disconnection comprising the left and right gastric veins as well as the epiploic veins is therefore necessary. Benefits include the much improved hepatic haemodynamics and the preserved clearance function. However, this shunt is technically more difficult and more time-consuming to implement, wide-lumen vessels are required and the rate of thrombosis can be as high as 50%. Moreover, due to the use of new venous links to the gastrosplenic area, the selectivity of the shunt is not guaranteed in the long term. **Splenoadrenal shunt** utilizing a left adrenal vein is deemed to be an excellent option in selected cases. (82, 96)

From a *haemodynamic point of view*, both complete and incomplete shunts are regarded as "complete shunts" because they lower portal pressure and decrease liver perfusion, albeit to varying degrees − depending on the technique and on subsequent structural changes to the liver or portal system. The portal perfusion rate in cirrhosis is reduced on average to approximately 30%, generally with arterial compensation and increased cardiac output. Cirrhosis patients show a stagnating or retrograde portal flow in 8−30% of cases. Shunt-associated *deficiency of the hepatic blood flow* would entail less serious consequences than total (or near total) failure of the liver as the major *clearance organ*.

3.7.3 Timing of shunt operation

When considering the ideal time point for a shunt operation, a distinction is made between (*1*.) emergency shunt, (*2*.) early elective shunt, and (*3*.) elective shunt.

► An **emergency shunt** is indicated in variceal bleeding that cannot be controlled by conservative measures. It is performed either as an **immediate shunt,** i. e. without previously attempted sclerosing, or as a **rescue shunt,** i. e. after unsuccessful sclerotherapy or ligation. Owing to the high rate of surgery-associated lethality (approx. 40%), the emergency shunt is generally used as a rescue shunt. In this respect, the *portacaval end-to-side shunt* is the most appropriate shunt form by virtue of its benefits: (*1*.) it is technically more simple to perform, (*2*.) the duration of the operation is relatively short (60−90 minutes), (*3*.) haemostasis is achieved rapidly, reliably and definitively, (*4*.) portal pressure is lowered swiftly and persistently, and (*5*.) with regard to the emergency situation, the surgical procedure is relatively well tolerated by the patient. Perioperative mortality is about 10% in Child A, 20−30% in Child B and over 50% in Child C. Moreover, this shunt entails the haemodynamic and functional late sequelae of a total shunt. The selective *distal splenorenal shunt* has also proved useful as an emergency measure, although the technique is more difficult and time-consuming, with greater operative lethality. If these emergency shunts are not feasible angiologically or for reasons pertaining to surgical techniques, a machine-performed block operation or oesophagogastric decongestion with splenectomy should be considered. (103, 108, 115, 152, 175, 180)

► An **early elective shunt** is created after initial haemostasis within one or two days if there are major grounds for immediate operative procedures. In principle, sclerotherapy or ligation should be continued for as long as possible, and thus such early elective shunts are rare.

► An **elective shunt** should be considered in situations where no definitive haemostasis was achieved (20−30% of cases) despite a sufficiently long sclerotherapy period and where there is still a danger of severe rebleeding. Choosing the most favourable shunt procedure should be done with due consideration of the individual case; there is no real answer to this issue, particularly as regards the decision in favour of a total or selective shunt, since the study data available can hardly be generalized (and are barely comparable). However, in most cases, preference is given to the distal renosplenic shunt and the mesentericocaval interposition shunt. (69, 121, 138, 141, 142, 182, 194)

3.7.4 Prognosis

The frequency of recurrent bleeding is 0−19% with elective shunts and 53−75% with sclerotherapy. Yet it is not possible to come to a universal decision in favour of a specific procedure. *In principle, all possibilities to prevent relapse that are afforded by conservative procedures should be fully exhausted.* (95, 113, 146, 175)

Operative lethality can be reduced to about 10% and the rate of recurrent bleeding to <10%. With careful internal treatment, the frequency of encephalopathy can be substantially diminished to 5−10% (from the previous rate of 20−30%). The *survival rate* (between 2 and 10 years) is 80−40% and can be decisively influenced by the patient's lifestyle, particularly as regards alcohol abstinence. Important *selective criteria* include: (*1*.) liver blood flow between 1,000 and 2,500 ml, (*2*.) selective portal blood flow of 15−40%, and (*3*.) timing of operation during the bleeding-free interval (elective) with careful pre- and aftertreatment.

