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Digestive Diseases
Clinical Reviews

# Emergencies and Complications in Gastroenterology

Editor
Petr Dítě, Brno

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# Emergencies and Complications in Gastroenterology

Editor
*Petr Dítě,* Brno

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# Editorial

Acute emergencies in gastroenterology are extraordinarily severe conditions with high morbidity and mortality. Particularly severe diseases include acute pancreatitis, a difficult course of non-specific intestinal inflammations manifested by toxic colon or acute intestinal obstruction, and even acutely developed intestinal pseudo-obstruction (Ogilvie's syndrome) or variceal and non-variceal bleeding into the gastrointestinal tract. Undoubtedly serious factors influencing the accuracy of diagnostics and effectivity of therapy are the etiological multifactorial characteristics of changes that induce the acute state. Polymorbidity is also frequent among these patients and requires a complex diagnostic approach, often limiting the possibility of using an optimal therapeutic approach.

Effective diagnostics and therapy for acute conditions in gastroenterology requires a multidisciplinary team approach. In diagnostics, endoscopic examination enabling a simultaneous therapeutical solution is of fundamental importance in managing most diseases, which is valid for example in patients with acute bleeding into the alimentary tract, in acute pancreatitis, acute cholangitis or acute intestinal obstruction. However, endoscopy is an invasive method, and as many of these patients suffer from polymorbidity, the usage of endoscopic approaches is limited by the general clinical condition of patients, particularly with respect to cardiopulmonary risks. In such cases, the application of non-invasive diagnostic methods is suitable. These involve imaging methods such as ultrasound abdominal examination, computer tomography or nuclear magnetic resonance. Moreover, modifications of these methods, e.g. CT enteroclysis or CT colonography, provide very precise and immediate results that allow the adoption of an optimal strategic course. Due to their increasing sensitivity and specificity, the above-mentioned methods may be expected to substitute, in future, endoscopic examinations, whose present efficiency remains of the highest value.

Optimal therapy for acute states in gastroenterology is unthinkable without the close cooperation of a number of disciplines, particularly gastroenterology and surgery. Correct timing in determining whether conservative therapy is an effective and safe treatment for a patient in a given situation or whether immediate surgery should be performed is the basic requirement for the disease outcome of a patient. Severe states in particular should be managed at centers that have sufficient experience with such problems, possess a complete range of diagnostic methods, carry out therapeutic endoscopy, and have available acute surgical care, i.e. provide complex diagnostic and therapeutical services.

Although acute conditions in gastroenterology and gastroenterological complications are undoubtedly extraordinarily severe states, systematically processed data about rational and correct diagnostics and therapy from the viewpoint of gastroenterologists and surgeons have not been sufficient and therefore they could not be generalized and utilized as recommendations for a rational approach in these states.

We believe that the topics published in this issue of *Digestive Diseases* will help, at least in part, fill this gap.

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Review Article

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# Management of Acute Variceal Bleeding

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**Key Words**
Liver cirrhosis · Variceal bleeding · Treatment · Transjugular intrahepatic portosystemic shunt

**Abstract**
Portal hypertension as a consequence of liver cirrhosis is responsible for its most common complications: ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy and the most important one – variceal hemorrhage. Variceal bleeding results in considerable morbidity and mortality. This review covers all areas of importance in the therapy of acute variceal hemorrhage – endoscopic and pharmacological treatment, transjugular intrahepatic portosystemic shunt, surgery and balloon tamponade. Indications and limitations of these therapeutic modalities are widely discussed.



## Introduction

One of the most important consequences of liver cirrhosis and portal hypertension is increased pressure in gastric and esophageal venous systems, dilatation of related vessels and increased blood flow through developed portosystemic shunts. The most enlarged are deep inner veins under the lamina propria and muscularis mucosae; first manifestation is usually seen in the so-called perforating zone of the distal esophagus. Clinically, the most important factor is the appearance of esophageal varices observed after increase of the hepatic venous pressure gradient (HVPG) >10 mm Hg. About 50% of patients with newly diagnosed liver cirrhosis have varices at the time of diagnosis and this number increase annually by 6% [1].

When the HVPG increases >12 mm Hg, the probability of variceal rupture is high. The first variceal bleeding was described in 1840 [2] and the relationship of esophageal varices, bleeding and liver disease in 1900 [3]. Variceal bleeding affects 30–60% of cirrhotic patients. In patients with compensated liver disease, bleeding occurs in only 30% of cases, and 60% in groups with decompensated liver disease. About one third of patients bleed within 2 years after the diagnosis of varices. Out of all gastrointestinal hemorrhages, variceal bleeding represents about 5–15% cases but 50% of severe bleeders – the presence of both decompensated liver disease and varices as source of the bleeding are independent predictors of high risk of gastrointestinal bleeding [4].

The spontaneous cessation of bleeding episode happens in up to 60% of cases, but untreated patients are jeopardized by rebleeding. This occurs in 30–40% within a 3-day interval and in 60% within 1 week. The mortality within 6 weeks from the onset of bleeding is described as high as 30–50%. The cause of death is multifactorial, most of patients do not die due to exsanguinations but due to complications of the hemorrhage, namely liver fail-

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ure. The most important factor predicting mortality is the liver disease. Thus, not only the incidence of bleeding but also its mortality correlates with the Child-Pugh classification and the mortality of patients with class C is 70–80% [5]. Patients >65 years are threatened also by ischemia and acute myocardial infarction due to anemia [6].

The Baveno III consensus conference [7] was held to update the consensus on the definitions of key events regarding the bleeding. Clinically significant portal hypertension (CSPH) was defined as an increase in the portal pressure gradient >10 mm Hg. The presence of varices, variceal hemorrhage, and/or ascites, is indicative of the presence of CSPH. Measurement of the HVPG and endoscopic assessment of esophageal varices are satisfactory tools for the diagnosis of CSPH.

## General Measures

The first and most important measure is the hemodynamic stabilization of the patient and prevention of aspiration of vomited blood. The intravenous access should always be ensured by large-bore and preferably multiple peripheral catheters, the central venous catheter is indicated in the presence of tachycardia >100/min and systolic pressure <100 mm Hg. These limits, together with the need of application of more than 2 blood units within 24 h, were recognized as attributes of severe bleeding by the Baveno II conference [8]. First laboratory tests include assessment of the blood group, blood count (hematocrit, hemoglobin, thrombocytes) and prothrombin time. Leukocytosis >8,500/mm$^3$ is a prognostic factor predicting more severe course of the disease [9]. The most common approach includes volume replacement with crystalloids first and subsequently with blood derivates. Sodium overload is unfavorable in ascitic patients. Intensive replacement of the blood volume is necessary for maintenance of the renal perfusion, but overload attributes to rebleeding due to portal pressure increase. The optimal parameters are 2–5 mm Hg of the central venous pressure, hematocrit between 25 and 30% and hemoglobin not >100 g/l. Remarked hypovolemia with systolic pressure <90 mm Hg and tachycardia >120/min together with signs of peripheral hypoperfusion are common indications for the application of oxygen (4 l/min). Vitamin K is indicated in most patients. Though cirrhotic bleeders do often have various blood coagulation abnormalities, there is no evidence that general application of fresh-frozen plasma or thrombocytes is helpful.

The importance of infection in the etiopathogenesis of variceal bleeding and the need for prevention of the systemic infection is an indication for antibiotic treatment (amoxicillin-clavulanic acid, norfloxacin). A meta-analysis of studies of the use of prophylactic antibiotics in this setting suggests that antibiotic prophylaxis substantially increases the number of patients who remain free from infection and improves short-term survival in patients with cirrhosis and variceal hemorrhage [10].

The increase of the ammonium in the gastrointestinal tract due to bleeding can cause development or worsening of the encephalopathy. Thus, gastric large-bore tube and early application of the lactulose are indicated, as well as vigorous correction of mineral unbalance, especially the potassium and magnesium levels.

## Endoscopic Therapy

Diagnostic endoscopy should be organized in acutely bleeding patients as soon as possible to determine the site of bleeding. Even patients with portal hypertension and documented varices can bleed from other sources than varices. If varices are found to be the real source of hemorrhage, endoscopic treatment is proved to decrease the short-term mortality and to decrease further bleeding. Methods in question include sclerotherapy, application of tissue adhesives, banding of the varices, application of detachable loops for strangulation of varices and some others [11].

Historically the first method introduced into the clinical practice was sclerotherapy. Which sclerosant is the most effective cannot be concluded. Comparative trials are lacking a sufficient volume of patients and uniform methodological standards regarding concentrations and doses, intervals between sessions, and patient population, etc. Basically, all of these agents have been documented to be effective in clinical trials. The intravariceal technique is perhaps more effective in controlling active bleeding than paravariceal injection, but more studies are needed to confirm this. On the other hand, it was shown that punctures intended to be intravariceal are in fact paravariceal around 35–45% of the time [12]. Trials of sclerotherapy in acute bleeding are also influenced by the experience of operators, schedule of follow-up and the number of patients who were not actively bleeding at the time of endoscopy. The experience of the operator is extremely important in decision-making in common clinical practice.

Compared to balloon tamponade, sclerotherapy has a significantly higher control of bleeding, specifically lower rebleeding which occurs in up to 50% of cases after deflation of the balloon. Trials comparing somatostatin with sclerotherapy in general found no significant differences in failure to control bleeding, rebleeding or mortality [13].

Variceal band ligation is superior to sclerotherapy in the rate of complications and perhaps improvement in survival. Control of active bleeding was in some trials achieved more readily with ligation than with sclerotherapy, but some trials found no significant differences [14]. It seems that severe bleeding responds better to banding and both methods are equally effective in mild bleeding. However, technically it is more difficult to employ banding in severe hemorrhage due to reduction of the visibility by the cylinder of the banding device and the further decrease of field of view by blood, which usually fills the cylinder to some degree. New clear outer cylinders improved the ease of use of banding devices and multi-shot instruments shortened the time necessary for placement of a sufficient number of rings. The expert dependence plays a major role in this situation.

Combination of sclerotherapy and banding is also possible. The so-called sandwich (ligation, sclerotherapy, ligation) approach was shown to be superior to ligation alone in prevention of recurrence of varices, but mortality eradication rates, recurrent bleeding and complication rates were similar for sandwich technique and banding alone. Technically this approach means deployment of the rubber band at the most distal point of the variceal column followed by the injection of 1–2 ml of the sclerosant (5% ethanolamine oleate in this study) proximal to the applied band, with another band subsequently being applied over the same column 3–4 cm proximal to the injection site [15]. Another approach uses utilization of the argon plasma coagulation to induce mucosal fibrosis in the distal esophagus. It was shown that the recurrence-free rate at 24 months after treatment is significantly higher with this treatment than with ligation alone [16]. All those attempts of technical improvement are intended to overcome the tendency of a higher recurrence rate of varices after banding as it does not obliterate deeper varices (peri- and para-esophageal varices) and perforating veins. At the moment, more studies are needed to evaluate the clinical benefit of application of newer methods in question. In individual patients it seems that it is not a mistake to choose banding or sclerotherapy according to the size of the varices, the degree of fibrosis of the esophageal wall (affecting the feasibility of sucking of the vessel into the cylinder), and the capability to obtain a good view in the distal esophagus during active bleeding, etc.

In patients resistant to endoscopic treatment, it is clear that more than two sessions of sclerotherapy are not helpful, do not improve control of bleeding and bring increased risk of aspiration, perforation and sepsis [17]. Development of deep post-sclerotherapy ulcers and multiple sessions of sclerotherapy cause general deterioration of the patient by itself. Vasoactive drugs can improve the technical feasibility of endoscopic therapy.

Tissue adhesives show a more than 90% rate of control of bleeding but were not generally proved significantly better in application in esophageal varices in terms of rebleeding and mortality [18]. This treatment is associated with a significant risk of complications as cerebrovascular accidents or jeopardizes the scope. Furthermore, the agents that are used are more costly. Some benefit was, however, proved in patients with progressed liver disease (Child-Pugh C) in a randomized prospective trial comparing cyanoacrylate and sclerotherapy with ethanolamine oleate. The immediate hemostasis achieved by cyanoacrylate was significantly more often observed than with sclerotherapy. This resulted in significantly lower rebleeding rates, need for surgery or transjugular intrahepatic portosystemic shunt (TIPS) and mortality [19].

Complications of endoscopic therapy include local and systemic events. The incidence of esophageal stricture formation and ulcer bleeding were significantly higher in sclerotherapy (both appearing up to 25%) compared with band ligation (incidence less than 5%). In fact, most ulcer bleeding episodes require no therapeutic interventions and strictures are usually treated with balloon dilatations. Major disasters as esophageal perforation and massive esophageal hematoma are infrequent in both techniques. Pulmonary complications and mediastinitis are significantly more common after sclerotherapy [20].

Generally, for control of acute bleeding episode, variceal band ligation is the method of first choice. If this proves to be technically difficult, endoscopic variceal sclerotherapy should be performed. Vasoactive drugs should be used parallel to endoscopic therapy for 5 days. In failure to control the bleeding, balloon tamponade can be used as a temporary measure en route to the radiological or surgical suite.

## Pharmacological Therapy

The biggest advantage of pharmacotherapy is its feasibility. It can be applied instantly without the need for specialized instruments and is independent on the physician's skill and practice. Its efficacy was proved to be similar to endoscopic measures but optimal in their combination.

Most drugs used for this indication cause splanchnic vasoconstriction. Vasoconstrictors decrease splanchnic perfusion and portal flow which results in decrease of the portal pressure. The decrease of blood flow and pressure is achieved in varices, too. The first drugs clinically used for this indication were hormones, vasopressin and somatostatin. Currently their synthetic analogues, terlipressin and octreotide, are more widely used.

*Vasopressin*

This is a hormone of the posterior lobe of the hypophysis (also causes reabsorption of water in kidneys) which was the first vasoconstrictor used in the treatment of bleeding due to portal hypertension [21] and was proved to be effective. It causes vasoconstriction in the splanchnic area but also in the systemic circulation. Its major disadvantage are side effects due to ischemia, especially myocardial [22]. It causes discontinuation of the treatment in up to 30% of cases. The combination with nitrates decreases the incidence of side effects but is not more potent than other therapeutical options [23]. Vasopressin is no longer used for this indication in Europe in contrast to the USA where it is still an alternative in combination with nitrates.

*Terlipressin*

Terlipressin is an N-triglycyl-8-lysine-vasopressin, a synthetic analogue of the vasopressin, developed in 1964 in Prague. It causes splanchnic vasoconstriction with a consequent decrease of the portal pressure and blood flow in portosystemic collaterals. In comparison with vasopressin, it has minimum side effects and a prolonged biological turnover (half-time 3.4 h) and this enables intermittent administration. In sufficient dose it decreases significantly not only the pressure in hepatic veins but also the intravariceal pressure [24]. The dose of 2 mg of terlipressin significantly decreases portal flow and flow in the azygos veins in a 4-hour interval and the dose of 1 mg has a similar effect [25]. Interesting is the combination with octreotide. In rats, administration of both drugs alone significantly decreases portal pressure and cardiac index. If octreotide is administered in animals pretreated with terlipressin, the effect is not changed, if terlipressin is administered in animals pretreated with octreotide, both systemic and splanchnic vasoconstriction are increased [26]. The combination with $\alpha_1$-adrenoreceptor antagonist increased the effect of terlipressin in animals [27]. Terlipressin in animals decreases portal flow significantly and thus the hepatic inflow through the portal vein, but the arterial inflow increases which is important from the point of hepatic function [28].

Clinically, terlipressin was proved to be significantly more effective than placebo in the treatment of variceal bleeding [29]. Its efficacy is similar to balloon tamponade [30], somatostatin [31], octreotide [32] or endoscopic sclerotherapy [33]. It is the only drug shown to decrease the mortality related to acute bleeding episode. It is important to note the effect of its pre-hospital administration during the transport which significantly improves the success of consequent treatment [34]. A recent large multicenter trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding has shown similar effects of both treatment measures in terms of bleeding control, rebleeding rate and 6-week mortality, number of blood units transfused, stay in the intensive care unit, and hospital stay. Side effects were similar, but less frequent in the terlipressin group [33].

*Somatostatin*

Somatostatin is a hormone produced namely in the hypothalamus and in the gastrointestinal tract. It was first isolated in 1973 and subsequently synthesized. Its main function is regulation of the somatotropin. It also has various other effects as decreasing the flow in the splanchnic region, inhibition of secretion of a variety of hormones (glucagons, insulin, gastrointestinal hormones) and decreases also the gastric, biliary and intestinal motility and secretion of the stomach and pancreas. The hemodynamic effect of the somatostatin and its analogue, octreotide, is not fully explained. In animal models it decreases portal pressure by decreasing the inflow [35]; this, however, was not confirmed in cirrhotic patients [36]. Some studies have shown its vasoconstrictive effect on the splanchnic region, but others did not confirm this. In cirrhotics it probably has an effect on the decrease of glucagons which contributes to vasodilatation. Also, somatostatin contributes to the decrease of blood volume and prevention of postprandial hyperemia in the splanchnic region. Its continuous administration in acute bleeding, however, decreases HVPG. Its disadvantage is namely very short biological half-time (approx. 2 min) requiring administration as a continuous infusion. Somatostatin

significantly decreases not only the portal pressure but also the gastric mucosa blood flow (GMBF) [37], which is potentially important in the bleeding from portal hypertensive gastropathy. However, trial data are conflicting. Meta-analyses have shown better control of bleeding compared with vasopressin [38]. A meta-analysis did not show significantly better efficacy in comparison to placebo [39]. Smaller studies, however, found a similar efficacy compared to sclerotherapy [40], terlipressin [31] and found a lesser need for blood transfusions and other urgent therapies [41].

*Octreotide*

Octreotide is a synthetic octapeptide derivate of somatostatin, first described in 1982. Besides octreotide, more than 20 synthetic analogues of the somatostatin are known. Lanreotide was tested mainly in animal models. Vapreotide was better in comparison with placebo and was proved to increase the efficacy of endoscopic treatment in variceal bleeding in humans [42]. None of these other analogues are currently used in common clinical practice.

Octreotide has a similar pharmacological effect as somatostatin. The differences are dependent on its binding to three out of five somatostatin receptors. In comparison to somatostatin, its advantages are its longer half-time (90–120 min) and especially longer pharmacological action (8–12 h). Octreotide (as well as somatostatin) decreases significantly the portal pressure in animals [43], but its influence on hemodynamics in cirrhotics, including decrease of the portal pressure, was not significantly proved [44]. It probably also influences the mesenteric circulation [45]. Meta-analysis studies using octreotide or somatostatin have shown a lower rate of complications and a similar effect as sclerotherapy or balloon tamponade [46]. A newer meta-analysis comparing octreotide to other medical therapy and placebo has shown a better effect of the octreotide on the bleeding control compared to placebo and other drugs and side effects comparable to placebo or no treatment [47]. The administration of the octreotide after sclerotherapy decreases the portal pressure and rebleeding rate compared to sclerotherapy alone [48, 49]; the effect on mortality, however, was not proved.

*Nitrates*

Intravenous nitrates are mostly used to counteract the vasoconstriction effect of vasopressin, of which isosorbide-5-dinitrate is the most common. Its hypotensive effects limits its use in the acute phase of the bleeding episode.

## Mechanical-Balloon Tamponade of the Varices

The balloon tamponade may have a life-saving effect but its inappropriate application has many complications. The ability to place properly balloon tamponade is surprisingly low outside specialized centers. Generally, nowadays it is seldom indicated. Currently it is accepted as a temporary measure after second unsuccessful endoscopic treatment en route to portosystemic decompression (surgical or TIPS). If indicated, the patient should be managed in the specialized intensive care unit. Most common is the three-lumen double-balloon (Sengstaken-Blakemore). In case of bleeding from subcardial- fundal gastric varices, the single-balloon (Linton-Nachlas) tamponade is more appropriate. The Minnesota balloon is a modification of the double-balloon device with four lumens; the fourth is used for sucking from the space above the esophageal balloon, thus it prevents aspiration better. Balloons must be inflated by the air, not liquid. Water, due to its weight, changes the shape of the balloon, which results in malfunction of the device, and is therefore not an appropriate filling medium. The gastric balloon is inflated first, then traction is ensured and the esophageal balloon is inflated. Its pressure should be higher than portal pressure, 40 mm Hg is usually sufficient, overinflation is contraproductive and causes complications. Suction should be provided for gastric content and swallowed saliva. The correct location of the balloon tube should be checked by X-ray.

The balloon should not be insufflated more than 24 h. Some authors recommend deflation of the balloon every 4–6 h for 30 min [50]. Up to 50% of patients do have rebleeding after balloon decompression. Thus this temporary measure should always be combined with other methods [51]. The complications include aspiration, retrosternal pain, esophageal or gastric rupture and mainly esophageal and gastric ulcerations. Overinflated or water-filled balloons or dislocated balloons as well as multiple sclerotization sessions cause significant damage to the esophagus which replaces varices as bleeding source. Seldom the upright movement of the inflated esophageal balloon causes obstruction of the airways and suffocation, most such cases are due to the rupture of the gastric balloon. In this case the cross section of the lumen causing immediate decompression of the balloon and subsequent extraction are indicated.

## Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS is a calibrated portosystemic shunt which reduces quickly portosystemic gradient and opens access to endovasal treatment of varices (endovasal obliteration by sealants). Therefore, it is highly effective in stopping variceal bleeding [52]. TIPS is indicated only when first-line methods (medical and endoscopic) have failed. This happens as 'chronic' or 'acute' failure. 'Chronic' means that patients do have repeated bleeding episodes despite adequate application of first-line treatment. An 'elective' TIPS may be indicated. 'Acute' failure means bleeding refractory to other measures and 'urgent – salvage' TIPS is often a life-saving procedure.

It is difficult to organize a study comparing the TIPS procedure as 'salvage treatment' as there is difficulty in setting up a comparable alternative. Even the first paper reporting TIPS dealt with uncontrolled bleeding in Child-Pugh class C patients and showed reasonably good results [53]. Most relevant papers investigating 'salvage TIPS' showed immediate control of bleeding in 91–100% of cases, 30-day rebleeding 7–30% and 1-month (or 42 days) mortality 28–55%. Child class C patients formed in most of them more than 60% of cases [54–56] and in one 41% of cases [57]. Retrospective comparison with esophageal transection [58] significantly favored TIPS (30-day mortality was 42 vs. 79%, rebleeding 16 vs. 26%). The role of TIPS is especially important in patients bleeding from gastric varices, which have a worse response to sclerotherapy and in bleeding portal hypertensive gastropathy which cannot be treated endoscopically at all. Gastric varices in rescue TIPS series form up to 73% of cases [55]. These impressive data show that rescue TIPS definitively has its place in therapeutic algorithm for bleeding patients. Most of TIPS procedures in question are performed with a combination of endovasal obliteration of varices as 'urgent' operations. It was proved that uncontrolled bleeding can be effectively treated with TIPS, and TIPS has lower morbidity and mortality compared to surgery.

### *Indications of TIPS and TIPS-Related Procedures in Bleeding Patients*

In general, accepted indications are patients with bleeding that is uncontrolled by pharmacological and endoscopic therapy. This is true both for emergency situations (urgent TIPS) and for patients with repeated episodes of hemorrhage despite adequate preventive treatment who are not surgical candidates (elective TIPS). These conclusions were confirmed by both the Reston and Baveno consensus meetings. Most patients appear with gastroesophageal varices. Clinical situations as chronic anemia due to portal hypertensive gastropathy, prevention of rebleeding from large gastric or intestinal varices, fresh portal vein thrombosis contributing to bleeding can be added to the list. Rare indications published include treatment of massive hemoptysis secondary to bronchial collaterals [59], bleeding from stomal varices in patients after external enteric diversion [60], bleeding from colonic variceal veins and intestinal varices [61] and traumatic bleeding from cirrhotic liver [62].

### *Limitations of TIPS in Control of Bleeding*

Not all cases with refractory or repeated bleeding are indicated for TIPS. Contraindications are technical and clinical. Technical contraindications are mainly due to portal vein obstruction. However, successful placement of TIPS is feasible also in selected cases of chronic occlusion [63], sometimes with the use of local thrombolysis [64]. Favorable clinical outcome was reported in retrospective studies and fairly good technical success reaching 75% [65]. Even in patients with cavernomatous transformation of the portal vein, successful TIPS placement is feasible by combined percutaneous and intravasal approaches. Further relative contraindication for TIPS placement is polycystic liver disease. Rare conditions include extreme obesity with body weight beyond the technical limits of X-ray equipment.

Clinical contraindication means a situation where relief of portal hypertension is likely to deteriorate the liver function or the decrease of HVPG cannot improve the general condition of the patient. Contraindication to elective TIPS is also sepsis and heart failure. It is obvious that TIPS can treat the complications of portal hypertension and not the liver disease. In a recent consensus conference, most investigators refused to perform TIPS with a Child-Pugh score of 12 points or above, so a jaundiced patient in coma with renal insufficiency and need of artificial ventilation is definitively not a candidate for TIPS [66]. Others have searched for individual variables and pointed out emergent TIPS, ALT level >100 IU/l (1.7 μkat/l), bilirubin >3 mg/dl (51 μmol/l) and pre-TIPS encephalopathy to predict overall mortality after TIPS [67]. Another important factor is renal insufficiency [68].

One should have in mind, however, that in cirrhotics protracted attack of esophageal bleeding has a deteriorating effect on liver function and the general status of the patient. Marked improvement is usually seen after cessation of the bleeding period and therefore the exclusion of

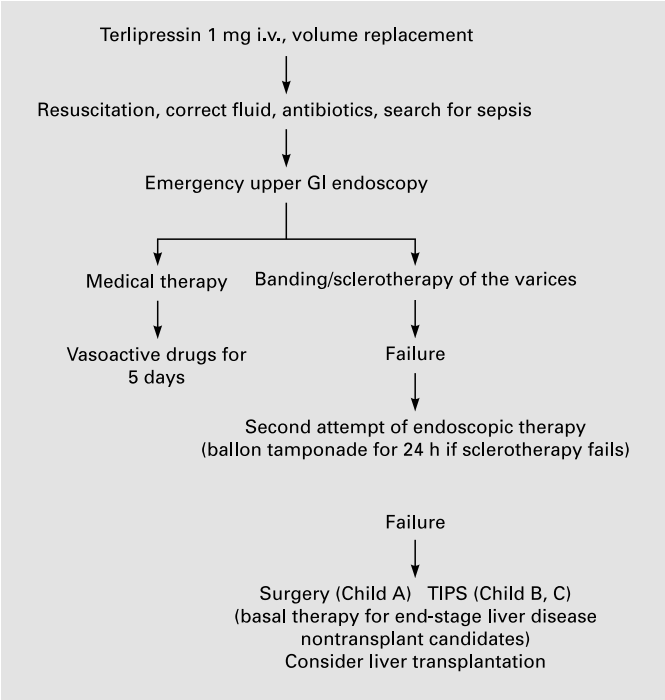


**Fig. 1.** Suggested algorithm of treatment of acute variceal bleeding.

an individual from candidates to rescue TIPS because ahigh Child-Pugh score should be based rather on the evaluation prior to a bleeding catastrophe. Furthermore, it appears that patients with varices due to alcoholic cirrhosis have the highest incidence of hemorrhage, especially if they continue to drink alcohol. The hepatocellular dysfunction may improve in cases who abstain from alcohol [69].

Cases of portal vein obstruction are tricky not only from a technical but also clinical point of view as the incidence of hepatocellular carcinoma in this condition reaches 35% [65] and is reported up to 22% even in cases without clinical or imaging evidence of hepatoma if examined histologically [65, 70]. The survival is in such patients limited to an average of 6 months and TIPS brings the risk of systemic metastasis. On the other hand, if portal blood is diverted by the thrombosis completely to varices, the sclerotherapy is very likely to fail in case of acute hemorrhage. Thus, TIPS is not contraindicated in clinical conditions of immediate concern as acute variceal or peritoneal hemorrhage, even if malignant portal vein thrombosis is present.

If TIPS is indicated in refractory bleeding patients with liver failure, it should be coordinated with a transplant center. Cases with Child-Pugh score >11 and/or other risk factors (emergent TIPS placement, elevated ALT levels, pre-TIPS encephalopathy, elevated bilirubin levels), who are not transplant candidates, have mortality reaching up to 90% within few weeks after TIPS placement [67] and therefore shunt is usually not appropriate. Bleeders who are transplant candidates are transplanted according to listing criteria.

Theoretically, TIPS has several advantages in transplant candidates who require pre-transplant shunt insertion because of the hemorrhage. All surgical shunts increase the difficulty of dissection, and some permanently reduce the available blood flow to the transplanted liver. Shunts that divert flow from the original liver can result in smaller, more fibrotic portal vein. On the contrary, TIPS maintains high volume flow through the portal vein, prevents portal vein thrombosis and could result in greater portal flow to transplanted liver. The TIPS is removed with the diseased liver entirely and there is no need for further surgery to close the fibrotic and sometimes fragile vascular shunt [71]. Published studies shown better results with TIPS than with surgical shunts [72, 73]. However, some surgeons do not prefer stenting prior to transplantation (fig. 1).

*Long-Term Follow-Up after TIPS*

The technical limitation of TIPS from a long-time point of view is dysfunction due to the clogging of the stent. That is why patients with TIPS should be meticulously followed up and the patency of TIPS regularly evaluated. Most centers use a 3-month interval as the minimal period for clinical and Doppler check-up. Stent dysfunction should be treated by balloon dilatation of the stent channel. Within such a protocol, rebleeding due to shunt dysfunction can be reduced to less than 5% within long-term follow-up and mild forms of encephalopathy can be diagnosed and treated before severe clinical consequences [74].

## Surgery

In the modern era, surgeons were the first to cope with bleeding varices. High mortality experienced in acutely bleeding patients with impaired hepatic functions reaching up to 80% forced accelerated introduction of nonoperative methods. The overall mortality of surgical procedures for all acutely bleeding patients refractory to medical treatment remains generally high, ranging from 33 to 56%. Moreover, surgical shunting does not appear to improve survival and is associated with a substantial incidence of portosystemic encephalopathy [75].

Currently the first-line methods (vasoactive drugs and endoscopic therapy) reach up to 90% success in cessation of a bleeding episode. The remaining 10% of cases are one of the most difficult groups to manage in hepatogastroenterology. In the pre-TIPS era, the only 'salvage therapy' accepted was surgery, but most patients with progressed liver diseases are excluded as surgical candidates. In surgically treated patients, mortality reached 82% in patients with Child class C [76]. Procedures as esophageal transection plus gastric devascularization and variety of shunt operations are technically possible. Portal-systemic shunts can be separated into two basic types: nonselective (total) shunts and selective shunts. Total shunts are designed to divert portal blood away from the liver and include end-to-side portacaval shunts, side-to-side portocaval shunts, interposition portocaval shunt, splenorenal shunts and mesocaval shunts. End-to-side shunts anatomically prevent any portal venous perfusion of the liver and theoretically tends to more rapid liver failure, worsened PSE and poor control of ascites, but this technique is technically simpler and is recommended in the emergency situation. Studies comparing different surgical shunting techniques are difficult to interpret and still remain an area of considerably controversy [77]. Randomized studies have shown that surgical shunts have a better hemostatic effect than local surgical treatment of bleeding vessels alone. In high-risk patients, sclerotherapy had a similar effect with fewer complications than transection of the esophagus, thus transection does not seem to be a good choice [78]. It can be concluded that surgery possibly still has a place in the treatment of patients in otherwise good condition, but practically it is rare for cirrhotics in good condition to have refractory bleeding. The most important objective measure for comparing invasive methods treating refractory bleeding is the 30-day mortality. Unfortunately, at the moment no studies are available fulfilling requirements for comparison of surgery and radiointerventions (TIPS). The only randomized study [79] is questioned from the point of imbalanced distribution of gender, Child class, and urgent timing disfavoring the TIPS group. The results of this study showed comparable 30-day mortality in 6 of 35 patients of the TIPS group and 5 of the 35 patients treated by the H-graft. Another uncontrolled large study comparing TIPS and surgical shunt [80] demonstrated 0% 30-day mortality in the surgical group and 26% mortality in the TIPS group. Child-Pugh class C patients were not operated at all, but received exclusively TIPS and formed 57% of the TIPS group. Comparison of this large surgical experience with results of the Freiburg group [81] shows similar results in terms of mortality and rebleeding for patients with less progressed disease (mortality 0% for Child A patients and 11% for Child B patients). The rebleeding from varices was demonstrated by two meta-analyses [82, 83] to be similar after TIPS (19%) and after surgical shunts (3–45%) [1].

Orthotopic liver transplantation is not a treatment measure of an acute bleeding episode but all bleeders should be evaluated as transplant candidates and those fulfilling standard criteria placed upon a waiting list. Transplantation of the liver is the treatment option that offers the best survival rates. The major mortality associated with the procedure occurs in the first year. The reported survival rate of patients with liver transplantation because of variceal hemorrhage is 79% at 1 year and 71% at 5 years [84]. The greatest survival advantage is conferred on the patient who falls in the Child's C class. Unfortunately, access to this procedure will never be open to all patients due to limited sources of grafts, and ethical and financial problems.

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Review Article

Digestive Diseases

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# Upper Gastrointestinal Hemorrhage – Surgical Aspects

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**Key Words**
Gastrointestinal hemorrhage · Endoscopic therapy · Peptic ulcer · Variceal bleeding · Acute surgery

**Abstract**
During the last decades, significant advantages have been achieved with the use of emergency endoscopy and respective hemostatic interventions. Rebleeding, however, remains a significant clinical problem, and currently re-endoscopy or surgical intervention offers advantages and disadvantages. With the discovery of *Helicobacter pylori* as a main causative factor behind peptic ulcer disease, a more conservative surgical approach is mandated even in situations with significant rebleeding. In case of large gastric ulcer, however, resection is a wise strategy depending on the risk of malignancy. Liver transplantation has immensely improved the prognoses for variceal bleeding in end-stage liver disease in carefully selected patients.



Acute upper gastrointestinal bleeding is a frequent event with an incidence of around 40–50 cases per 100,000 persons per year. Since the early 1970s, emergency endoscopy has been widely used in the diagnosis and management of upper gastrointestinal hemorrhage. Acid-suppressive drugs have become available and since the introduction of endoscopic intervention modalities in the 1980s, the mortality rate from this severe clinical manifestation has decreased slightly but still remains around 10%. One of the main reasons for the remaining high mortality is probably the fact that the patients are at an advanced age and have concomitant complicated diseases. A quarter of the admitted patients are older than 80 years. Another factor might be the extensive use of NSAIDs and anticoagulants [1–22].

If endoscopy is performed within 24 h of admission, the cause of bleeding is identified in more than 90%. However, in large epidemiological studies, the percentages of undiagnosed patients vary widely between 0 and 25% (table 1). Gastroduodenal peptic ulcers account for about 40% of the cases, where duodenal ulcers are most frequently seen followed by hemorrhagic gastritis, variceal bleeding, esophagitis, duodenitis, Mallory-Weiss tears and malignancies (1–5%). A meta-analysis showed that endoscopic therapy, including injection therapy, was effective in reducing the risk of rebleeding and need for emergency surgery and mortality in patients with active bleeding or non-bleeding visible vessels. Furthermore, the routine use of a second endoscopic treatment in the case of rebleeding has been suggested, although a more widespread consensus and acceptance of this strategy has not been achieved. Rebleeding and requirement for emergency and urgent surgical intervention remains and for

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**Table 1.** Endoscopic diagnosis in patients presenting with upper gastrointestinal bleeding; review of the literature (mean and ranges are shown)

| Years | n | DU | GU | Esophagitis | Varices | Mallory-Weiss | Gastritis/erosions | Malignancies | Misc. | Unclear |
|---|---|---|---|---|---|---|---|---|---|---|
| 1973–1998 | 13,178 | 25% (12–53) | 15.9% (9–26) | 7.4% (4–13) | 10.5% (1–23) | 6.1% (0.5–12) | 15.4% (4–41) | 2.3% (1–5) | 5.2% (0.5–15) | 8.9% (3–22) |

instance recent trials have shown a rebleeding rate of around 20–25% with a 8–15% need for urgent surgery (table 2). One trial has tried to assess whether elective endoscopic retreatment is better than early elective surgery after initial endoscopic hemostasis, but the issue is far from settled. Apparently endoscopic reintervention has advantages over surgical intervention in terms of lower morbidity.

**Table 2.** Failure rates on modern endoscopic therapies for actively bleeding ulcers; review of the literature (mean and ranges are shown)

| Patients | Rebleed, % | Urgent surgery, % | Mortality, % |
|---|---|---|---|
| 1,328 | 17.1 (0–40) | 10.5 (0–32) | 4.4 (0–16) |

## Surgical Intervention

Depending on the timing of the operation, surgery for hemorrhage can be divided into three main groups: emergency surgery, elective early surgery and delayed surgery. Emergency surgery carries a mortality rate between 10 and 20% but if surgery is inappropriately delayed, mortality increases rapidly. Therefore, patients who are likely to rebleed are the best candidates for early elective surgery after the initial bleeding has been stopped with endoscopic therapy. Most surgical studies have been performed before effective endoscopic therapy became available, and it is therefore very difficult to compare the different studies and strategies because of these methodological weaknesses. Morris et al. [8] prospectively compared early surgery with non-operative management in patients with bleeding ulcers, and stratified them by age and ulcer location. Over the age of 60 years, early surgery had a mortality rate of 7% compared to 43% for those with delayed surgery. However, the different types of surgery were not comparable in both groups and in those with delayed surgery more patients received gastric resection, which carries a higher procedure-related mortality. Overall mortality was 4% for early surgery and 15% for delayed surgical management in all patients. In patients with ulcers in the posterior wall of the duodenal bulb, with active bleeding or a visible vessel, early surgery may be recommended. Endoscopic hemostasis is difficult in these patients and recurrence of bleeding is often fulminant because of large side branches of the gastroduodenal artery being involved.

## Gastric Ulcers

Gastric ulcers more frequently require surgery due to uncontrolled bleeding than duodenal ulcers. At the time of a laparotomy, each gastric ulcer has to be excised including in most instances a formal resection. The main reason for this strategy is that gastric ulcers always carry the potential of being malignant. Concomitant duodenal scaring and/or ulcers do not pose a significant problem in the days of *Helicobacter pylori* eradication therapies. Therefore, vagotomy procedures should only exceptionally be added due to the associated morbidities.

## Duodenal Ulcers

For bleeding duodenal ulcers, nowadays extensive operations are almost never indicated, if ever, because many patients are *H. pylori* infected and/or have the hemorrhage occurring as a consequence of NSAID usage. Therefore, duodenal ulcer hemorrhage should mainly be treated by under-running the ulcer which, if correctly done, frequently elicits adequate hemostasis. If for any specific reason surgical acid suppression is required, a selected gastric vagotomy should be recommended due to its lower morbidity and less frequent side effects.

## Variceal Bleeding

In many institutions, operative portosystemic shunts are no longer used as treatment for variceal bleeding. When the first-line options of non-selective β-blockade or endoscopic treatment fail to control bleeding, a transjugular intrahepatic portosystemic shunt (TIPS) is usually placed. The advantages of TIPS are that it is non-operative, it effectively decompresses the portal venous circulation during the short-term perspective and early complications and procedure-related mortality are infrequent. However, late TIPS failure rates are high, with thrombosis or stenosis developing in approximately in 50% of patients within 1–2 years. Although TIPS revisions are successful in many patients, in most series, rebleeding rates after TIPS are considerably higher (10–30%) than after surgically constructed shunts (<10%). When patent, TIPS is usually a non-selective shunt with encephalopathy rates in most trials similar to those seen after a portocaval shunt. Despite these disadvantages, TIPS is an excellent option for patients in whom endoscopic treatment is unsuccessful and who require relatively short-lasting portal decompression while on the waiting list for a liver transplant or whose anticipated survival is limited due to the underlying liver disease.

Long-term survival has been particularly impressive for patients undergoing surgery since the advent of liver transplantation, especially for those who are potential liver transplantation candidates and who can be salvaged by this procedure when hepatic failure develops.

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Review Article

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# Lower Gastrointestinal Bleeding – The Role of Endoscopy

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**Key Words**
Lower gastrointestinal bleeding · Endoscopy

**Abstract**
Endoscopy is the method of choice in diagnosing the cause of lower gastrointestinal bleeding, and it offers the opportunity to treat patients suffering from lower gastrointestinal bleeding. Endoscopic procedures must be integrated with other approaches to reach a correct diagnosis rapidly, safely, and economically. In all patients, evaluation begins with a history and physical examination. The sequence of other tests depends on many factors, especially the rate of bleeding. New technologies such as wireless capsule endoscopy will influence the management of patients with lower gastrointestinal bleeding.



## Definition

*Lower intestinal bleeding* is defined as acute or chronic abnormal blood loss distal to the ligament of Treitz. 10–20% of all gastrointestinal bleeding disorders occur distal of this point, but bleeding of the small intestine is a rare condition (3–5%).

*Acute bleeding* is arbitrarily defined as bleeding of <3 days' duration resulting in instability of vital signs, anemia, and/or need for blood transfusion [1, 2]. Hematochezia is the most common clinical symptom in patients with acute lower gastrointestinal bleeding (LGIB).

*Chronic bleeding* is defined as slow blood loss over a period of several days or longer presenting with symptoms of occult fecal blood, intermittent melena or scant hematochezia. *Occult bleeding* means that the amounts of blood in the feces are too small to be seen but detectable by chemical tests [3]. In 48–71% the source will be found and an origin in the colorectum is to be expected in 20–30% [3].