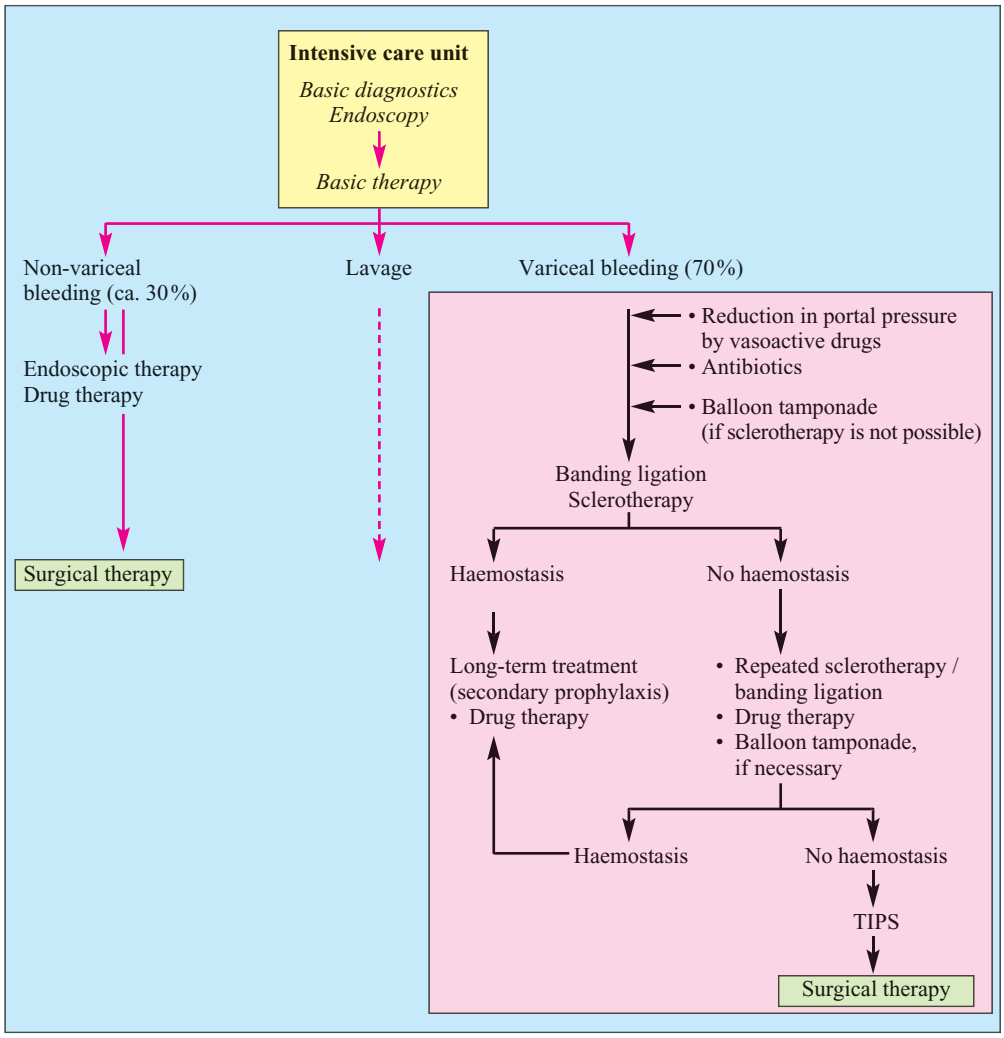

Fig. 19.15: Flow diagram: therapeutic spectrum for acute upper gastrointestinal bleeding, including bleeding oesophageal and gastric varices

3.8 Liver transplantation

Liver transplantation is the only way of ensuring elimination of the underlying liver disease with portal hypertension – and thus also eradication of the predominant and life-threatening complex of collateral circulation with its recurrent incidences of bleeding. A transplant operation is technically feasible both after TIPS and following block surgery. A mesentericocaval shunt is the surgical procedure of choice when a transplantation is planned at a later date. By contrast, the distal splenorenal shunt entails problems with operative techniques and haemodynamic difficulties. The four-year survival rate of patients who merely underwent sclerotherapy was 17%, whereas with an additional transplantation at a later date, a frequency of 73% was recorded. In appropriate cases, liver transplantation is a well-established therapeutic measure, equally suitable for the management of bleeding oesophageal varices. (108, 154)

4 Lower gastrointestinal haemorrhage

Lower gastrointestinal haemorrhage shows a frequency of 10–15%; some 3–5% of these cases develop in the small bowel. Intestinal bleeding as a result of liver disease is rare. The initial problem consists in the fact that (*1.*) numerous and varied causes of bleeding must be clarified by differential diagnosis and (*2.*) severe blood loss together with a concurrent liver disease is always particularly hazardous.