*Obscure gastrointestinal bleeding* often presents as LGIB and means a bleeding from an unclear site, that persists or recurs after a negative initial or primary endoscopy. In 6% a repeat colonoscopy will identify the lesion in the colon. Push enteroscopy will be helpful in 38–75% to find the bleeding lesion, however, in two thirds the lesions are detectable within the range of a conventional gastroscope [3].

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## General Aspects of Lower Gastrointestinal Bleeding

The incidence of lower gastrointestinal bleeding is only one fifth of that of the upper gastrointestinal tract and is estimated to be 21–27 cases per 100,000 adults/year [4, 5]. LGIB usually is chronic and self-limiting and can be treated on an outpatient basis. Nevertheless, 21 of 100,000 adults/year require hospitalization due to severe bleeding. Among those, male gender and older patients suffer from more severe LGIB [4]. There is a 200-fold increase from the third to the ninth decade due to diverticulosis and angiodysplasia [6].

There is some evidence that upper gastrointestinal bleeding (UGIB) differs in acuity and severity from LGIB: Patients with LGIB are significantly less in shock (19 vs. 35%, respectively), require fewer blood transfusions (36 vs. 64%) and have a significantly higher hemoglobin level (84 vs. 61%) [7, 8]. Similar to UGIB, the majority of bleeding disorders (80–85%) in the lower gastrointestinal tract will stop spontaneously.

Mortality and morbidity increase with age. The overall mortality rate varies between 2.0 and 3.6%. Those patients with bleeding episodes after hospital admission have significantly higher mortality rates (23.1%) compared to those who bleed before hospital admission [4].

## Diagnosis

Endoscopy is the method of choice to diagnose and if possible to treat lower gastrointestinal bleeding. While colonoscopy has been accepted for years in patients with chronic bleeding, urgent colonoscopy in acute bleeding has been evaluated in the last few years and is meanwhile also accepted as a safe method.

Before starting colonoscopy, history and clinical examination should lead to a tentative diagnosis in order to plan the diagnostic procedures. In patients with chronic LGIB, colonoscopy is the first diagnostic step. The time point of colonoscopy is elective and optimal bowel preparation is standard. If the origin of bleeding cannot be detected, further steps are necessary.

In contrast, patients with acute LGIB are a challenge for optimal diagnostic procedures and there are still open questions. It is generally accepted that in patients with hematochezia, especially in combination with circulation instability, an UGIB must be excluded, since in 11% patients with suspected acute LGIB have their bleeding source proximal to the ligament of Treitz. Although placement of a nasogastric tube is safe and easy, it misses UGIB in 7%. The rate might even be higher in patients with duodenal ulcer since pylorospasm can prevent reflux of blood into the stomach [9, 10].

While anoscopy and sigmoidoscopy were mandatory procedures in the pre-colonoscopy era, their role is less obvious in the era of emergency and early colonoscopy. In recent years it could be demonstrated that in experienced hands colonoscopy plays the same role in acute LGIB as upper gastrointestinal endoscopy in acute UGIB.

All patients with acute LGIB must be stabilized and contraindications for colonoscopy are severe active inflammation and also inadequate visual conditions. Furthermore, the endoscopy should be aborted if the patient becomes unstable, the bleeding is so severe that identification of a bleeding source is impossible, or the risk of perforation is too high. It is unclear whether urgent unprepared colonoscopy is more effective in detecting the bleeding source as compared to prepared colonoscopy with a delay of several hours, since no randomized trial exists to this question.

The amount, location or pattern of blood are important signs which make a detection of the bleeding source in a circumscribed segment of the colon easier. Most studies, however, prefer bowel preparation before urgent colonoscopy. Their arguments are the frequent spontaneous bleeding stop and the improvement of visualization. The bowel preparation can be performed by enemas and/or polyethylene glycol solutions administered by mouth or via a nasogastric tube. There exist no data that cleaning the bowel might reactivate bleeding.

The detection rate of the bleeding source after bowel preparation varies between 62 and 78%, and in patients without preparation the urgent unprepared colonoscopies could identify the bleeding source in 76% [8, 11, 12]. Therefore, urgent colonoscopy seems to be reasonable in most patients.

In patients with intermittent or obscure gastrointestinal bleeding, wireless capsule endoscopy may become an interesting diagnostic approach. In two trials, capsule endoscopy was compared to X-ray of the small bowel or push enteroscopy.

Costamagna et al. [13] could demonstrate that in 13 patients with intermittent bleeding, the capsule was able to detect the bleeding source in 11 cases while X-ray only in 1 case, respectively. Ell et al. [14] examined 32 patients – the capsule detected a pathologic lesion in 66% and the X-ray in 28%, respectively.

## Differential Diagnosis

Acute LGIB occurs most frequently in diverticular (35%), followed by vascular malformation (21%), colitis (16%), neoplasia/postpolypectomy (10%), anorectal diseases (5%), and small bowel (5%). In 11% the acute UGIB is falsely diagnosed as LGIB. Differential diagnosis of severe acute LGIB is mainly dependent on the patient's age. While in children and young adults inflammatory bowel disease and Meckel's diverticulum are the main bleeding sources, diverticula are predominantly found in adults up to 60 years, and in the elderly, angiodysplasia is the most common cause for severe LGIB.

*Diverticular Disease*

The true incidence of diverticular disease is difficult to measure, mainly because most patients are asymptomatic. The incidence however clearly increases with age from 10% under 40 years to an estimated 50–66% in patients older than 80 [15, 16]. The estimated risk of a severe bleeding has been reported to be 3–5% [16, 17], but including milder forms of bleeding a risk up to 48% has been described [18]. Among LGIB disorders, diverticula are the cause in 15–27% [19]. The clinical presentation of patients with diverticular bleeding is mostly abrupt with a painless onset, associated with mild lower abdominal cramps and the urge to defecate. The stool consists of red voluminous or maroon blood or clots. Melena is uncommon [16]. Approximately 80% of the bleeding episodes stop spontaneously. The risk of a first rebleeding is 25% but increases with definite bleeding stigmata (active bleeding, nonbleeding visible vessel, adherent clot: 67, 50 and 43%, respectively) [19–21]. A third bleed after a second episode will occur in 50%, therefore surgical resection is recommended after a second bleeding episode [16].

*Colitis*

LGIB from IBD are rarely life-threatening (0.1% ulcerative colitis, 1.3% Crohn's disease), bleeding stops mostly spontaneously and endoscopic treatment is not necessary in most cases with diffuse bleeding. Bleeding from ischemic colitis occurs mainly in elderly patients (>65 years) and is associated with pain. Vascular diseases and atrial fibrillation are risk factors which are associated with ischemic colitis. Patients with infectious colitis suffer mainly from diffuse bleeding similar to ulcerative colitis. Among bacteria, *Salmonella, Shigella, Yersinia, Campylobacter* and *Escherichia coli*, especially enterohemorrhagic *E. coli* (EHEC), most notably 0157:H7, are the most frequent infectious agents. Acute radiation colitis occurs a few days after radiation but bloody diarrhea is uncommon at this time point. Most patients complain of transient diarrhea and tenesmus. The endoscopic picture is similar to ulcerative colitis with edema, fragility, hemorrhage and some erosions or ulcers [16]. The clinical manifestation of chronic radiation colitis occurs after 1–2 years. Pale mucosa with teleangiectasia and rarefaction of mucosal vessels is typical in mild forms. In severe radiation colitis, excessive hemorrhage, necrosis and ulcerations occur leading to extensive bleeding [16].

*Neoplasia*

Acute bleeding in colon cancer or polyps is not frequent but has been described in 2–33 and 5–11%, respectively [16, 17]. The majority of these lesions present with chronic bleeding. Among patients with LGIB, postpolypectomy bleeding occurs in about 4% [4]. Bleeding occurs either immediately (within 24 h) or delayed (occurring as long as 21 days after colonoscopy) [22]. The risk of bleeding depends on several factors: polyp size, type of polyp (pedunculated or sessile), hemostatic disorders, medication and endoscopist's experience influence the postpolypectomy hemorrhage risk. Although the use of NSAID did increase the incidence of minor self-limited bleeding, an increase in the rate of major bleeding was not observed [23]. The overall risk of bleeding after polypectomy ranges from 0.4 to 2% [24].

*Angiodysplasia*

In patients with LGIB, angiodysplasia is the responsible bleeding disorder in 3–12% [4, 5]. Bleeding can be chronic, slow, intermittent or recurrent. Massive bleeding has been described in 2% of the cases, but bleeding stops spontaneously in up to 90%. Unfortunately the rebleeding rate is high and can reach values up to 85% [16].

The prevalence of angiodysplasia among healthy asymptomatic people was 0.83%. 87% of these usually small lesions (4 mm) were located in the right colon, and there was no risk for later bleeding [25]. Angiodysplasia often appears together with systemic diseases such as cardiovascular disorders (aortic stenosis) or chronic renal failure [26, 27]. However, there exist also systematic examinations which could not confirm an association of angiodysplasia and aortic valve disease [28]. Capsule endoscopy may improve the detection of these lesions in the small bowel in the near future.

**Table 1.** Endoscopic treatment of LGIB

| Bleeding source | Endoscopic treatment | Comments |
|---|---|---|
| Diverticula | Injection, clip | Bleeding mainly stops spontaneously, perforation risk |
| Colitis (IBD, radiation, ischemia, infection) | Injection of ulcer<br>APC in radiation colitis with teleangiectasia | No endoscopic treatment is necessary in most cases; high risk of perforation! |
| Neoplasia | Thermal, injection<br>Polypectomy of bleeding polyps | Seldom severe bleeding |
| Postpolypectomy bleeding | Injection, clip | Prophylactic loop? |
| AV malformations | APC, thermal, injection of sclerosing agents | High risk of rebleeding!<br>Hormone therapy not useful<br>No prophylactic treatment |
| Anorectal diseases | Ligation, sclerotherapy | TIPS in patients with esophageal and rectal varices |

*Anorectal Diseases*

Due to anorectal lesions, LGIB is mainly caused by hemorrhoids, rectal varices and fissures. 2–9% of all LGIB are caused by hemorrhoids [4, 5]. Among patients with AIDS, anorectal diseases are more frequent as bleeding sources and may be severe in case of thrombocytopenia. Rectal varices are to be differentiated from hemorrhoids. Bleeding is sometimes profuse but painless. Portal hypertension is the main reason for rectal varices and is present in 79–89% in these patients.

## Therapy

Endoscopic therapy of LGIB is similar to UGIB and is the therapy of choice. In a recent survey of the American College of Gastroenterology, endoscopic therapy was performed in 27% in LGIB and in 51% in UGIB, respectively [2]. Jensen et al. [29] recently demonstrated that emergency colonoscopy with endoscopic treatment was superior to conservative treatment in combination with surgery if necessary. Different endoscopic techniques such as injection therapy, thermal methods, clipping and so on, which have been successful in UGIB, are also useful in the treatment of LGIB (table 1).

Angiodysplasia can be treated effectively by thermal methods, and argon plasma coagulation is meanwhile the treatment of choice. For prophylactic treatment of nonbleeding, incidental angiodysplasia is not recommended and a hormone therapy of bleeding angiodysplasia has shown no benefit in a recent randomized trial. Vascular malformations in patients with chronic radiation colitis can be treated with argon plasma coagulation in the same way.

While bleeding polyps can effectively be treated by polypectomy and adjuvant methods such as injection therapy or application of a loop before snaring the polyp, bleeding from colorectal cancer can be treated with thermocoagulation by Nd:YAG laser or argon plasma coagulation. If endoscopic treatment is not possible due to severe bleeding, angiography is recommended: Application of drugs such as vasopressin is as effective as embolization to achieve initial hemostasis (71 vs. 70%, respectively). However, rebleeding rate after vasopressin is 25% compared to embolization (0%).

The ultima ratio in treatment of severe LGIB is surgery, which occurs in 10–25%. Criteria for (emergency) surgery are: >4 units of blood/24 h or a total of 10 units overall; bleeding continues for ≥72 h, and significant rebleeding within 1 week of initial cessation [16, 17].

Blind segmental colectomy is associated with an unacceptable high morbidity (rebleeding rate as high as 75%) and mortality (up to 50%). Therefore, an aggressive approach for an accurate preoperative localization is most important. Directed segmental resection is the treatment of choice because of its low morbidity, mortality (about 4%) and rebleeding rate (about 6%) [16]. Angiographic localization has been shown to be more precise than scintigraphic methods. The 1-year rebleeding rate could be decreased from 42% without angiographic localization to 14% with angiography (fig. 1).

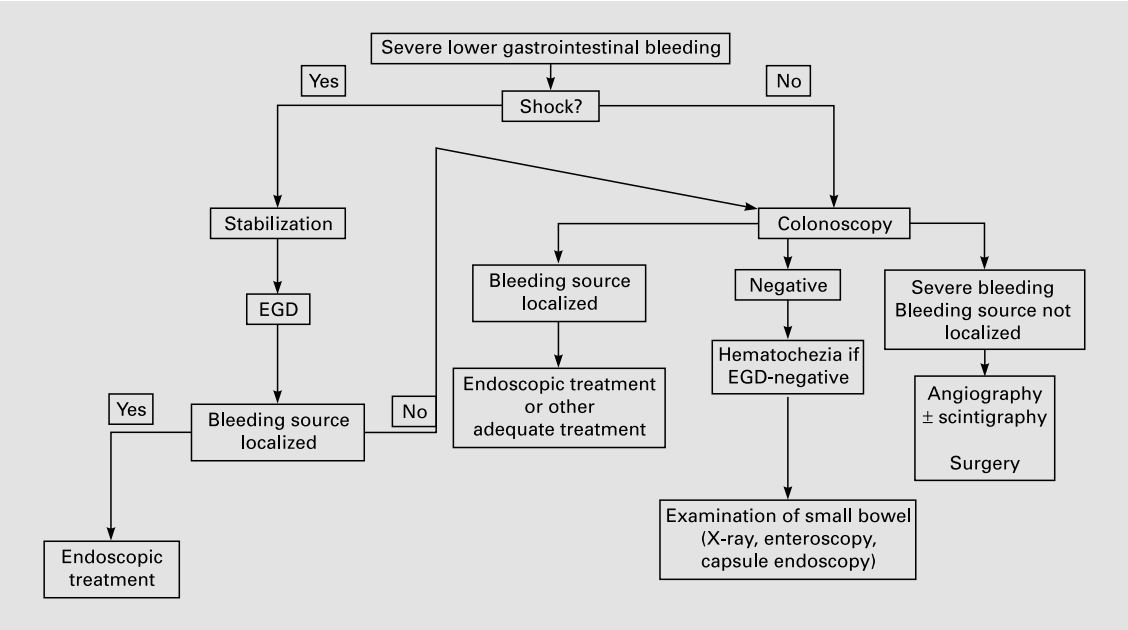


**Fig. 1.** Management of acute severe LGIB.

Intraoperative diagnostic endoscopy has become most attractive to examine the small or large bowel with enteroscopes or colonoscopes after laparotomy, pleating of the bowel on the instrument, and translumination. Identification of bleeding sites has been possible in 83–100% [30]. Preliminary studies report on a theoretical advantage of this combined approach, especially in the management of small bowel hemorrhage, which cannot be identified with usual techniques [31]. New techniques such as wireless capsule endoscopy may improve the diagnosis in patients with LGIB as well.

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Review Article

Digestive Diseases

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# Management of Acute Cholangitis

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**Key Words**
Acute cholangitis · Endoscopic sphincterotomy · Laparoscopic CBD exploration · Common bile duct stones

**Abstract**
Endoscopic sphincterotomy (ES) is the treatment of choice for patients with (severe) acute cholangitis. For fit patients without co-morbidity with mild cholangitis and CBD stones with a gallbladder in situ, the one-stage laparoscopic approach could be considered as an alternative in centers with sufficient experience. The results of both procedures are comparable. Open surgery is relatively safe. It has a high success rate, good/excellent long-term results, but is not very attractive for the patient and should not be used routinely nowadays. Therefore, the indication should be limited for management of severe complications after ES as perforations of the duodenum, large CBD stones and patients with Mirizzi's syndrome or intrahepatic stones with stenosis of the bile duct. ES as primary treatment for CBD stones should be followed by laparoscopic cholecystectomy in 'fit' patients. In patients with malignant disease, particularly after repeated stent failure and subsequent cholangitis, bypass surgery should be considered in patients with a life expectancy of >3 months.



After the introduction of endoscopic sphincterotomy (ES) and percutaneous drainage procedures, the indication for different surgical and non-surgical approaches of biliary disorders changed radically and is still subject of controversy. There is however general agreement that patients with severe cholangitis should preferably be treated non-surgically by ES instead of (open) CBD exploration after a randomized trial of Lai et al. [1] clearly showed a reduction in morbidity from 66 to 34% and a reduction in hospital mortality from 32 to 10%. Recently, another trial has been published showing that even in the absence of CBD stones during the attack of cholangitis, ES decreased the duration of fever in patients with acute cholangitis and reduced hospital stay from 4.3 to 2.2 days and 9.1 to 8.1 days, respectively [2]. However, it did not decrease the incidence of recurrent acute cholangitis during follow-up.

The development of high-quality ES in general hospitals has resulted in a decrease of surgical procedures for acute cholangitis as well as for the initial management of CBD stones without cholangitis in many European countries, particularly in The Netherlands and Germany. In The Netherlands only 20% of patients with CBD stones underwent a surgical approach during the past decade. A minority of these patients suffered from severe cholangitis, the others having symptomatic CBD stones.

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A recent nationwide survey in Germany, reporting the surgical management of 98,482 patients with symptomatic gallstone disease and 8,433 patients with CBD stones, showed that surgical CBD exploration decreased from 7.4% in 1991 towards 3.8% in 1996. In 1998, all university hospitals used a two-stage management with preoperative ERCP and ES – the so-called 'therapeutic splitting' [3]. Again, no doubt exists today that patients with severe cholangitis will primarily be managed non-surgically. Therefore, the discussion about the role of surgery should also focus on whether there is still a role for surgery in the treatment of patients with CBD stones with mild cholangitis or without cholangitis.

There have been four randomized trials that compared open surgery versus ES for the treatment of CBD stones [4–7]. In the Spanish trial [4], high-risk patients with cholangitis and mild biliary pancreatitis were also randomized. These trials showed a high success rate for both procedures, around 90–95%, no significant difference in morbidity and mortality, but a significantly longer hospital stay after surgery. ES however was associated with significantly more recurrent biliary symptoms and a higher requirement of additional procedures (>20%) [4–7]. In a second study by the same group [8], ES was followed by laparoscopic cholecystectomy and the recurrence of biliary symptoms in that study reduced to 4%.

Summarizing these trials, open surgery is not inferior to ES, it is safe and effective but is associated with a longer hospital stay and in particular, after introduction of the minimal invasive procedures, it is not very attractive for patients and therefore not generally accepted nowadays. More recently, laparoscopic CBD exploration has been introduced for the management of CBD stones including patients with mild cholangitis. Again it was generally accepted that ES should be the treatment of choice for poor-risk patients with severe cholangitis and pancreatitis [9].

There have been two randomized trials that compared laparoscopic CBD exploration (LCBDE) with ES. In the first trial, Rhodes et al. [10] compared LCBDE with laparoscopic cholecystectomy and postoperative ES showing that LCBDE is as effective as ES in overall clearance of the CBD stones. There was a significantly shorter hospital stay in patients treated by LCBDE. A second multicenter trial [9] compared LCBDE with ES and subsequent laparoscopic cholecystectomy and showed an equivalent success rate for both procedures, no significant difference in complications and mortality but a shorter hospital stay after LCBDE compared with ES. The authors concluded that laparoscopic CBD exploration should be preferred for fit patients (ASA I and II). More recent studies also showed that primary closure of the bile duct after bile duct exploration without an external drain by a T-tube drainage is safe and efficient even in patients with acute cholecystitis, mild cholangitis or pancreatitis provided that laparoscopic skills are available [11–12].

Laparoscopic CBD exploration without drainage even reduced biliary complications from 16 to 4% [12]. In a recent review on management of CBD stones it was concluded that single-stage laparoscopic treatment without drainage of the CBD (primary closure) should be advocated as the primary treatment in centers with sufficient experience in laparoscopic exploration [13]. So far in other hospitals, ES still remains the treatment of choice, however training issues and experience will also arise concerning gastroenterologists performing ERCP and ES. There is no doubt that all patients with CBD stones after previous cholecystectomy should undergo ES.

Despite increased interest in minimal invasive surgery, there is an enormous difference in Europe about the acceptance of laparoscopic CBD exploration and still the majority of patients, around 90%, are treated with ES. Therefore, the next question arises, i.e. if the gallbladder should be removed after successful stone clearance after ES. As shown in previous trials comparing open surgery and ES, additional procedures were performed in 20–26% of the patients after ES [4–7]. In a recent trial from The Netherlands comparing a wait-and-see policy versus laparoscopic cholecystectomy after ES and CBD clearance, 47% of the patients in the wait-and-see group suffered from recurrent biliary pain and 47% needed an additional procedure (10% ERCPs and 37% cholecystectomy) within 2 years after initial ES. It was concluded that laparoscopic cholecystectomy should be advocated in fit patients after ES [14].

Another indication for surgery is failure after endoscopic treatment or the existence of retained stones. In a series from the area of open surgery for CBD stones, we showed that a choledochojejunostomy, as the final solution for complicated CBD stones, was successful in 98% even after 8 years of follow-up [15]. These procedures can now also be performed laparoscopically, as mentioned before. In elderly patients in particular (>70 years), gastroenterologists generally prefer multiple stent exchanges even in patients with retained stones and recurrent cholangitis instead of a relative simple surgical bypass procedure (choledochoduodenostomy). They should realize that mortality of these procedures these days is nearly zero for these patients.

Patients with cholangitis due to Mirizzi's syndrome are also an indication for (open) surgery or for a laparoscopic approach with an extremely high conversion rate. These

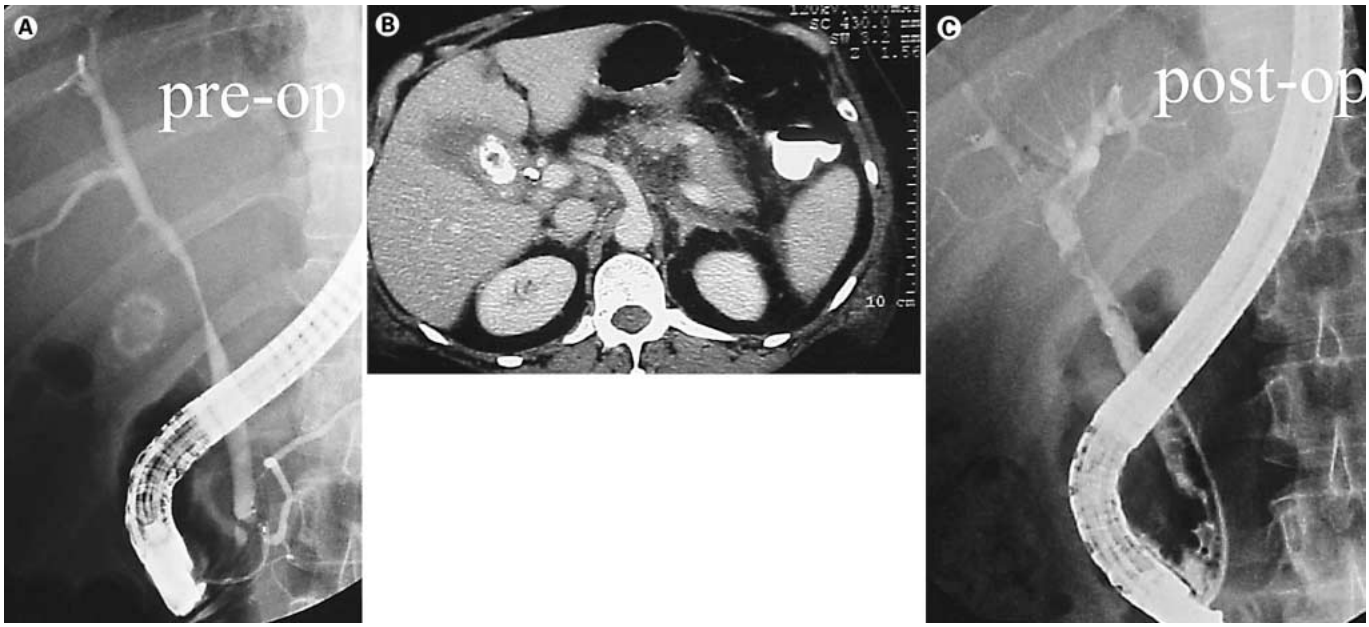


**Fig. 1.** Patients with obstructive jaundice due to Mirizzi's syndrome. **A** ERCP showing a stenosis of the CBD. **B** CT scan showing an inflammatory mass. **C** Control ERCP 6 weeks after surgery and primary repair of the CBD.

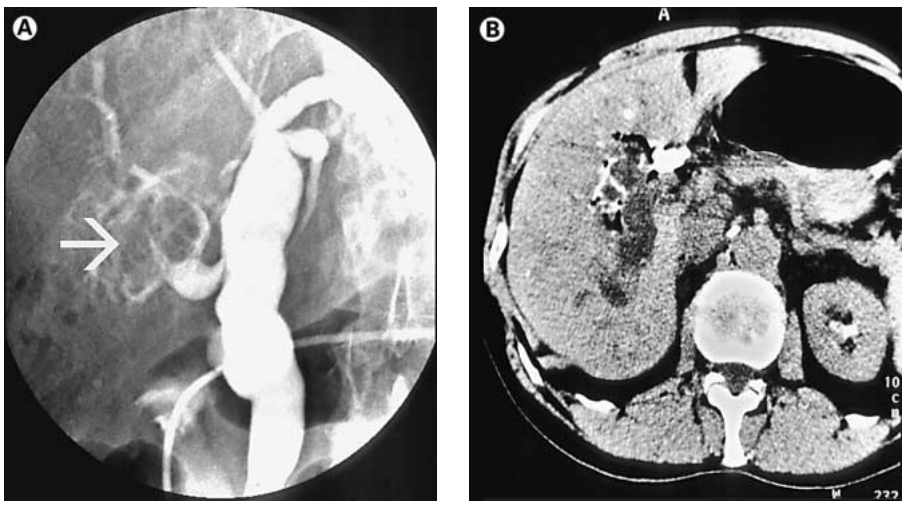


**Fig. 2.** Patient with intrahepatic bile duct in the right hepatic duct with a stenosis at the distal right hepatic duct (**A**) and CT scan (**B**) showing entrahepatic bile duct dilatation and stones.

patients generally present with obstructive jaundice or cholangitis and endoscopic drainage can be performed easily as the initial treatment because of the relative smooth stricture by the impacted stone (fig. 1A). After adequate biliary drainage and resolving of the inflammation around the hepatoduodenal ligament (fig. 1B), cholecystectomy should be performed with closure of the defect in the CBD and the stent can be removed after a few weeks (fig. 1C).

Patients with recurrent cholangitis due to multiple intrahepatic bile duct stones are generally treated by a combined endoscopic and percutaneous approach. In particular if only one lobe is affected and after failure of non-surgical treatments to remove the stones, these patients are also candidates for surgery and a hemihepatectomy should be performed (fig. 2A, B). The surgical approach is well established in South-East Asia for this common problem and is even performed laparoscopically nowadays

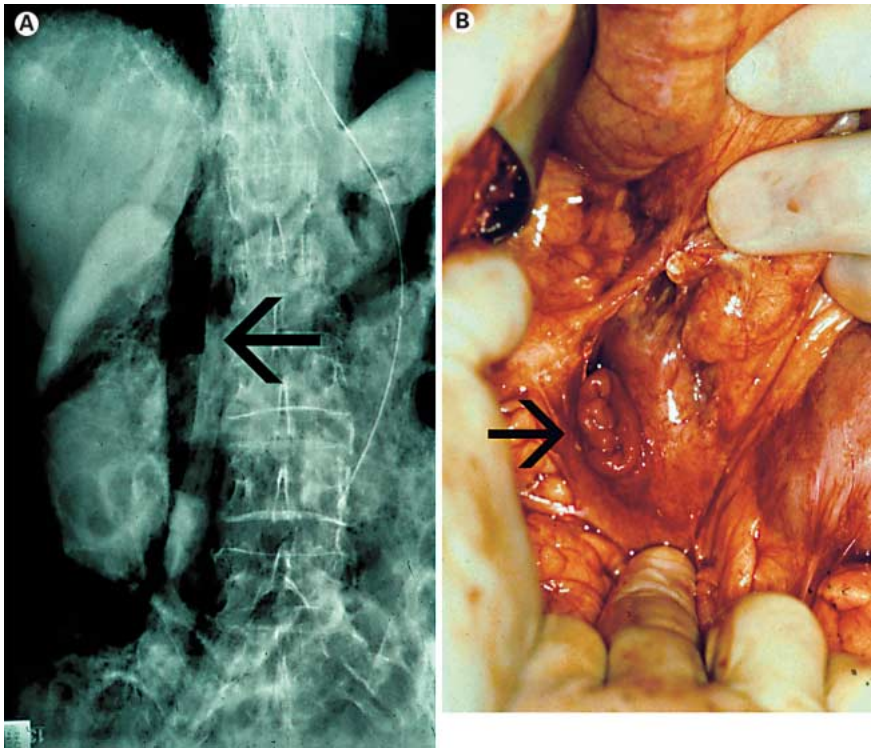


**Fig. 3.** A patient with a perforation after ERCP and free air in the retroperitoneum (**A**) and perforation of the duodenum during exploration (**B**).

[16]. Surgery is also sometimes indicated for severe complications after ES (bleeding/perforation) but in particular after free perforation of the duodenum or a perforation of the endoscope at the anastomosis (gastroenterostomy) after a previous BII resection. Early intervention is warranted in these patients.

In a period of 7 years, 27 patients underwent surgery for complications of ERCP at the AMC Amsterdam. The majority suffered from perforations of the duodenum (n = 7) (fig. 3) or at the anastomosis after BII resections (n = 7). In 1 patient a pancreatoduodenectomy was performed. The other patients underwent cholecystectomy, closure of the defect, subsequent CBD exploration with or without a choledochoduodenostomy or choledochojejunostomy. In patients with perforations during sphincterotomy or even small retroperitoneal perforations of the duodenum, conservative management is nearly always sufficient. If subsequent leakage and abscess formation occurs, percutaneous drainage should be performed and finally if not successful diversion of the duodenum should be considered.

Endoscopic biliary stenting has generally been accepted as the treatment of choice for palliative treatment in patients with obstructive jaundice due to distal bile duct or pancreatic malignancy with a limited life expectancy. Four randomized trials comparing stenting and bypass surgery showed that there is no difference in relief of obstruction by both methods. Surgery was initially associated with a higher postoperative morbidity, mortality and a longer hospital stay. Non-operative treatment with an endoprothesis however led to recurrent jaundice and cholangitis in up to 40% and gastrointestinal obstruction in up to 17% during follow-up [17–20]. In two more recent studies from our center, the mortality after palliative surgical bypass procedures decreased to 2.5 and 1% respectively and postoperative complications were 17 and 12% [21, 22]. Other studies showed similar results and in selective patients with a life expectancy of >6 months, bypass surgery is safe nowadays [23, 24].

In a recent randomized trial comparing stenting and bypass surgery in patients who proved to have metastasis during diagnostic laparoscopy, we clearly showed that patients after stenting had a shorter hospital-free survival and more readmissions because of stent dysfunction and cholangitis compared with patients after bypass surgery [25]. Therefore, we conclude that patients with recurrent cholangitis after stent treatment for malignant tumors should of course first undergo stent exchange, or insertion of metallic stents, but in a selected group of patients a biliary bypass should also be considered, particularly in patients with a life expectancy of >3 months.

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Review Article

Digestive Diseases

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# Acute Pancreatitis: Treatment Strategies

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**Key Words**
Pancreatitis · Endoscopy · Pain · Drug therapy · Enteral nutrition

**Abstract**
Acute pancreatitis is an acute painful abdominal disease of sudden onset that ranges from a mild and self-limited illness to a severe and severe life-threatening condition. In spite of decades of intensive research, there are no causal therapeutic options. Treatment relies on supportive treatment principles based on adequate volume replacement to compensate for fluid loss in the intraperitoneal space and analgesics for pain relief. In cases with acute pancreatitis predicted to have a severe course of the disease, antibiotic therapy is recommended to avoid infection of pancreatic necrosis. Despite a substantial set of clinical trials in favor of antibiotic treatment to reduce morbidity, there is no general consensus on the prophylactic antibiotic treatment. Adequate nutritional support is required for patients with severe acute pancreatitis and a protracted course of the disease. Enteral nutrition appears to be superior to enteral nutrition.



## Introduction

Acute pancreatitis is characterized by severe pain with sudden onset (fig. 1). The course of the disease ranges from a mild and self-limited illness to a severe and rapidly or delayed progressive severe or life-threatening condition. The ratio of mild to severe acute pancreatitis is approximately 5:1. Patients with severe acute pancreatitis may develop systemic complications due to either the systemic inflammatory response syndrome (SIRS) or to sepsis which may lead to multiorgan failure (MOF). The death rate of severe acute pancreatitis, despite important progress in clinical management, is still within the range of 10–20% [1–7].

## Etiology and Prognostic Assessment

The clinical assessment of acute pancreatitis requires certainty in diagnosis, identification of etiology and prognostic evaluation.

Alcohol and gallstones represent 75–80% of all causes of acute pancreatitis in Western industrialized countries, but the prevalence of these two different factors varies widely between countries in different parts of the world [8]. Around 20% of patients with acute pancreatitis will have the severe from of the disease with a significantly

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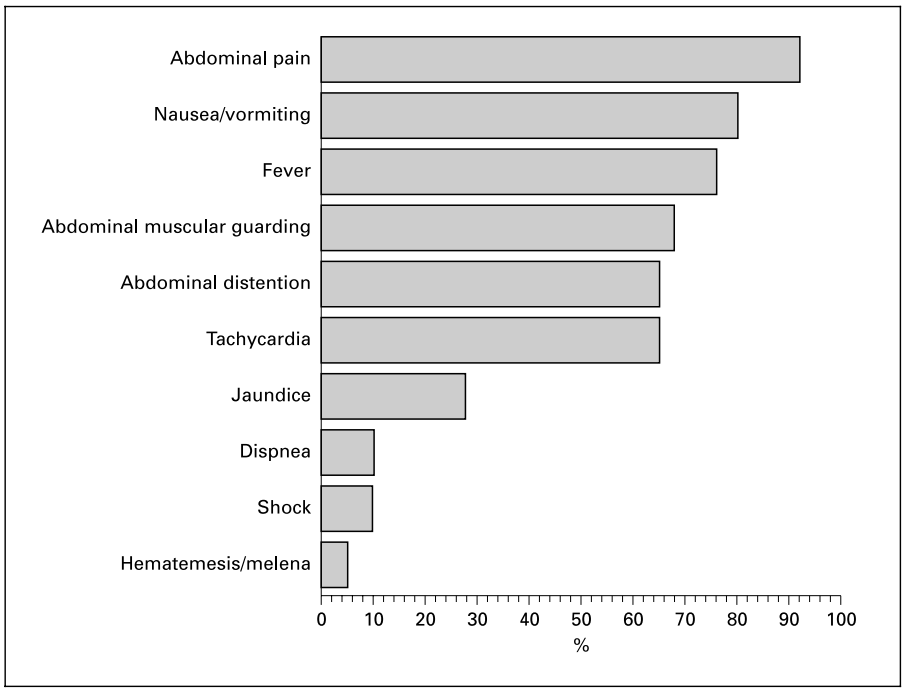


**Fig. 1.** Clinical symptoms of acute pancreatitis.

increased risk of death [1–7]. For proper monitoring, selection of diagnostic procedures and treatment modalities, patients need early assessment for prognosis. The standard and traditional approach for identifying the severity of acute pancreatitis is the application of a variety of scoring systems [9–12].

For educational purposes for trainees it is very valuable to include these scoring systems in the clinical assessment, but their limitations due to complexity must be acknowledged. In specialized centers, measurement of biochemical markers has become a standard for prognostic assessment. These markers have the advantage that they can be measured repeatedly and can draw attention to the development of severe disease more simply than the complex scoring criteria. The use of the acute-phase protein C-reactive protein (CRP) has been validated in several centers and by choosing the proper validated cut-off (>120 mg/l) it is reported to accurately detect pancreatic necrosis in up to 90% [13].

The increase of CRP during acute pancreatitis occurs however with a delay of 1–2 days as it reflects the stimulation of hepatic synthesis of the acute phase protein mediated by interleukin-6 (IL-6). The release of inflammatory mediators such as IL-6 and PMN-elastase occurs more rapidly [14–17]. However, due to technical simplicity and general availability, serum CRP determination is still the most widely used individual marker for prognostic assessment of acute pancreatitis and it indicates pancreatic necrosis within 48–72 h after disease onset with an accuracy of around 90% [13].

Interleukins, trypsin activation peptide, procalcitonin, procarboxypeptidase-activation peptide or phospholipase $A_2$ are also markers of disease severity with proven validity [15, 17–23], but they are either too expensive or to time-consuming for clinical routine. A single serological marker with absolute reliability to predict a severe attack of acute pancreatitis at any times after onset of the disease is still not available.

## Therapy of Acute Pancreatitis

Conservative treatment of acute pancreatitis consists of basic supportive therapy (volume replacement, rehydration, analgesics) and additive treatment in predicted cases (table 1). Adequate volume replacement (3–9 l, electrolyte substitution) should be based on the central venous pressure. Severe cases should be treated depending on systemic complications according to current principles adopted by strategies of intensive care management.

*Analgesic Treatment*

Several treatment options are available for pain relief, but there are only a few clinical trials dealing with an opti-

**Table 1.** Standard therapy in acute pancreatitis

| |
|---|
| *Effective medical therapy* |
| Volume replacement and hydration |
| Analgesics for pain relief |
| Correction of electrolyte abnormalities and diabetes mellitus |
| *Effective in predicted severe cases* |
| Antibiotics |
| Parenteral or jejunal feeding |

mal treatment for pain relief in patients with acute pancreatitis. Intravenously administered opioid derivates and procaine hydrochloride, celiac plexus blockade, application of NSAIDs, enzymes or transdermal acting opioids are recommended [24–32].

The application of indomethacin in a double-blind randomized trial could show a significant effect of indomethacin on pain, but even patients treated with the drug needed significant amounts of opiates for pain relief [31]. The only paper dealing with a transdermal acting opioid is based on a study comparing the efficacy of the TTS-fentanyl vs. intramuscular injections of analgesics. It seems that the TTS-fentanyl was superior, but the drawbacks of this study are significant, especially with regard to the used alternative [32].

The widely recommended procaine hydrochloride is questionable at least with its analgesic potency [33]. Nowadays there are two randomized clinical trials showing that intravenously administered procaine hydrochloride is ineffective in pain treatment: the first one was able to show that procaine is less effective compared to buprenorphine [28]. Our own data prove that procaine hydrochloride is ineffective compared to pentazocine [34].

An excellent level of analgesia can be expected when using epidural anesthesia. The effectiveness and safety of epidural anesthesia was demonstrated in a large randomized clinical trial [35]. In this study, even in patients with marginal cardiovascular stability, epidural injection of local anesthetic solution was tolerated well.

Based on the current literature data, we recommend intravenous pain treatment with opioid analgesics in patients with less intense pain, responding to this treatment. Epidural analgesia in patients with more severe pain is a valuable alternative. This should be further evaluated in randomized clinical trials.

*Antibiotics*

The majority of deaths in acute pancreatitis are because of late infections and septic complications. These complications are usually seen around the 10th to 14th day after onset of the disease. Patients with necrotizing pancreatitis are at highest risk for secondary infection and death. This increases with the greater extent of pancreatic necrosis.

Current advice is that patients with a severe attack of acute pancreatitis should undergo an intravenous contrast-enhanced (dynamic) computed tomography between 3 and 10 days after admission for the assessment of the degree of pancreatic necrosis and surrounding peripancreatic and intra-abdominal fluid collections [36]. The use of the acute-phase protein CRP has been validated by choosing the proper validated cut-off (>120 mg/l) and it is reported to accurately indicate the presence of pancreatic necrosis in up to 90% [13]. There is an impressive time-dependent increase in infection rates of pancreatic necrosis with the duration of the disease [37]. Most of these infections are caused by *Escherichia coli, Pseudomonas, Staphylococcus aureus*, or *Klebsiella* [38, 39].

The benefit of early – within the first 48 h after onset of disease – prophylactic antibiotic therapy in patients with necrotizing pancreatitis to prevent infected pancreatic necrosis and septic complications is under debate [39–45]. The antibiotics must penetrate into pancreatic tissue and cover the full bacterial spectrum [46]. On this background, studies were carried out with imipenem and cephalosporins [47–49]. Both classes of antibiotics show good tissue penetration and high antibactericidal efficacy.

In a direct comparison of pefloxacin (400 mg, twice daily, 14 days) vs. imipenem (500 mg, 3 times daily, 14 days), imipenem proved significantly more effective in prevention of the infection as well as of extrapancreatic infections than pefloxacin [47]. However, the latest and largest randomized controlled multicenter study finished in 2002 including 114 patients with necrotizing acute pancreatitis compared ciprofloxacin and metronidazole vs. placebo and could not show any beneficial effect of antibiotics on mortality [50].