4.1 Definition

In lower gastrointestinal haemorrhage, the bleeding site is distal to the duodenojejunal ligament (Treitz's ligament) or the duodenojejunal recess (i. e. the passage of the duodenum retroperitoneally and its transition to the intraperitoneal jejunum).

4.2 Forms

Lower gastrointestinal bleeding is subdivided into the same *forms* as upper gastrointestinal bleeding: acute or chronic bleeding, minor or major bleeding, arterial or venous bleeding. (s. tab. 19.4) The *intensity of bleeding* may vary between acute or even life-threatening

bleeding and chronic or occult loss of blood in the stools. Acute bleeding lasts less than three days. Occult bleeding is the most common form − in fact, the screening of symptom-free elderly people for occult blood in stools yielded positive results in 3% of cases. As regards the *nature of bleeding*, distinction must be made between melaena, reddish-brown stool, haemochezia and occult bleeding.

Melaena (= *tarry stool*) (s. p. 355) is defined as tarry, sticky stools resulting from the decomposition of blood by intestinal bacteria. The occurrence of melaena depends on the amount of blood and the time of gastrointestinal passage. Usually, melaena is only to be expected in lower gastrointestinal bleeding with a bleeding site in the upper part of the transverse colon. However, it may also be observed in the case of massive bleeding from the upper gastrointestinal area. • Melaena may be simulated by the intake of iron (iron preparations, black pudding), charcoal tablets, bismuth, liquorice, blueberries, etc.

Reddish-brown stool is generally encountered in chronic recurrent lower gastrointestinal bleeding, mostly below the right part of the colon.

Haemochezia (= bloody faeces) is defined as the discharge of fresh blood or small blood clots in the stools. This may be recognized as *blood on the surface* of a formed stool (especially with bleeding from the rectal or anal area) or *admixture of blood* in the stool (generally with a bleeding site in the upper sections of the colon). Major amounts of blood may greatly accelerate the gastrointestinal passage, which is why massive oesophageal or gastric bleeding can sometimes appear as a form of haemochezia.

Occult blood is defined as traces of blood in the stool which are not perceptible to the naked eye. Usually, the passage of blood into the intestinal contents is around 2 ml/day. Proof of occult blood is obtained by *chemical testing* (e. g. peroxidase reaction), although it is only possible to detect amounts of blood in excess of 1.5−2.0 ml/100 ml stool or to demonstrate them by means of an *immunological rapid diagnostic test* with a specificity of virtually 100%. The test usually comprises three specimens collected at different points in time. (s. p. 355)

4.3 Diagnostics

Lower gastrointestinal bleeding is less frequent than upper gastrointestinal bleeding (15−20% vs. 80−85%). Consequently, the presence of upper gastrointestinal bleeding has to be excluded first − even in the case of severe anal passage of blood and/or in cases of haemochezia. (202, 205, 209)

Inspection: Inspection of the stool facilitates an initial rough assessment of the nature of the gastrointestinal bleeding.

Laboratory parameters: Like in upper gastrointestinal bleeding, certain parameters are initially important, such as haemogram, haematocrit, blood group, coagulation values, electrolytes, plasma urea, creatinine, Allgöwer-Burri index. (s. p. 355)

Rectal examination: Rectal examination by inspection and palpation of the anus and rectum (especially after straining) is imperative. The presence of haemorrhoids must not be accepted as a potential source of bleeding without further diagnostic clarification.

Endoscopy: Basically, we consider intestinal endoscopy to be the method of choice. With a massive passage of blood, the examination is naturally very difficult; it requires optimum intestinal cleansing before and during the examination as well as expertise in managing the required techniques. Due to the multiplicity of the potential causes of bleeding, endoscopy should always be used as a primary diagnostic method (s. fig. 19.16).