Recently there are data about a germ shift from gram-negative to gram-positive bacteria and an increase in fungal infections after antibiotic treatment [43, 45]. Whether it is always a sequel of prophylactic antibiotic treatment or not is an open question. Together with the facts of unaffected mortality after prophylactic antibiotic treatment, this option is partly further open for discussion. The main questions which should be answered immediately are the optimal choice of the antibiotic, the starting point and duration of antibiotic treatment. If infection of pancreatic necrosis is suspected, CT-guided percutaneous aspiration

**Table 2.** Outcome from selected randomized trials comparing enteral vs. parenteral nutrition

| Group (first author) | Ref. | n | Outcome |
|---|---|---|---|
| Kalfarentzos, 1997 | 56 | 38 | Less septic complications ($p < 0.01$) and complications in general ($p < 0.05$)<br>Enteral nutrition is more cost-effective |
| McClave, 1997 | 58 | 32 | No influence of enteral nutrition on morbidity and mortality<br>Enteral nutrition is more cost-effective |
| Windsor, 1998 | 61, 82 | 34 | Modulation of acute-phase response, positive effect on severity and course of the disease (including sepsis and MOF) |
| Powell, 2000 | 62 | 27 | No effect of enteral nutrition on inflammatory response or gut permeability |
| Eatock, 2000 | 63 | 26 | Nasogastric feeding is practicable and safe |
| Olah, 2001 | 65 | 133 | Enteral nutrition reduces septic complications<br>No influence of enteral feeding on septic complications or mortality |
| Olah, 2002 | 64 | 45 | Enterally given *Lactobacillus plantarum* reduces the number of infected pancreatic necrosis |
| Abou-Assi, 2002 | 66 | 50 | Less septic complications with enteral nutrition<br>Enteral nutrition is more cost-effective |

has proven to be a safe and accurate method of distinguishing sterile from infected necrosis. In cases of infected pancreatic necrosis, the currently accepted practice is to perform surgical debridement as soon as infected necrosis is evident [51, 52]. In well-selected cases, interventional therapy offers an excellent option. Prospective studies are warranted to test the benefit of non-surgical therapies in infected pancreatic necrosis as compared to the surgical approach.

*Enteral vs. Parenteral Nutrition*

In mild acute pancreatitis, total parenteral nutrition is unnecessary. Total parenteral nutrition via a central venous catheter is recommended in patients with predicted severe acute pancreatitis or in cases with protracted disease. In severe cases of acute pancreatitis, parenteral nutrition is recommended to be started within the first 72 h after onset of acute pancreatitis, but there is no definite evidence available that total parenteral nutrition improves outcome of severe acute pancreatitis [53–55].

Some recent studies have shown an improvement in clinical outcome of patients with acute pancreatitis if they received enteral nutrition by a nasojejunal or nasogastric tube if compared to patients with parenteral nutrition [56–77]. The concept that promotes early enteral nutrition is to protect the gut from mucosal injury. Without nutrition from the luminal site a few hours after the onset of acute pancreatitis, the intestinal permeability for toxins or bacteria is increased. Endogenous cytokines stimulated by endotoxins and bacterial products from the paralyzed gut will enter the systemic circulation and may damage different distant organ systems and lead to SIRS, sepsis, MOF and death [78, 79].

Windsor et al., Kalfarentzos et al. and Nakad et al. showed that enteral nutrition is safe, controls the acute phase response and improves disease severity and clinical outcome in patients with severe acute pancreatitis [80–82]. Table 2 summarizes the available data from the literature. At the moment, enteral nutrition, even via a nasogastric line, can be recommended: There are no data that enteral feeding intensifies acute pancreatitis; enteral nutrition via a nasogastric line seems to be easy and cheaper than parenteral nutrition [83]. However, there may be patients with advanced gut paralysis which may not be candidates for enteral feeding. Further randomized clinical trials to measure all relevant outcome variables and for final proof of the enteral feeding concept as substitute for the parenteral route are essential. The very latest Cochrane review on this topic supports this idea [70].

*Causal Treatment*

There is still no causal therapy available for patients with acute pancreatitis despite continuous and recent attempts to introduce novel drugs with the aim of antagonizing activated proteases or proinflammatory or toxic mediators [7, 84–86].

Gabexate mesilate is a synthetic, broad-spectrum, low-molecular-weight antiprotease capable of penetrating into

**Table 3.** Therapeutic approaches in acute pancreatitis

| Indication | | Therapies | Drugs | Dosage | Application |
|---|---|---|---|---|---|
| *All patients* | | | | | |
| Dehydration | | Volume replacement | Intravenous fluids, water, glucose and amino acids | 3–9 litres | IV; according to the central venous pressure and balanced |
| Pain | Mild | Analgesics | Acetaminophen<br>Tramadol | 2–3 × 1,000 mg<br>3–4 × 100 mg | Oral, if not possible tramadol IV |
| | Mild to moderate | | Buprenorphine | 6–8 × 0.3 mg (max. 9 µg/kg b.w. dosage) | IV |
| | Severe | | Local anesthetic solution | | Peridural anesthesia |
| Elevated blood glucose, diabetes mellitus | | Correction of blood glucose level | Insulin | According to blood glucose | Continuous IV infusion |
| Nutritional support | | Enteral feeding | Nutrients via nasogastric tube | Balanced | Enteral, as soon as possible |
| Electrolyte abnormalities, severe hypocalcemia | | Correction of serum calcium level | Administration of calcium | According to serum calcium level | IV |
| *Predicted severe cases* | | | | | |
| Nutritional support | | Parenteral nutrition | Water, glucose and amino acids | Balanced | IV, as long as necessary because of atonic bowel |
| Prevention of infected pancreatic necrosis and septic complications[1] | | Antibiotics | Meropenem<br>Imipenem | 3 × 500 mg<br>3 × 500 mg | IV |
| Nutritional support and prevention of septic complications and reduction of mortality[1] | | Enteral feeding | Nutrients via a nasogastric tube | Balanced | Enteral, as soon as possible |

[1] Further studies are needed.

the pancreatic parenchyma and interstitium. It holds the most promises in the last decade. While a large multicenter study failed to show a significant benefit [7], another one using the drug very early in the course of the disease reported a reduction of pancreatic damage [87]. This condition however is not very useful in clinical practice and is limited to the use of gabexate mesilate for prevention of ERP-induced acute pancreatitis.

Lexipafant, a potent antagonist of platelet-activating factor (PAF), was a new promising candidate probably effective in experimentally induced pancreatitis in rats, as well as in an initial pilot study in humans showing reduced pancreatic and extrapancreatic inflammation as well as a reduction in organ complications [88]. However, in a recent large unpublished multicenter study, a beneficial effect was not confirmed [89]. It is only in patients with predicted severe acute pancreatitis of biliary etiology that the early performance of endoscopic retrograde cholangiography (ERC) combined with papillotomy has proven to be of significant clinical benefit [90, 91].

There are four published randomized prospective studies with different results concerning if and when to perform endoscopic retrograde pancreaticography (ERC) with endoscopic sphincterotomy (EST) in suspected acute biliary pancreatitis [90–93]. In the study of Neoptolemos et al. [91], the patients significantly benefited from ERC with EST within 72 h compared to conventional treatment. The outcome was identical in patients with mild attacks irrespective of the treatment but was significantly improved when ERC was performed in patients with predicted severe acute pancreatitis. If we focus only on patients with gallstones, the study of Fan et al. [90] reported results similar to those of Neoptolemos et al. [91].

The German Multicentre Study [93] did not find any benefit of ERC for patients with suspected acute biliary pancreatitis. In this study, patients with obstructive jaundice were excluded as this represents an indication per se for ERC and EST. The data about ERC and EST in patients with acute biliary pancreatitis still leaves several

questions open. The studies published up to now do not answer the question as to when to perform an interventional endoscopy. From the available data we would recommend that an interventional endoscopy (ERC plus EST) should be performed in cases of acute biliary pancreatitis with severe prognosis in specialized centers that provide optimal trained personnel, and technical and logistic support.

## Conclusion

Basic therapy in patients with acute pancreatitis consists of volume replacement and analgesic therapy. For pain relief, opioid analgesics (intravenously given) are the first choice. Epidural analgesia is a valuable alternative in patients with more intense pain, who do not respond to intravenously administered opioids. In severe cases with suspected pancreatic necrosis, antibiotics should be administered to prevent infection and to avoid surgery. This strategy is not proven to be more effective at all, but it seems to offer advantages.

Enteral nutrition should be started as soon as possible. There are no controlled data from larger studies about positive effects on morbidity or mortality in enterally fed patients, compared to patients with parenteral nutrition. But in most cases, enteral nutrition is harmless and does not cause any negative side effects. Table 3 summarizes the current management options for patients with acute pancreatitis.

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Review Article

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# Modern Phase-Specific Management of Acute Pancreatitis

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**Key Words**
Acute pancreatitis · Pancreatic necrosis · Pancreatic infection · Organ failure · Non-surgical management · Surgical treatment

**Abstract**
The management of acute necrotizing pancreatitis has changed significantly over the past years. In contrast to the early surgical intervention of the past, there is now a strong tendency towards a more conservative approach. Initially, severe acute pancreatitis is characterized by the systemic inflammatory response syndrome. Early management is non-surgically and solely supportive. A specific treatment still does not exist. In cases of necrotizing disease, prophylactic antibiotics should be applied to reduce late septic complications. Today, more patients survive the first phase of severe pancreatitis due to improvements of intensive care medicine, thus increasing the risk of later sepsis. Pancreatic infection is the major risk factor with regard to morbidity and mortality in the second phase of severe acute pancreatitis. Whereas early surgery and surgery for sterile necrosis can only be recommended in selected cases, pancreatic infection is a well-accepted indication for surgical treatment in the second phase of the disease. Surgery should ideally be postponed until 4 weeks after the onset of symptoms, as necrosis is well demarcated at that time. Three surgical techniques can be performed with comparable results regarding mortality: necrosectomy combined with the (1) open packing technique, (2) planned staged relaparotomies with repeated lavage, or (3) closed continuous lavage of the retroperitoneum. However, the latter method seems to be associated with the lowest morbidity compared to the other approaches.



## Introduction

The management of acute pancreatitis has been controversial for more than 100 years, varying between a conservative medical approach on the one hand and a surgical approach on the other. There has been great improvement in knowledge of the natural course and pathophysiology of acute pancreatitis over the past 20 years [1–8]. The clinical course of acute pancreatitis varies from a mild transitory form to a severe necrotizing disease. Most episodes of acute pancreatitis (80%) are mild and self-limiting, subsiding spontaneously within 3–5 days. Patients with mild pancreatitis respond well to medical treatment and generally do not need intensive care treatment or pancreatic surgery. Thus, morbidity and mortality rates are below 1% [9–13]. In contrast, severe pancreatitis is associ-

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ated with organ failure and/or local complications such as necrosis, abscess formation, or pseudocysts [14]. Severe pancreatitis can be observed in 15–20% of all cases.

In general, severe pancreatitis develops in two phases. The first 2 weeks after onset of symptoms are characterized by the systemic inflammatory response syndrome (SIRS). The release of proinflammatory mediators is thought to contribute to the pathogenesis of SIRS-associated pulmonary, cardiovascular, and renal insufficiency. Mediators include pancreatic proteases, cytokines, reactive oxygen species, and many more [5, 6, 15–17]. In parallel, pancreatic necrosis develops within the first 4 days after the onset of symptoms to its full extent [18]. However, it is important that SIRS in the early phase of severe pancreatitis may be found in the absence of significant pancreatic necrosis and is frequently found in the absence of pancreatic infection [19, 20]. In contrast, infection of pancreatic necrosis is still the major risk factor of sepsis-related multiple organ failure and the main life-threatening complication in the second phase of severe acute pancreatitis [2, 9, 21]. Infection of pancreatic necrosis most commonly develops 2–3 weeks after the onset of symptoms and can be observed in 40–70% of patients with necrotizing disease [18, 22, 23]. The risk of infection increases with the extent of intra- and extrapancreatic necrosis [18, 21]. The present article presents the different non-surgical and surgical strategies of acute pancreatitis in the two phases of the disease.

## Management of Acute Pancreatitis in Phase I

Although the majority of patients will have mild disease that resolves spontaneously, it is difficult to detect patients at risk of complications early on admission to the hospital. The main problem has been the lack of accurate predictors of disease severity indicating development of necrosis and organ failure in the early stages, and infected necrosis, multi-organ failure, and sepsis in the later phase. On admission, clinical assessment of severity has been shown to be inaccurate [24, 25]. Contrast-enhanced computed tomography (CE-CT) is the 'gold standard' for the diagnosis of pancreatic necrosis [7, 26]. However, it will not reveal the complete extent of pancreatic necrosis before the fourth day after the onset of the disease [18]. In most cases, CE-CT is not capable of revealing the presence of superinfected necrosis in the later course of the disease [7, 26, 27], and the diagnosis of pancreatic necrosis does not predict the development of remote organ complications [19, 20]. Several scoring systems for the assessment of severity of acute pancreatitis exist, including the Ranson, Glasgow, and APACHE II score [28, 29]. These multiple factor scoring systems have been designed to assess the risk of complications in patients with acute pancreatitis, and to categorize patients into groups at high risk of complications. However, they are only moderately accurate in assessing the disease severity of an individual patient. Moreover, due to their complexity, the scoring systems are rarely used in the clinical practice [30]. Although multiple single markers have been proposed as predictors of disease severity, CRP is still the reference parameter of all single indicators [31]. CRP predicts severe pancreatitis and pancreatic necrosis accurately from the third day after onset of symptoms onwards [31–33]. Moreover, measurement of CRP is readily available almost everywhere. In contrast, no single parameter has been developed which is suitable for early prediction of infected pancreatic necrosis. Consequently, it is wise to treat every patient aggressively until disease severity has been established [9–13].

There are two primary objectives in the treatment of patients with acute pancreatitis. The first is to provide supportive therapy and treat the specific complications which may occur. The second is to limit both the severity of pancreatic inflammation and necrosis as well as the systemic inflammatory response by specifically interrupting their pathogenesis.

All patients with signs of moderate to severe acute pancreatitis should be admitted to an intensive care unit (ICU) and referred to specialized centers for maximum supportive care [10, 12, 13]. Since complications may develop at any time, frequent reassessment and continuous monitoring are necessary. The most important supportive therapy is an adequate and prompt fluid resuscitation with intravenous fluids and supplemental oxygen with a liberal indication for assisted or controlled ventilation to guarantee optimal oxygen transport [34–36]. Cardioinotropic drugs, hemofiltration or dialysis may also be needed to allow optimal fluid therapy despite acute renal failure or hypoperfusion. Due to the popular belief that the pancreas should be put to 'rest' during acute pancreatitis, the parenteral route of administrating nutrition is still predominantly used in acute pancreatitis [12, 13, 37]. However, there has been increasing concern about the gut being the main source of microorganisms causing infectious pancreatic complications and multiple organ failure [38]. In patients with severe pancreatitis, oral intake is inhibited by nausea and subileus. Whereas some reports demonstrated that enteral feeding is possible in acute pancreatitis and associated with fewer septic complications

[39, 40], others did not show any beneficial effects [41]. Although the evidence is not conclusive to support enteral nutrition in all patients with severe acute pancreatitis, the enteral route may be used if that can be tolerated. The supportive therapy also includes an adequate analgesia [34, 35]. Several treatment regimens including opioids, procaine infusion, epidural blockade have been widely advocated. However, these strategies of pain management are rather based on empirical experience than on results of controlled, prospective trials [42].

In addition to the sole supportive care, the principles of intensive care therapy in severe pancreatitis include elimination of the cause of the primary insult whenever possible. A causative therapy exists for severe gallstone pancreatitis with an impacted stone, biliary sepsis, or obstructive jaundice [43–45]. Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy ameliorate symptoms and progression of the disease when applied early [46]. Secondary causes of organ failure such as hypovolemia, tissue hypoperfusion, and hypoxemia must also be identified and treated promptly. There is some evidence that vigorous fluid resuscitation may be associated with resolution of organ failure [47]. As plasma expanders are more effective and long-acting, colloids should be preferred compared to crystalloids [35, 36]. Dextran 60 seems to be the most potent colloid available for treatment of acute pancreatitis, as it is characterized not only by a long intravascular persistence, but also by antithrombotic properties and inhibitory effects on leukocyte adhesion [48, 49]. Moreover, a clinical trial indicated that dextran can be applied safely in acute pancreatitis [50].

Multiple mediators of the inflammatory cascade, including oxygen free radicals, vasoactive mediators, cytokines, as well as leukocyte and endothelial activation and pancreatic ischemia, have been identified as important steps in the pathogenesis of acute necrotizing pancreatitis and its systemic complications [5, 6, 15–17, 51–56]. In experimental studies, several drugs which inhibit those pathogenetic steps specifically, e.g. protease inhibitor, oxygen free radical scavenger, cytokine antagonists, nitric oxide agonists, and inhibitors of adhesion molecules, attenuated biochemical and histological changes. However, until today neither the inhibition of pancreatic autodigestion nor the inhibition of any other single pathogenetic step has effectively reduced mortality or increased long-term survival in severe acute pancreatitis [5, 57–59]. Thus, treatment of acute pancreatitis is still symptomatic, with no specific medication being available today.

The most significant change in the clinical course of acute pancreatitis over the last decade has undoubtedly been the decrease in mortality. Overall mortality is now about 5% and for severe cases in the range of 10–20% [9, 19, 60–62]. The major improvements include intensive care medicine, the accurate diagnosis of necrosis by CE-CT, the reliable diagnosis of infected necrosis by FNA, the ERCP concept in gallstone pancreatitis, administration of prophylactic antibiotics in severe necrotizing pancreatitis, and the improved surgical procedures [62]. Despite the reduction in overall mortality in severe pancreatitis, the percentage of early mortality of the disease differs between less than 10 and 85% among various centers and countries [1, 5, 9, 19, 63]. This wide variation in early mortality may partially be explained by differences of the health systems, socio-economic reasons, or patient selection.

## Management of Acute Pancreatitis in Phase II

Today, more patients survive the first phase of severe acute pancreatitis due to improvements of intensive care medicine, thus increasing the risk of later sepsis [9, 64–66]. There is no doubt that pancreatic infection is the major risk factor in necrotizing pancreatitis with regard to morbidity and mortality in the second phase of the disease [9, 18, 67]. Infection of pancreatic necrosis develops most frequently 2–3 weeks after the onset of symptoms. Naturally pancreatic infection correlates with the duration of the disease, and up to 70% of all patients with necrotizing disease present with infected pancreatic necrosis 4 weeks after the onset of the disease [18, 22, 23]. Moreover, the risk of infection increases with the extent of intra- and extrapancreatic necrosis [18, 21]. Therefore it appears that the presence of more than 50% of pancreatic necrosis on CT scanning is predictive for severe disease, and helps to identify patients who might develop septic complications [68].

Unlike the use of antibiotics in the treatment of proven infection, the rationale for the use of prophylactic antibiotics in severe pancreatitis is to prevent infection from affecting areas of pancreatic necrosis and consequently reduce the need for surgery and mortality. Evidence for the effectiveness of prophylactic antibiotics in the reduction of septic complications and mortality of necrotizing pancreatitis has been demonstrated by several randomized controlled trials [69–73]. A meta-analysis of eight previously published trials about prophylactic antibiotics in acute pancreatitis has shown a positive benefit for anti-

biotics in reducing mortality [74]. However, the advantage was limited to patients with severe pancreatitis who received broad-spectrum antibiotics that achieved therapeutic pancreatic tissue levels. Büchler [75–77] and others have identified imipenem as the antibiotic agent of first choice because it reached higher pancreatic tissue levels and provided higher bactericidal activity against most of the bacteria present in pancreatic infection compared to other types of antibiotics. An alternative antibiotic regimen is either ciprofloxacin or ofloxacin in combination with metronidazole, although a previous trial has not shown any benefit with this regimen [78].

When pancreatic necrosis has developed, the differentiation between sterile and infected necrosis is essential for the management of patients. Infection of necrotic pancreatic tissue is usually suspected in patients who develop clinical signs of sepsis [11]. These patients should undergo CT- or ultrasonography-guided fine-needle aspiration (FNA) of pancreatic or peripancreatic necrosis [9, 11]. FNA is an accurate, safe and reliable approach to differentiate between sterile and infected necrosis [22, 79]. Complication rates of this procedure are low with only very few serious complications such as bleeding, aggravation of acute pancreatitis or death reported in the literature [80, 81]. With bacterial testing including Gram staining and culture of the aspiration material, a diagnostic sensitivity and specificity of 88 and 90%, respectively, has been reported for this procedure when guided by ultrasonography [82].