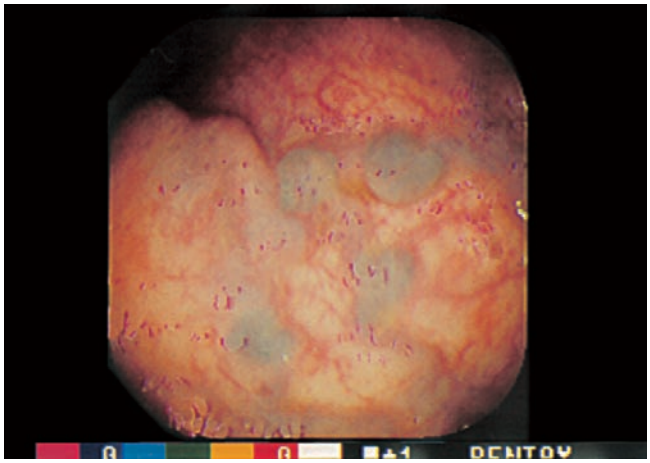

Fig. 19.16: Colonic varices in alcohol-toxic cirrhosis

With the help of **push enteroscopy,** it is possible to assess about 60 cm of the proximal jejunum. In this way, previously undetected sources of bleeding can be localized. (204) **Wireless capsule endoscopy** will improve endoscopic diagnosis of the small bowel considerably. The use of this capsule is currently limited to clarifying cases of intermittent bleeding. (203) Using this technique, mesenteric variceal bleeding could be identified.

Scintigraphy: Scintigraphy (e.g. with ^{99m}Tc-labelled erythrocytes) is the method of choice if endoscopy fails because of severe discharge of blood or due to technical difficulties, or if it yields no diagnosis. Amounts of blood exceeding 0.05−0.12 ml/min. are demonstrable. With an accuracy rate of 94%, overall reliability is higher than for angiography. One disadvantage is the imprecise localization of the bleeding source. (202, 205)

Angiography: Strong lower gastrointestinal bleeding can also be confirmed and possibly localized (in up to 70% of cases) by selective angiography of either the coeliac

trunk or the (superior or inferior) mesenteric artery. A prerequisite condition for this is a bleeding rate in excess of 0.5 ml/min. By using anticoagulants to provoke bleeding, it was possible to raise the positive bleeding rate from 32% to 65%. Arteriography may also contribute to the differential diagnosis of lower gastrointestinal bleeding (e. g. diverticular bleeding, vascular anomaly, tumour). (202, 205)

All these diagnostic measures, when implemented specifically and step-by-step, yield a reliability of over 90% in lower gastrointestinal haemorrhage.

4.4 Aetiology

Numerous diseases of the lower gastrointestinal tract may be accompanied by bleeding. The **aetiological spectrum** is wide; the percentage frequency depends on the age distribution of the respective patients. Men are more frequently affected than women. At an advanced age, diverticulosis (overall frequency of bleedings about 50%, in old age about 40%) and angiodysplasia (overall frequency 1−3%, in old age about 30%) as well as haemorrhoids are the primary causes of bleeding. Furthermore, anal fissures, enterocolitis, polyps as well as benign and malignant tumours are worthy of mention. • Among the rare causes observed were proctitis, infections, parasitoses, endometriosis, collagenoses, congenital diseases (e. g. Meckel's diverticula, Osler-Rendu-Weber's disease) and mesenteric infarction. Some 80−85% of cases cease spontaneously. Lethality is 2−3%. (202, 209)

Lower gastrointestinal bleeding due to *liver disease* is very rare. The sources of bleeding develop in the course of portal hypertension. Intestinal erosions constitute the predominant mucosal changes in **portal hypertensive vasculopathy** in the gastrointestinal tract. They are usually responsible for the frequency of occult intestinal bleeding in cirrhosis patients.

During portal hypertension accompanied by the development of collaterals, **varices** also occur in the area of the duodenum, small intestine, colon and rectum. (205) Very severe, even life-threatening variceal bleeding may appear. (207)

4.5 Therapy

The therapeutic measures for lower gastrointestinal bleeding correlate with the **basic therapy** for upper gastrointestinal bleeding with respect to volume replacement, circulatory stabilization, restoration of the electrolyte balance and intestinal cleansing. • Depending on the respective findings, endoscopic **sclerotherapy**, the **banding ligation** of varices or the **clip technique** is carried out. (206, 209) The presence of portal hypertension is generally an indication for drug-induced **pressure reduction.** This may be necessary as a situation-related primary measure as well as in the form of adjuvant treatment with endoscopic techniques (208) or the placement of a **TIPS.** (207)

In the case of bleeding due to benign or malignant proliferation as well as in upper gastrointestinal bleeding, **thermic haemostatic procedures** are indicated.

Medicinal therapy is similar to that used for upper gastrointestinal bleeding, e. g. vasopressin, FFP, PPSB, fibrinogen (s. p. 358) and octreotide. • A novel therapeutic option in refractory bleeding from portal hypertensive gastropathy is given by the administration of thalidomide. (32)

If bleeding cannot be stopped endoscopically or conservatively, interventional radiology is indicated before any surgical measures can be taken. Exact localization of the source of bleeding is absolutely essential.

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