Two distinctive forms of infection in acute pancreatitis need to be differentiated: *infected pancreatic necrosis* and *pancreatic abscess*. At the 1992 Atlanta Consensus Conference [14] these terms were defined as follows: *Pancreatic necrosis* is a diffuse or focal area of non-viable pancreatic parenchyma which is typically associated with pancreatic fat necrosis. In contrast, a *pancreatic abscess* is a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreatic necrosis, which arises as a consequence of acute pancreatitis. Probably pancreatic abscesses are a consequence of limited necrosis with subsequent liquefaction and secondary infection. It is important to distinguish between infected pancreatic necrosis and pancreatic abscesses since significantly lower mortality rates are described for patients with pancreatic abscesses [83]. Furthermore, pancreatic abscesses in general develop later in the course of disease (usually after 5 weeks), whereas infected pancreatic necrosis may already be found within the first week after onset of symptoms [18]. Due to their less aggressive behavior, several groups have introduced minimal invasive treatment strategies for pancreatic abscesses [84–86]. However, their role remains to be defined in randomized controlled clinical trials.

*Indications for Surgery*

Proven infected necrosis as well as septic complications resulting from pancreatic infection are well-accepted indications for surgical treatment [9, 61, 87]. The mortality rate for these patients is higher than 30%, and more than 80% of fatal outcomes in acute pancreatitis are due to septic complications [9, 18, 63]. When treated non-surgically, mortality rates of up to 100% have been reported for infected necrosis associated with multiple organ failure [67]. With surgical treatment, the mortality rate for patients with infected pancreatic necrosis was decreased to about 20–30% in various specialized centers [9, 61, 63, 88–90].

While surgical debridement is mandatory in pancreatic infection, a conservative approach is accepted in sterile necrosis as long as the patient responds to therapy [9, 67, 89, 91, 92]. In a series of 38 patients with necrotizing pancreatitis, Bradley and Allen [60] reported an overall survival rate of 100% in patients with sterile necrosis treated conservatively. However, when sterile necrosis is associated with organ failure, the role of surgery remains controversial [92–95]. It is still unclear why some patients with sterile necrosis can be treated non-surgically while others die without timely intervention. The manifestation of single or multiple organ failure in acute pancreatitis is associated with mortality rates of 23–75% [19, 94–96]. Therefore, some authors favored early surgical therapy in extended pancreatic necrosis, as in theory necrosectomy eliminates the risk of necrosis getting infected. Furthermore, removal of necrosis is thought to prevent or reduce the risk of inflammatory mediators and toxic substances being released into the systemic circulation, thereby ameliorating the systemic inflammatory response. However, since proinflammatory mediators are released very early in the course of the disease [55], surgery is not the tool to interfere with the stimulation of the various cascade systems contributing to SIRS. Another drawback of early surgery is the risk of secondary infection of preoperative sterile necrosis, which has been shown in about 30% of patients [92, 97]. Thus, surgical intervention in sterile necrosis even seems harmful with worsening the prognosis of patients. Intensive care therapy including prophylactic antibiotic treatment has been shown to generate better survival [9, 97, 98].

Nevertheless, some patients with sterile necrosis do not improve despite maximal therapy in the ICU. In this

subset of patients, some authors advocate surgery. In a large retrospective series of 172 patients with sterile necrosis published by Beger's group [92], 62% of patients were managed surgically whereas the remainder were treated conservatively. Mortality rates were not significantly different between the two groups, with 13.1% for surgically treated patients and 6.2% for those treated non-surgically. Therefore, persistent or progressive organ complications despite maximal ICU treatment is an indication for surgery in patients with sterile necrosis [11]. However, there is no established uniform definition of when a patient should be considered a 'non-responder' to ICU therapy. Also in the rare event of rapidly progressive multiple organ failure in the first days of acute pancreatitis despite ICU therapy, so-called 'fulminant acute pancreatitis' surgery may be indicated [11]. Nevertheless, given the poor outcome with both surgical and conservative therapy and the lack of published data, the optimal therapy for this subset of patients remains unclear.

As defined at the 2002 IAP Consensus Conference [11], indications for surgical treatment of acute necrotizing pancreatitis comprise (1) infected pancreatic necrosis and (2) sterile necrosis in case of (a) 'fulminant acute pancreatitis' or (b) persistent severe pancreatitis ('non-responder').

*Timing of Surgery*

Patients with severe necrotizing pancreatitis can progress to a critical condition within a few hours or days after onset of symptoms. Years ago, early surgical intervention was favored, especially if systemic organ complications required a quick response [95, 99]. Furthermore, if diagnosis remained unclear despite various examinations, surgery was requested [28]. Today, there is general agreement that surgery in severe pancreatitis should be performed as late as possible [11]. The rationale for late surgery is the ease of identifying well-demarcated necrotic tissue from the viable parenchyma, with the effect of limiting the extent of surgery to pure debridement. This approach decreases the risk of bleeding and minimizes the surgery-related loss of vital tissue which leads to surgery-induced endocrine and exocrine pancreatic insufficiency [93, 100, 101].

Mortality rates of up to 65% have been described with early surgery in severe pancreatitis [18, 102, 103], questioning the benefit of surgical intervention within the first days after onset of symptoms. In the single prospective and randomized clinical trial comparing early (within 48–72 h of symptoms) versus late (at least 12 days after onset) debridement in patients with severe pancreatitis, the mortality rates were 56 and 27%, respectively [103]. Although the difference did not reach statistical significance, the trial was terminated because of the evident risk of early surgery. In our experience, surgery should not be performed earlier than 4 weeks after the onset of symptoms. The optimal surgical conditions for necrosectomy are present at the later phase of the disease, when necrosis has been demarcated. The initial hemodynamic instability can be treated effectively in the ICU. As we avoided surgery in the early course of the disease, we hardly had any early deaths, even in patients with multiple organ failure [9, 63]. In conclusion, only in the case of proven infected necrosis or in the rare case of a complication, such as massive bleeding or bowel perforation, must early surgery be performed [9, 11].

*Surgical Procedures*

In most patients with necrotizing pancreatitis, surgery is performed to remove infected pancreatic necrosis. The aim is to control the focus, so that further complications are avoided by stopping the progress of infection and the release of proinflammatory mediators. However, resection procedures such as partial or total pancreatico-duodenectomy, that also remove vital pancreatic tissue or healthy organs, are associated with high rates of mortality and postoperative exo- and endocrine insufficiency [99, 104, 105]. In many cases of necrotizing pancreatitis, only the external parts of the gland are necrotic, whereas the parenchyma in the center is not affected. This so-called 'superficial necrotizing pancreatitis' can mistakenly be considered as total pancreatic necrosis, leading to a wrong surgical procedure. Therefore, the surgeon should be aware of the preoperative morphology of the pancreas, and should use modern imaging techniques, such as CE-CT, which provide reliable information about viable pancreatic parenchyma [7, 26]. Thus, pancreatic resection procedures with subsequent exo- and endocrine insufficiency can be avoided in most cases.

In the past, various surgical procedures have been propagated for the treatment of necrotizing pancreatitis [105–108], but mortality rates remained high. Consequently, surgical procedures that combined necrosectomy with a postoperative concept that maximizes further evacuation of debris and exudate have been advocated: necrosectomy combined with the open packing technique [101], planned, staged relaparotomies with repeated lavage [61], and closed continuous lavage of the retroperitoneum [93]. In hands of experienced surgeons, mortality rates below 15% have been described for all three techniques. However, a positive correlation between repeated

surgical interventions and morbidity including gastrointestinal fistula, stomach outlet stenosis, incisional hernia, and local bleeding have frequently been observed.

Both the open packing technique [87] and the planned, staged relaparotomy with repeated lavage [61] are characterized by a relatively high morbidity. Especially the number of pancreatic and colonic fistula was significantly higher compared to necrosectomy with subsequent closed continuous lavage of the lesser sac [9]. At our institution a single surgical approach was successful in 83%, and relaparotomy or reintervention had to be performed in only 17%.

Recently, non-surgical approaches such as interventional drainage of pancreatic necrosis using percutaneous techniques have been introduced. Even in infected necrosis, a few specialized centers reported that some patients recover with non-surgical or limited surgical management in selected cases [84, 86, 109]. However, about 50% of patients managed by percutaneous drainage had to be reoperated on at a later time point. Therefore, the non-surgical management of infected necrosis has to be regarded as an experimental approach, and should strictly be limited to well-defined subsets of patients enrolled in randomized controlled trials.

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Review Article

Digestive Diseases

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# Severe Inflammatory Bowel Disease: Medical Management

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**Key Words**
Ulcerative colitis · Crohn's disease · Toxic megacolon · Intestinal failure, treatment

**Abstract**
The majority of patients with inflammatory bowel disease (IBD) have mild or moderate disease. However, a minority have a severe attack requiring hospital admission. Acute severe colitis (ulcerative colitis and Crohn's colitis) continues to be a medical emergency requiring careful joint management by physicians and surgeons. Extensive Crohn's jejuno-ileitis can also present major management problems, particularly in children. The evidence base for the management of this potentially severe form of Crohn's disease is limited and thus treatment has to be largely tailor-made for individual cases. Acute intestinal failure occurs in Crohn's disease in a variety of clinical settings, but the most challenging problem in the acute phase is the management of the major losses of fluid and electrolytes.



## Introduction

The majority of patients with inflammatory bowel disease (IBD) have mild or moderate disease which responds well to medical therapy, remains uncomplicated and does not require hospital admission. However, about 15% of patients with ulcerative colitis (UC) will have a severe attack requiring hospital admission. Twenty-five percent of these patients will fail to respond adequately to corticosteroid therapy and require an alternative medical intervention such as cyclosporin or if that fails, surgery. Monitoring of these patients during the first 5–7 days of therapy is absolutely vital to minimise the chances of developing complications and to ensure timely, appropriate surgery. Crohn's colitis may also present as acute severe total colitis that must be managed with similar care.

Another form of Crohn's disease that can present major management problems is diffuse, extensive jejunoileitis. This form of the disease is not common but can have important metabolic effects such as hypoalbuminaemia, weight loss and in children, growth failure. The evidence base for the management of this potentially severe form of Crohn's disease is limited and thus treatment has to be largely tailor-made for individual cases.

Intestinal failure has been defined as an impairment of absorptive capacity necessitating prolonged fluid and/or

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nutritional support. Acute intestinal failure occurs in Crohn's disease in a variety of clinical settings including extensive jejuno-ileitis, a high jejuno-cutaneous or jejuno-colonic fistula or following extensive small bowel resection. The most challenging problem in the acute phase is the management of the major losses of fluid and electrolytes.

## Severe Extensive Colitis

Extensive colitis that may lead to toxic megacolon can be an extremely serious and life-threatening disorder [1]. When the condition is recognised and treated promptly, either medically or surgically, the mortality should be extremely low. Deaths however do occur usually because the severity of the condition is not recognised early enough and appropriate therapy is instituted too late. Thus the management of pancolitis and toxic megacolon relies on rapid and accurate diagnosis, exclusion of intestinal infection as a cause of the colitis and rapid introduction of anti-inflammatory, immunosuppressive and other supportive therapy. Patients with active pancolitis usually always have diarrhoea and increased stool volume. As the severity of the colitis increases, the presence of blood becomes more evident, but in its most severe form stool volume may actually decrease as the patient stops eating with blood and mucus remaining as the predominant components of the stool. Severe extensive colitis may be associated with cramping, abdominal pain and fever. Other important features are summarised in table 1.

**Table 1.** Defining the severity of an attack of UC

| | Mild | Moderate | Severe |
|---|---|---|---|
| Bowel frequency, n/day | <4 | 4–6 | >6 |
| Blood in stool | ± | + | ++ |
| Temperature | normal | intermediate | >37.8°C |
| Pulse rate, beats/min | normal | intermediate | >90 |
| Haemoglobin | normal | intermediate | <75% |
| ESR, mm in 1st hour | <30 | intermediate | >30 |

**Table 2.** Enteropathogens causing bloody diarrhoea

| | |
|---|---|
| *Bacteria* | *Protozoa* |
| *Shigella* sp. | *Entamoeba histolytica* |
| *Salmonella* sp. | *Balantidium coli* |
| Enteroinvasive *E.coli* (EIEC) | |
| Enterohaemorrhagic *E.coli* (EHEC) | *Viruses* |
| *Campylobacter jejuni* | Cytomegalovirus |
| *Clostridium difficile* | (immunocompromised) |
| *Yersinia enterocolitica* | |
| *M. tuberculosis* | *Helminths* |
| *Aeromonas* sp. | *Schistosoma* sp. |
| *Plesiomonas* sp. | *Trichuris trichiura* |

*Diagnosis*

One of the most critical steps in the diagnosis of severe, non-specific colitis is the exclusion of gastrointestinal infection [2]. A substantial number of enteropathogens can cause colitis with bloody diarrhoea, some of which produce a predominantly right-sided colitis with rectal sparing (table 2). However, not all invasive organisms cause bloody diarrhoea and thus in practice it is often extremely difficult to make a diagnosis on the basis of history and general physical examination alone. An unprepared, limited examination of the rectosigmoid colon either with a rigid or flexible sigmoidoscope is advisable to confirm the presence of colitis and to obtain mucosal biopsies. Early in the course of a bacterial colitis there may be histological features that are more suggestive of infection rather than non-specific IBD, although as the infection progresses the reliability of histology diminishes. Occasionally, however, it may be diagnostic, such as the detection of the typical 'owl's eye' inclusion bodies of cytomegalovirus infection or the ova of *Schistosoma* sp. It is essential that at least three faecal specimens are sent for microscopy and culture, including evaluation for *Clostridium difficile* toxin. The most common bacterial pathogens will be detected by culture, but *Entamoeba histolytica* can only be identified by microscopy of fresh faeces or by serological testing.

*Initial Assessment*

Patients with fever, tachycardia, abdominal pain and profuse diarrhoea usually require inpatient management, at least in the initial stages. A plain abdominal radiograph is often the most useful investigation to confirm the diagnosis and assess the extent and severity of the disease. Faecal residue does not accumulate where there is active inflammation and therefore extent usually reflects the proximal limit of ulceration. Complete absence of residue suggests total colitis [3]. The extent of both small and large bowel gas increases with severity of colitis and the presence of excessive small bowel gas is a poor prognostic indicator [4]. However, in up to 50% of patients, insufficient gas is present to outline the colon. Gentle insuffla-

**Table 3.** Severe acute colitis: % medical failure [adapted from 13]

| Bowel frequency/24 h | Albumin, g/l | Pulse rate/min | |
|---|---|---|---|
| | | <89 | >90 |
| 0–5 | <30 | 11 | 47% |
| 0–5 | >30 | 1 | 6% |
| 6–9 | <30 | 16 | 58% |
| 6–9 | >30 | 3 | 22% |
| >9 | <30 | 32 | 62% |
| >9 | >30 | 7 | 22% |

tion of gas per rectum can provide a useful air enema that may satisfactorily define the extent and severity of disease [5], or simply changing the position of the patient may move air into the diseased segment. The upper limit of normal for the diameter of the transverse colon is 5.5 cm. In acute colitis, dilatation beyond this implies transmural disease resulting in paralysis of the muscularis propria with risk of toxic dilation or perforation.

The severity of ulceration may be predicted on the plain film by an assessment of the mucosal line as outlined by intraluminal gas. The usually smooth margin becomes indistinct with ulceration and progresses to irregularity and disruption, with blunting and eventual loss of the normally sharp pastoral cleft. A deep ulceration results in bowel wall oedema and apparent thickening with the formation of 'mucosal islands' as disease progresses towards toxic megacolon [6, 7]. Linear pneumatosis implies deep ulceration with air tracking into the bowel wall and is usually a prelude to perforation. A radiograph will also reveal evidence of perforation; this may be the typical appearance on an erect film of air under the diaphragm or as Krigler's sign when the presence of air outside the bowel produces a double bowel wall outline.

In some clinical states, particularly in pregnancy where X-rays are undesirable or in fulminant disease, ultrasound may contribute useful information. Bowel wall oedema results in thickening of the wall which is seen on ultrasound as alternating hyper- and hypoechoic layers with preservation of the normal stratification producing a 'target' appearance. Oedematous mucosa may become very thickened and hypoechoic, which increases with the development of inflammatory pseudopolyposis [8]. In acute colitis confined to the mucosa, CT has only a limited role. In severe colitis, the increased sensitivity of CT to small amounts of air may allow earlier recognition of bowel wall pneumatosis than is possible on plain film or barium studies [9]. The loss of clarity of the pericolic fat implies severe transmural disease. There is no mandate to proceed to an endoscopic examination of the colon providing these radiological examinations are of diagnostic quality and histological examination of the rectal mucosal biopsy supports the diagnosis of non-specific IBD.

*Treatment*

Patients with severe colitis require hospital admission. Corticosteroid medication is usually given as prednisolone (60 mg daily in divided doses), or hydrocortisone (100 mg every 6 h) for 5–10 days [10, 11]. Several series have suggested that colectomy can be avoided in 40–73% of cases using this regimen. However, this gold standard therapy has never been submitted to a randomised placebo-controlled trial. Oral intake of food and fluids is often stopped for the first 24–72 h, although again there is no controlled trial evidence to support this intervention. However, in patients with severe colitis who might require an urgent colectomy, it is wise to keep them nil by mouth during this initial critical period. There is no evidence that IVN or antibiotics influence the outcome of severe colitis although many clinicians will administer broad-spectrum antibiotics in severe toxic colitis when there are concerns about perforation [12].

*Monitoring Progress*

Patients with severe colitis should be managed jointly by physicians and colorectal surgeons, and if there is no improvement within 5 days, surgery should be seriously considered. Several studies have attempted to identify objective criteria for predicting failure of medical therapy before the development of advanced radiological features of incipient perforation. Lennard-Jones et al. [13] used bowel frequency, serum albumin and pulse rate to predict outcome in patients with severe UC (table 3). 62% of patients with bowel frequency of >9 stools/24 h, a serum albumin of <30 g/l and a pulse rate >90/min would fail medical therapy and require surgery. Travis et al. [14] used only bowel frequency and C-reactive protein (CRP) and found that patients with 3–8 stools/24 h and a CRP >45 mg/l had an 85% chance of requiring colectomy.

Providing there are no absolute indications for urgent surgery and the patient wishes to continue with medical therapy, then it is reasonable to consider a trial of intravenous cyclosporin [15]. Initial studies with cyclosporin 4 mg/kg/day compared with placebo demonstrated a significant benefit with response rates of 64–83% [16]. Cyclosporin 4 mg/kg/day is commonly associated with paraesthesiae, hypotension and hypomagnesaemia. Other major toxic effects include renal insufficiency, infection

and seizures. Cyclosporin 2 mg/kg/day has a lower rate of toxicity. Hypercholesterolaemia and hypomagnesaemia increase the risk of seizures. Maintenance of the response to cyclosporin is significantly improved by the addition of azathioprine as maintenance therapy.

### Toxic Megacolon

Toxic megacolon is a severe complication of colitis characterised by generalised toxic state (fever, prostration and usually abdominal pain) associated with dilatation of the colon radiologically [17–19]. Toxic megacolon occurs in approximately 2% of patients with chronic UC. The prevalence rises to 10% in ill patients requiring hospitalisation. These patients usually have a high fever >38°C, tachycardia, abdominal distension and abdominal pain which may be diffuse or localised. There may be local tenderness with rebound and if perforation has already occurred, this may be widespread in the abdomen. Bowel sounds are usually reduced or absent. Dilatation on an abdominal radiograph is the hallmark of this complication with the colonic diameters reported between 8 and 9 cm. Dilatation may be localised to a short segment or may be generalised. In an acute attack, daily abdominal films are justified to monitor colonic diameter and the state of the mucosa, to determine the need for surgical intervention. Intraperitoneal perforation is the most serious complication, the risk being highest in the initial attack [20]. The first sign of impending perforation is linear pneumatosis paralleling the bowel wall, commonly first seen in the sigmoid colon. This may be more sensitively detected on CT than on plain films. Toxic megacolon is usually associated with anaemia, neutrophil leukocytosis and raised inflammatory markers such as ESR and CRP. The albumin is usually reduced. Once the colon is dilated on a plain abdominal radiograph, there is a strong likelihood that colectomy will be required. The presence of 'mucosal islands' is indicative of severe mucosal loss and disruption of smooth muscle function of the colonic wall. Although such patients do occasionally respond to medical therapy, there is no doubt that the safest course of action is to recommend colectomy [21–23]. Patients with severe fulminant colitis are at risk of thrombo-embolic complications before and particularly after surgery. Providing rectal bleeding is not heavy it is wise to institute prophylaxis with subcutaneous low-molecular-weight heparin.

Severe pancolitis and toxic megacolon also occur in Crohn's disease. The clinical approach to the patient is identical to that in severe UC. However, in patients who are refractory to intravenous corticosteroids and immunosuppressive agents such as azathioprine and methotrexate, anti-TNF-α therapy (infliximab) should be considered, providing there are no absolute indications for colectomy.

### Severe Crohn's Jejuno-Ileitis

Diffuse involvement of a large proportion of the small intestine is uncommon but can present a major therapeutic challenge. These patients often have major nutritional problems including profound weight loss and hypoalbuminaemia. The condition can have particularly serious clinical effects in children and adolescents such as retardation of growth and development. Diagnosis is based on conventional small bowel radiology (barium follow-through or enteroclysis), colonoscopy and small intestinal biopsy. In the absence of colonic involvement the radiologic appearances may be confused with ulcerative jejunitis associated with gluten-sensitive enteropathy and small bowel lymphoma. It is advisable therefore to always confirm the diagnosis histologically.

In adults, the therapeutic approach is similar to that for other forms of Crohn's disease and should include the conventional treatment escalation, beginning with corticosteroids, azathioprine or methotrexate and finally anti-TNF-α therapy (infliximab) if the disease is refractory to standard immunosuppressive therapy [24]. However, in children and adolescents with remaining growth potential, it is wise to avoid corticosteroid therapy. There is now compelling evidence that enteral feeding with polymeric diets can induce remission in children with Crohn's disease while at the same time optimising the opportunity for growth promotion [25]. Evidence in animal models of IBD have shown clearly that growth failure is due to a combination of anorexia and impaired food intake and to an effect which relates specifically to the inflammatory process which is independent of the effect on appetite [26]. Limited anecdotal evidence in patients with extensive jejuno-ileitis suggests that long-term liquid enteral feeding with a polymeric diet may contribute to achieving remission while supporting nutritional status. Although meta-analysis has shown that both elemental diets and polymeric liquid diets are inferior to corticosteroids in the treatment of adults with active Crohn's disease [27], efficacy appears to be more impressive in children and young adults [25], particularly when there is associated growth retardation.

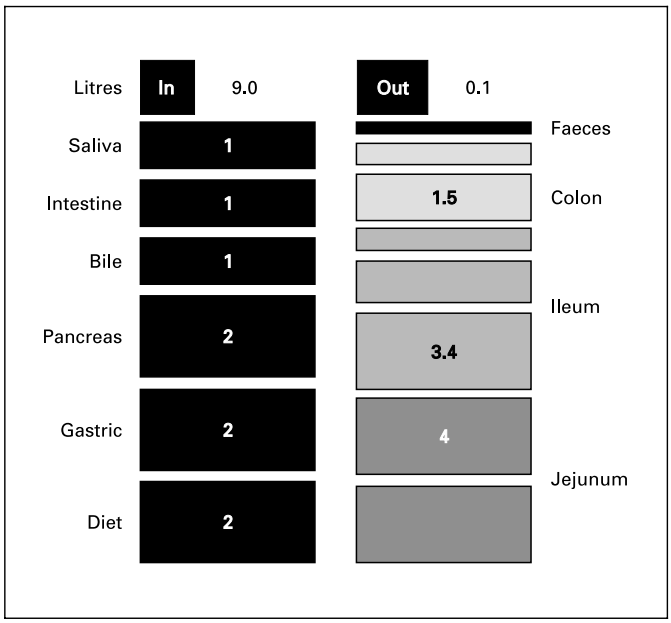


**Fig. 1.** Intestinal fluid balance.

## Acute Intestinal Failure

Chronic intestinal failure may occur in a variety of settings including severe motility disorders (systemic sclerosis, intestinal pseudo-obstruction), radiation injury, and occasionally malignancy, but the most common cause of admission to an intestinal failure unit is small bowel Crohn's disease. These conditions may require long-term intravenous nutrition (IVN), but this can usually be planned and thus cannot be considered a medical emergency [28, 29]. However, intestinal failure may develop acutely presenting initially with major problems in fluid and electrolyte balance with substantial losses of other cations. This situation most commonly arises following massive intestinal resection for mesenteric infarction, volvulus, Crohn's disease or desmoid tumours [30].

Two major groups of patients with intestinal failure have emerged; those with a high jejunostomy in which the colon, ileum and part of the jejunum have been resected and patients with a jejuno-colic anastomosis in which all or a substantial part of the colon remains in situ [28, 29, 31]. The risk of developing intestinal failure or the short bowel syndrome is determined not by length of bowel that is removed but by how much remains. The length of normal small intestine varies widely between individuals when measured at laparotomy, ranging from 320 to 846 cm, with a mean of about 500 cm. The length of the remaining intestine is a good predictor of future needs with respect to fluid, electrolyte and nutritional support [32].

*Pathophysiology of Intestinal Failure*

Although the intestinal loss in intestinal failure can be extremely high, sometimes in excess of 5 litres/24 h and resembling a secretory diarrhoea, the fundamental problem is failure of absorption. Failure to absorb fluid and electrolytes, particularly sodium and magnesium, results in the most clinically important deficits during the initial phase of the illness. There are however qualitative and quantitative differences between the anatomical variants of intestinal failure in respect of the fluid, electrolyte and nutritional losses that occur.

The greatest fluid losses generally occur in jejunostomy patients because of failure to re-absorb secretions from the proximal gut. Nine litres of fluid enter the jejunum every 24 h (fig. 1) but the jejunum has only a limited capacity for retrieval. There is a moderately good correlation between the length of remaining small intestine and the ability to obtain a net positive balance of fluid and electrolytes. It has been possible to classify patients with a high jejunostomy into those that are *net absorbers*, that is jejunal efflux is always less than oral intake, and *net secretors*, in which jejunal efflux always exceeds oral intake. Net absorbers generally have a residual length of >100 cm, whereas net secretors generally have <100 cm (fig. 2) [32]. These observations have important sequelae when planning fluid and electrolyte supplements. Net secretors virtually always require intravenous fluid and electrolyte support, whereas net absorbers can usually manage on oral supplements with some surviving solely on a normal diet. Carbohydrate absorption is also closely related to the length of residual jejunum [33]. An additional factor that probably contributes to fluid losses in patients with a jejunostomy is the rapid gastric emptying of liquids.

In patients with an intact colon, fluid and electrolyte balance is easier to maintain and it has been estimated that the colon is equivalent to 50 cm of small intestine with respect to sodium and water absorption [34]. The presence of the colon can make the difference between a life-long dependency on IVN and the ability to survive on a normal diet or possibly a normal diet supplemented with oral supplements. Magnesium deficiency is also less common in patients with a colon [29]. The colon is also important for energy retrieval of malabsorbed carbohydrate amounting to up to 500 kcal/24 h [35]. Patients with a colon are however more likely to develop oxalate renal

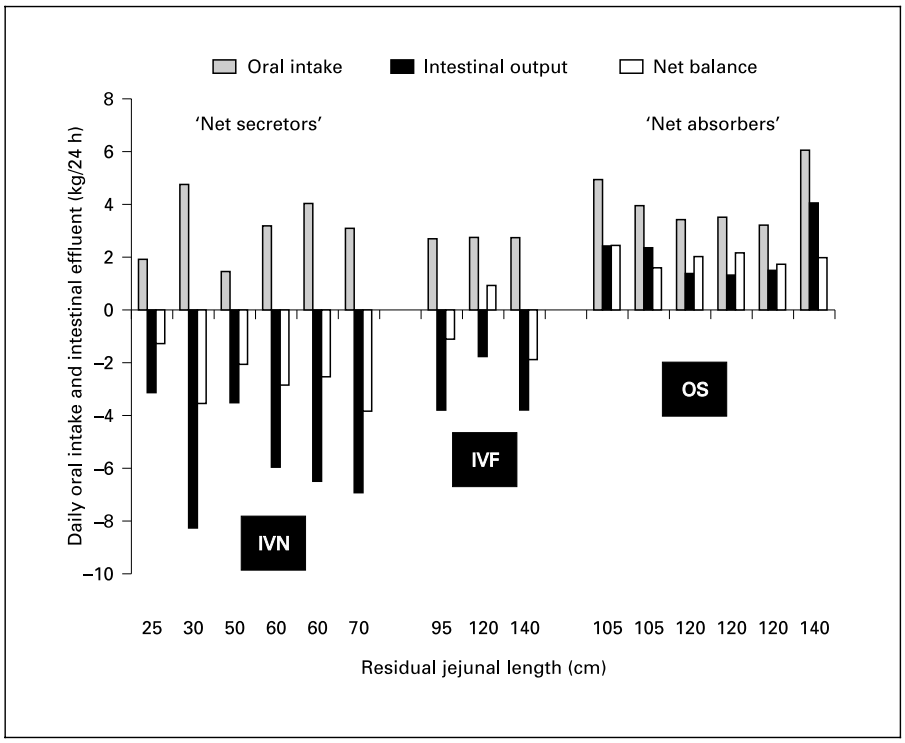


**Fig. 2.** Daily oral intake and intestinal effluent. IVN = Intravenous nutrition; IVF = intravenous fluid; OS = oral supplements [adapted from 30].

stones due to enhanced oxalate absorption from the colon [34].

*Initial Management of Acute Intestinal Failure*

The rational management of intestinal failure depends on an assessment of fluid, electrolyte and nutrient losses. The aims of this assessment are two-fold, namely to rapidly correct any major deficiencies that have occurred during the early phase of the condition and secondly to plan the long-term management, particularly to predict whether or not there will be a need for IVN [28, 29].

Although intestinal losses in excess of 2 litres/24 h are often indicative that some form of intravenous support will be required, it is essential that the initial assessment be carried out when the patient is fluid and electrolyte replete. Patients may have been drinking vast quantities of low sodium liquids in an attempt to deal with thirst promoted by dehydration and hyponatraemia. This will exacerbate sodium and magnesium deficiency and increase intestinal effluent.

It is advisable therefore to stabilise the situation by giving appropriate volumes of intravenous saline to rehydrate until body weight is stable and confirm that there is adequate sodium in the urine (>20 mmol/l). When rehydration and sodium repletion is achieved, the patient can then be progressively transferred to a normal diet and intestinal effluent volume (or weight) assessed. If intestinal losses continue to exceed 2 litres/24 h then it is highly likely that intravenous replacement of saline will be required, and as losses approach 3–4 litres/day then this will be essential. If losses are less than 2 litres/24 h, it is likely that fluid and electrolyte homeostasis can be maintained orally, but such patients may require supplementation with 1–2 litres of a high sodium (>90 mmol/l) glucose-electrolyte solution [36, 37]. Many of the commercially available oral rehydration solutions have inadequate sodium concentrations for patients with a high output jejunostomy. It may be necessary to make up an appropriate solution in the home or hospital pharmacy.

In patients with intestinal effluents exceeding 2 litres/24 h there is always the risk of magnesium deficiency [28]. The risk is substantially reduced when the colon is retained. Deficiency should be screened for during the initial assessment by measuring plasma magnesium concentration although deficiency may be apparent clinically with symptoms in the peripheral and central nervous system including paraesthesiae, tetany, lassitude, depression and occasionally convulsions. There may also be muscle weakness. In symptomatic cases of magnesium deficiency, potassium and calcium concentrations are also re-

duced. In severe acute deficiency, magnesium sulphate should be given intravenously with careful monitoring of plasma magnesium concentration. Many patients with a chronically high intestinal effluent will require replacement on a regular basis, magnesium oxide (12–24 mmol/24 h) being the preferred preparation.

Potassium deficiency is uncommon in intestinal failure and is usually only seen when there is <50 cm of residual small intestine. Hypokalaemia in jejunostomy patients may be indicative of sodium depletion as a result of either secondary hyperaldosteronism or a magnesium deficit.

*Drug Therapy to Reduce Intestinal Effluent*

Pharmacological approaches to reducing intestinal effluent are only modestly effective and in general are unable to change a patient's status from being dependent on IVN or IV fluids to an individual who can survive on oral intake alone. However, a reduction in effluent can be achieved by either improving intestinal absorption or by inhibiting intestinal secretion. Synthetic opioid drugs such as loperamide or the opiate, codeine phosphate, are the first-line medications to be evaluated. Although it has been difficult to unequivocally demonstrate efficacy because of the relatively small numbers of patients that are available for inclusion in clinical trials, detailed balance studies in an individual patient clearly show beneficial effects with respect to reducing sodium and fluid loss [38]. An alternative approach is to use the somatostatin analogue, octreotide, that slows intestinal transit and reduces gastric, pancreatic and biliary secretion. A variety of small studies have shown that octreotide reduces intestinal output and some have also shown a reduction in sodium and potassium loss [39]. These effects have been sustained long term and no major adverse effects have been reported. Unfortunately these effects are insufficient to convert a patient from being a net secretor to a net absorber or render a patient no longer dependent on IVN. However, reducing intravenous fluid requirements for a patient will decrease the time that the individual needs to be connected to the infusion system.

An alternative approach to reducing secretion into the gut is to use an $H_2$-receptor antagonist or a proton pump inhibitor [40]. The efficacy of these drugs is probably within the same range as octreotide although responses in individual patients may be idiosyncratic and it therefore worthwhile beginning in a hierarchical way with the acid inhibitors and then moving on to octreotide to determine whether additional benefits can be achieved.

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Review Article

Digestive Diseases

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# Surgical Treatment of Severe Inflammatory Bowel Diseases

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**Key Words**
Crohn's disease · Ulcerative colitis · Surgical treatment

**Abstract**
Surgical treatment of severe inflammatory bowel diseases is required in failed medical treatment, in emergencies and for complications. Indications for surgery and operative techniques have changed significantly over the last few years. There is a clear tendency towards earlier and less invasive surgical interventions performed in specialized and experienced centers. Improved quality of life of patients with Crohn's disease or ulcerative colitis after surgical therapy supports an earlier consideration of the surgical treatment option. A close cooperation with the involved gastroenterologist is mandatory in this context.



## Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory disorders of the gastrointestinal tract of unknown etiology. Both diseases are primarily a domain of conservative medicine. However, about one third of patients with CD or UC do not respond to conventional medical treatment. In this subgroup of patients with severe inflammatory bowel diseases, surgery can lead to a significant relief of symptoms and in UC patients even cure the disease.

## Crohn's Disease

CD is an idiopathic, chronic inflammatory disease of the gastrointestinal tract that primarily affects the small intestine and colon, which may be caused by environmental and genetic factors.

The incidence rate varies between different geographical regions, with an average of 3–6 cases/100,000/year [1]. There is a typical 'bimodal' age distribution at diagnosis with a first peak between the age of 15 and 30 and a second peak later in life in the sixth or seventh decade. Regarding the gender distribution, several studies described a slight female predominance, with an increased risk for women of about 20–30%. CD appears to be associated with a significant genetic predisposition with an increased relative risk for first-degree relatives of affected patients between the age of 18 and 36. Proven risk factors are smoking [2], oral contraception [3] and a high socioeconomic status.

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The etiology of CD is still unknown, but three fundamental theories are presently being discussed [4–6]: (1) an impaired intestinal epithelial barrier function with a loss of tolerance towards intraluminal antigens; (2) a disturbed immunological response in the intestinal wall towards ubiquitous luminal antigens, and (3) a specific infection.

CD is a transmural, predominantly submucosal inflammatory disease that most commonly affects the distal ileum and colon but may occur in any part of the gastrointestinal tract. Macroscopically, segments of affected bowel are characteristically sharply demarcated from adjacent normal bowel ('skip lesions'). Transmural inflammation leads to bowel wall thickening and lymph edema and can result in extensive fibrosis with strictures. Patchy, mucosal longitudinal and transverse ulcers with intervening mucosal edema can develop which then appear as the typical cobblestone relief. Often the attached mesentery is markedly thickened and lymph edematous with adherence of the inflamed segment to neighboring organs, forming conglomerates with sometimes interenteric or blind fistulas and abscesses. Mesenteric fat typically extends on over the serosal surface of the bowel. Microscopically, there are submucosal edemas, lymphoid aggregations, lymphoplasmacellular infiltrates, ulcers and fibrosis with influx and proliferation of macrophages. Noncaseating granulomas with multinucleated giant cells are detectable in up to 60% of patients.

*Clinical Symptoms and Complications*

Clinical symptoms vary with the location of the inflamed region. Chronic diarrhea with abdominal pain, fever, anorexia, weight loss, and a right lower quadrant mass or fullness are the most common presenting features. Many patients are first seen with an acute abdomen due to intestinal obstruction, sometimes simulating acute appendicitis. In the selected surgical setting, there is an increased percentage of patients with perianal fistulas. Extraintestinal manifestations include joints (arthritis), skin (pyoderma gangrenosum), kidneys and the urinary tract (stones, fistulas), gallbladder and bile ducts (stones, sclerosing cholangitis).

Due to the varying locations of the disease, the development of complications has a wide spectrum. Intestinal bleeding, perforation, obstructions, development of enteroenteric, enterovesical, retroperitoneal, or enterocutaneous fistulas, and abscess formations are common complications in CD, often requiring surgical intervention. The risk of developing a CD-associated carcinoma is increased about 5- to 6-fold [7].

*Surgical Therapy*

The mainstay of CD treatment remains medical therapy, which is beyond the scope of this review. Interested readers are referred to the literature [8] or the Cochrane Library (www.update-software.com).

Patients suffering from severe CD require surgery either to manage complications or in case of failure of medical treatment. 2,070 cases with CD were treated at the Surgical Department of the University of Heidelberg between 1982 and January 2003.

Surgery, as well as conservative medical treatment, cannot cure the disease. However, more than 90% of all patients treated surgically in our institution declared that they experienced a complete remission of symptoms (68%), or a significant relief of complaints. Nevertheless, the recurrence rate in the following 10–15 years in these patients was still high (50%) [9]. Most of these recurrences can be effectively treated with a further operation. The former widespread fear of a 'short-bowel syndrome' is now unfounded. The modern principles of Crohn's surgery restrict resection to inflamed sections only without so-called 'security margins' as practised in cancer surgery [10]. Short fibrotic strictures can be treated with strictureplasty, also known as 'conservative surgery'. Minimally invasive techniques can now be used in a large number of cases. Therefore, surgical therapy should be considered early in the treatment of symptomatic stenoses, fistulas, septic complications and situations refractory to conservative treatment. Furthermore, complications of long-term therapy with glucocorticoids or immunosuppressants, as well as malignant transformation may be avoided by surgical treatment.

*Specific Indications for Surgery*

Controversy still remains regarding the right time for surgery. A major reason for early surgical intervention is the high rate of symptomatic relief after surgery. Furthermore, the resected bowel parts are mostly without function. Opponents of this concept state that delayed surgery is associated with fewer resections and therefore a lower risk of short-bowel syndrome. We believe that time of surgery should be based on the clinical symptoms. It is important to consider the preoperative medication with its side effects and the potential increase of perioperative complications due to the medications. The application of these principles should lead to a reasonable decision regarding the time of surgery with a maximum relief of complaints and a minimum incidence of surgery-related disadvantages. These principles, however, are not yet adequately considered. Scott and Hughes [11] found that

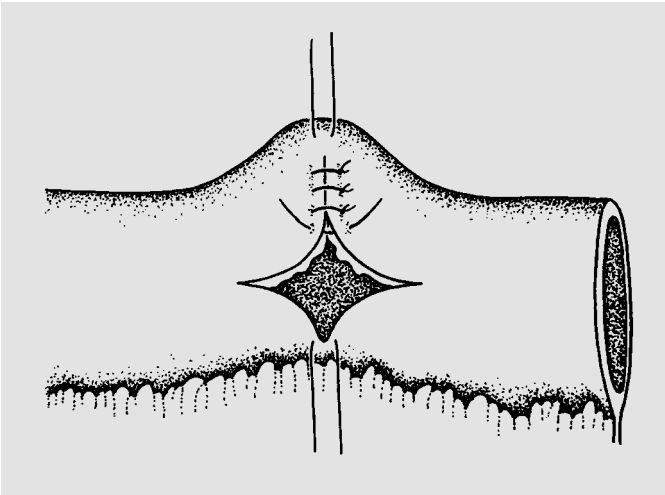

**Fig. 1.** *Stricturoplasty:* After opening the bowel on the anti-mesenteric aspect of the loop, proximal and distal to the stricture, sutures are placed in such a way as to change the longitudinal incision into a transverse one.

74% of all operated patients would have preferred an earlier operation if they had known the postoperative result beforehand. After having taken the decision for an operation, a 'Crohn staging' should be performed to evaluate affected areas and to determine an individual surgical concept.

*Preoperative Investigations*

A detailed patient's history and clinical examination, including rectal examination, are mandatory. The whole gastrointestinal tract should be examined thoroughly to evaluate all sites of possible Crohn manifestations preoperatively. Sonography can show thickening of the bowel wall, fistulas or abscesses. Gastroduodenoscopy and colonoscopy are standard preoperative investigations. Distal small bowel affection may often be identified by colonoscopy if intubation of the terminal ileum is possible. Proximal small bowel involvement can be evaluated by barium meal or hydro-MRI. In Heidelberg, hydro-MRI with filling of small bowel and colon with water is done to evaluate the extent of the disease. This investigation can at the same time assess direct affection of the colon and small bowel, as well as extraluminal findings, such as fistulas and abscesses in one step without radiation exposure [12]. For verification of fistulas or abscesses, proctoscopy or rectoscopy complemented by endosonography are essential to assess rectal mucosa and fistula morphology. Sometimes fistulography or barium enema are useful.

*Stenosis and Obstruction*

Patients with acute symptoms of bowel obstruction should be nil per os and should be nourished and rehydrated parenterally. Inflammatory stenoses are primarily treated conservatively with glucocorticoids. Surgical therapy of stenoses, strictures or other obstructions depends on the localization of the affected areas. The most frequently performed operation for CD is the resection of the ileocecal region or isolated small bowel resection. In short strictures, not exceeding 8–10 cm stricturoplasty (Heineke-Mikulicz) can be performed (fig. 1).

This indication is well suited for a minimally invasive procedure, alternatively median laparotomy is performed. Stenoses of the colon can sometimes be problematic, because the recurrence rate is higher in Crohn's colitis than in small bowel affections. However, the basic principle remains the same: 'resect as much as necessary, but as little as possible'. Bypass operations of Crohn's associated conglomerate tumors have been abandoned due to blind-loop problems, neoplastic transformation and septic complications.

*Abscesses*

In the majority of the cases, abscesses in CD are the result of sealed perforations of the bowel. The most frequent location of these abscesses is the lower right abdomen and the perianal region. Most of the abscesses can be treated by interventional drainage. After achieving control of the septic situation, patients can then undergo elective surgery with resection of the affected segment later. Sometimes, especially when multiple interenteric or multilocular abscesses are present, surgical drainage is necessary. Perianal fistulas and abscesses distal to the sphincter can be incised and drained perineally. Perirectal abscesses proximal to the sphincter and levator muscle should be drained through the abdomen due to the risk of persisting translevatoric or transsphincteric fistulas. In the presence of a visible fistula proximal to the sphincter and simultaneous severe inflammation of the rectum, a protective ileostomy should be considered.

*Fistulas*

Fistulas mostly originate from primarily CD affected segments of the gastrointestinal tract. There is often a stenosis distal to the inflamed segment increasing the intraluminal pressure in the transmurally inflamed bowel wall, predisposing to fistula formation. These fistulas can penetrate all neighboring structures and organs. In the worst case a complex system of communicating fistulas and abscesses with consecutive secondary affection of other

organs develops. To outline the distribution of different fistulas, see table 1.

Internal Fistulas

About one third of all CD patients develop an internal fistula as described above [13]. Interenteric such as ileosigmoidal fistulas are the most common ones. This situation is not necessarily an indication for surgery. The terminal ileum is often the primarily affected organ, the sigmoid or other diseased bowel is only involved secondarily. If the stenosis of the terminal ileum is symptomatic, the therapy of choice is the resection of the terminal ileum with excision of fistula opening in the sigmoid or other affected bowel segments. An absolute indication for surgery is a blind-ending retroperitoneal fistula. This is often the origin of a psoas abscess and various other secondary affections of different organs with further complications. Enterovesical fistulas are also an absolute indication for operative treatment. These fistulas can lead to life-threatening recurrent ascending urinary tract infections.

Several other types of internal fistulas can occur, but they are less frequent.

Enterocutaneous Fistulas

Enterocutaneous fistulas generally originate from the terminal ileum or from an anastomosis from previous operations. Colocutaneous fistulas are more difficult to treat. An uncomplicated enterocutaneous fistula itself is not necessarily an indication for surgery. However, it is associated with an increased risk for additional fistulas and abscesses and is an indicator for active, often stenosing, CD in the organ of origin. This usually results in the affected organ having to be resected and the fistula tract excised. Anastomotic recurrence of CD is treated by resection of the frequently stenotic anastomosis.

Perianal Fistulas

Five to 10% of all CD patients and 40–60% of surgically treated patients show perianal fistulas. An aggressive operative therapy should only be performed if the patient has significant complaints, because perianal fistulas tend to recur. If surgical therapy is undertaken, the anal sphincter should be treated with utmost care. In this context it sometimes can be necessary to construct a temporary protective stoma. Incision and drainage of abscesses and the placement of a Seton, however, is often sufficient to stabilize the local situation and prevent recurrent abscesses.

For infrasphincteric or submucous fistulas, an open-lay technique together with adequate medical treatment should be used. Inter- or transsphincteric fistulas originating in the anal canal are more difficult to treat. A careful excision of the fistula in an open-lay technique, the suture of the sphincter and a mucosa flap covering the internal fistula opening is the treatment of choice. Suprasphincteric or translevatoric fistulas often do not heal without temporary stool deviation. Associated abscesses should be incised and drained, followed by the construction of a protective loop ileostomy. After reduction of inflammation by local and systemic anti-inflammatory therapy, excision and mucosa flap or even rectal resection should

**Table 1.** Surgical interventions in patients with Crohn's disease in the Surgical Department of the University of Heidelberg, 1982–2000

| | |
|---|---|
| *Resections* | |
| Small bowel | 224 |
| Ileocecal region | 254 |
| Anastomoses | 207 |
| Colon | 53 |
| Hemicolectomy | 95 |
| Subtotal colectomy | 99 |
| Proctocolectomy/proctectomy | 64 |
| *Fistulas* | |
| Interenteric | 216 |
| Enterocutaneous | 84 |
| Enterogenital | 67 |
| Enterovesical | 35 |
| Retroperitoneal | 35 |
| Anal | 260 |
| *Others* | |
| Abscess | 156 |
| Ureterolysis | 20 |
| Explorative lap. | 22 |
| Lavage | 29 |
| Endosc. intervention | 36 |
| Others | 178 |
| *Reconstruction* | |
| Stricturoplasty | 175 |
| Mucosa flap | 159 |
| Omentoplasty | 83 |
| Reconstruction of continuity | 14 |
| Ileostomy closure | 111 |
| Colostomy closure | 6 |
| Pouch formation | 4 |
| *Deviation* | |
| Ileostomy | 251 |
| Colostomy | 39 |
| Hartmann operation | 19 |
| Intestinal bypass | 3 |
| Gastroenterostomy | 6 |

**Table 2.** Morbidity of 1,941 operations between 1981 and 9/2002 in patients with CD

| | | |
|---|---|---|
| No complications | | 87% |
| Mortality | | 0.5% |
| Relaparotomy | | 4.7% |
| Anastomotic leaks | 1.5% | |
| Abscess | 1.5% | |
| Ileus | 0.7% | |
| Others | 1.0% | |
| Other septic complications | | 3.9% |
| Others | | 2.8% |

follow. Recto-vaginal fistulas should be treated by elective excision, mucosa flap and reconstructive levatorplasty, in most cases under temporary stoma protection [14].

*Emergency Indications for Surgery in CD*

*Fulminant or Toxic Colitis.* Similar to UC, Crohn's colitis can also take a fulminant course. Surgical therapy should be urgently undertaken if the patient's condition fails to improve under intensive care medicine. After 72 h, mortality increases significantly [15]. Partial colectomy with a terminal ileostomy, followed by secondary reconstruction of continuity, is the therapy of choice in most cases.

*Perforation.* 1–3% of all surgically treated CD patients suffer free perforations of the small or large bowel [16]. They usually present with an acute abdomen and free air in the abdomen on plain X-ray. An immediate operation with resection of the perforated bowel and, if present, with the associated stenotic bowel segment is obligatory. Preferably discontinuity resections should be performed, especially in severe peritonitis where the mortality rate after primary anastomoses is significantly increased [17].

*Hemorrhage.* A massive life-threatening hemorrhage is the reason for 1–13% of all surgical emergencies in CD patients. It occurs more often in young men and often originates in the terminal ileum. An immediate mesentericography can usually localize the source of the bleeding and warrants a precise resection [18]. In such a situation we leave the angiocatheter in place and inject isosulphan blue in the operating room to specifically identify the bleeding bowel segment that needs to be resected.

*Operative Technique*

The basic principle is the minimal possible resection to achieve a defined goal. A resection with unaffected margins has not been shown to have a beneficial effect [10, 19, 20]. Resective surgery for CD can now also be performed using a laparoscopic approach. The potential advantages associated with laparoscopic intestinal surgery include less postoperative pain, and wound infections, quicker resumption of oral feeding, a reduced hospital stay and earlier return to work. Other advantages such as less postoperative intra-abdominal adhesions and improved cosmetic results may be particularly attractive in patients who are likely to undergo multiple operations during their lifetime [21]. No differences in recurrence rate or in disease-free interval were noted between groups of patients operated on with an open technique or laparoscopically [22]. If the surgeon has enough experience in minimal invasive surgery, primary surgery should be performed with a laparoscopically assisted technique. Suitable operations are ileocecal, small bowel and colon resections, stricturoplasty and stoma construction.

There is no agreement in the literature as to which type of anastomosis is preferable. In our institution, we used to perform one-layered end-to-end anastomosis with interrupted sutures. We have now changed to a two-layered running suture technique (either end-to-end or end-to-side with 5/0 PDS suture) because we feel that this is safer with a lower leak rate.

*Postoperative Morbidity and Mortality*

Between 1981 and September 2002, 1,941 operations were performed on patients with CD at the Surgical Department of Heidelberg. Overall morbidity was 12.5%, including all major complications requiring a surgical reintervention; mortality was 0.5% (table 2).

## Ulcerative Colitis

UC is a chronic, idiopathic inflammatory and ulcerative disease of the rectal and colonic mucosa of unknown etiology. UC usually extends from the distal rectum to the more proximal segments of the colon and most commonly affects only the mucosa, rarely deeper layers of the bowel.

The incidence in North and Central Europe, as well as in North America, is 2–8 cases/100,000/year. Age at diagnosis has two peaks with a first peak between the age of 20 and 30 years and a second one at the age of 60. Women seem to be affected slightly more often and the incidence in Jewish people is higher than in non-Jewish [23].

Although the etiology of UC remains unknown, several possible factors are presently being discussed [24], namely environmental, microbial, genetic and immune factors.

Deeper layers of the bowel wall are generally not affected in UC. One of the few exceptions is toxic megacolon, where transmural involvement can occur. Inflammation and destruction of deeper layers lead to dilatation of a colonic segment or the whole colon. Remission of the inflammation can lead to loss of the mucosal relief and subsequently shortening of the colon. Microscopically, crypt abscesses and a mononuclear infiltrate of lymphocytes, macrophages and mast cells are typical.

*Clinical Symptoms and Complications*

Bloody and mucous diarrhea, high stool frequency and day and night urgency, abdominal pain and cramps and subfebrile temperatures are common clinical signs of UC, and these symptomatic episodes are frequently interrupted by asymptomatic intervals. 18% of all patients only have one single episode. In about two thirds of the cases, however, the disease becomes chronic and recurrent. Total proctocolectomy within 10 years after the first episode becomes necessary in about 11% of all patients and this rate further increases in the following years. In 30% of the cases the rectum is the only affected bowel segment during the first episode of UC. In 40% the inflammation reaches further proximal up to the transverse colon. Only 30% of the patients have a total colitis.

Extraintestinal manifestations occur in about 10% of the patients [23]. Most frequently, patients suffer from arthritis. Less common are aphthous stomatitis, uveitis or conjunctivitis and skin manifestations, such as pyoderma gangrenosum and erythema nodosum. A primary sclerosing cholangitis can rarely necessitate liver transplantation.

Major complications are the development of a toxic megacolon, perforation and bleeding, all of which require emergency treatment. A large percentage of UC patients is admitted for surgery due to severe drug side effects, especially from glucocorticoids. Furthermore, the incidence of UC-associated colorectal cancer is significantly increased in pancolitis when disease duration exceeds 10 years, independent of disease activity. After 10 years the cancer risk increases about 1% per year [25].

*Diagnosis*

Total colonoscopy with biopsy is mandatory to obtain the histological diagnosis and to evaluate the grade and extent of inflammation and neoplastic changes. If there is a severe stenosis, double contrast barium enema or hydro-CT of the colon may be helpful to exclude a further problem proximal to the stenotic segment.

**Table 3.** Indications for colectomy in 621 UC patients between 01/1982 and 12/2001

| | |
|---|---|
| Therapy-refractory situation | 75.1% |
| Dysplasia | 5.8% |
| Colorectal carcinoma | 9.8% |
| *Emergency* | |
| Toxic colon | 6.8% |
| Perforation and bleeding | 2.5% |

*Surgical Treatment*

Surgical treatment of UC significantly differs from surgery for CD. While in CD the surgical principle is 'resect as much as necessary, but as little as possible', the aim of surgery for UC is to remove the whole colon with a proctomucosectomy. Therefore, it is essential to definitely clarify the histological diagnosis preoperatively. Surgical therapy for UC patients aims at curing the disease itself. Side effects of medical treatment may thus be avoided and malignant transformation prevented or, if they have already occurred, adequately treated. Quality of life may significantly be improved by surgical therapy. Extraintestinal manifestations such as activity-related polyarthropathy seem to be independent from the colonic affection, but will sometimes respond to surgical therapy.

*Specific Indications for Surgical Treatment*

Surgery for UC can either be indicated in the emergency or the elective setting. Indications for urgent surgery include toxic colitis (6.8%), perforation and severe bleeding (2.5%).

*Emergency Surgery*

Acute severe colitis requires interdisciplinary specific intensive care medicine. Vital signs, bowel function and electrolytes and malnutrition have to be monitored carefully. Anti-inflammatory treatment usually includes high-dose intravenous steroids. Remission occurs in about 50–60% of patients. If there is no clinical improvement within 72 h or the patient's condition is deteriorating, surgery is indicated even in the absence of an acute abdomen [15].

Toxic dilatation, perforation and bleeding are indications for emergency surgery. The operative technique in emergency surgery in UC patients usually is subtotal colectomy with terminal ileostomy and the preservation of a rectal stump. Surgical procedures without resection of the diseased colon should be avoided. The poor prognosis of a toxic colon in former days can be markedly improved

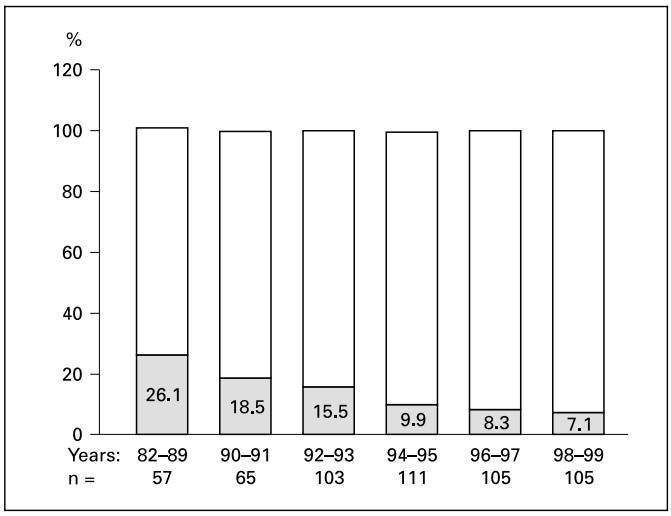


**Fig. 2.** *Learning curve:* Decrease of pouch-related septic complications by specialization, high frequency of operations, modifications of indications and technical development of pouch formation [from 38, with permission].

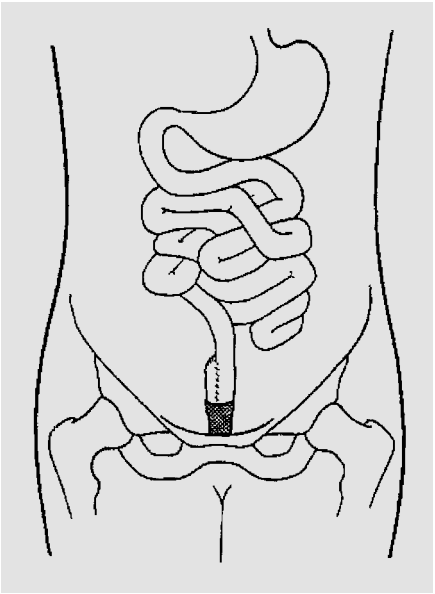

**Fig. 3.** Ileoanal J-pouch.

by an early diagnosis of the toxic condition, interdisciplinary management, and rapid surgical resection of the colon [15].

*Elective Surgery*

There are three indications for elective surgery: failed medical treatment, premalignant or malignant changes and growth retardation in children.

Today, the golden standard in surgery for UC is total restorative proctocolectomy with ileal J pouch-anal anastomosis (IPAA) formation, which implies the removal of the complete colonic mucosa including the rectum and proctomucosectomy. The anal sphincter is preserved and an ileoanal anastomosis is constructed after the creation of an ileal reservoir (fig. 2). In Heidelberg a two-stage procedure is generally performed, the temporary protective loop ileostomy is usually closed 3 months after the ileoanal pouch procedure. Our data demonstrate a clear 'learning curve', showing that even a large specialized center needs some time and experience to reduce specific complications and implies that this complex operation should only be performed by experienced surgeons (fig. 3). The same operation is also used for treatment of patients with familiar adenomatous polyposis. A protective stoma may be omitted in selected patients.

*Postoperative Morbidity and Mortality*

The most frequent complications after IPAA are pouch-related septic complications and pouchitis [26]. Between January 1982 and December 2001, 885 IPAAs were performed in our institution, 621 for UC and 164 for familial adenomatous polyposis (table 3). Early and late complications occur in up to 50% of all patients, including general complications like ileus. Specific complications of this procedure, also referred to as pouch-related septic complications, are present in 18.6% of UC patients, comprising anastomotic leaks, parapouchal abscesses, and pouch-anal fistulas [27]. The morbidity of 621 IPAAs for UC is presented in figure 4. Lethality in this collective of patients was 0.1%.

*Minimally Invasive Techniques*

Restorative proctocolectomy can also be performed with the help of minimal invasive techniques. The technical feasibility of this approach has been shown in several series in specialized centers [28, 29]. However, there is controversy in the literature on the actual benefit of minimal invasive techniques for such extensive colorectal surgery. Numerous smaller randomized and case-controlled studies have shown distinct advantages for laparoscopic compared to open colorectal procedures in the early postoperative phase, but the large randomized COST study on colorectal cancer procedures could only find minimal short-term quality of life benefits in the

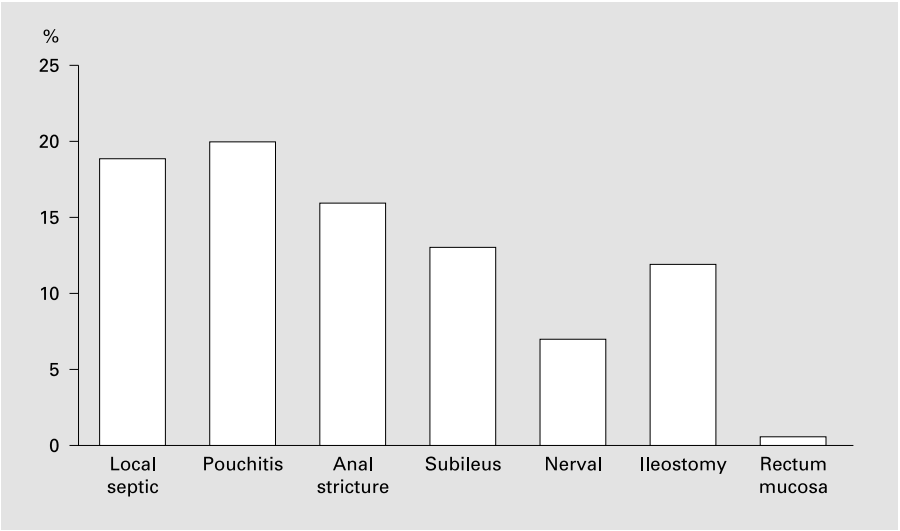


**Fig. 4.** *Morbidity of IPAA for UC:* Morbidity of 621 patients with UC who underwent total proctocolectomy with ileo-pouch anal anastomosis between January 1982 and December 2001 at the Surgery Department of Heidelberg. Lethality was 0.1%. Median follow-up time was 3.4 years.

minimally invasively treated group [30]. There is little comparative data on restorative proctocolectomy performed via conventional or minimal invasive approach. Excluding the obviously better cosmetic result, the majority of uncontrolled studies have not been able to show clear advantages for the laparoscopic procedure [31]. Only one larger case-matched study documented advantages for the minimally invasive treated group in terms of faster return of intestinal function and shorter hospital stay [32].

On the other hand, most studies revealed longer operative times for minimal invasive restorative proctocolectomy [33]. This problem may be overcome by employing the laparoscopically assisted technique, which has been advocated as being less time consuming and safer compared to purely laparoscopic techniques [34]. Laparoscopic purists, on the other hand, argue that the usage of a laparoscopically assisted technique probably minimizes the potential advantages of a true minimally invasive approach. In our experience, when comparing the laparoscopically assisted technique and the pure laparoscopic approach, the conversion rate with both techniques was comparable. The operative times were significantly lower in the laparoscopic group. The difference in estimated blood loss was 250 ml in favor of the laparoscopic group, when only including patients with protective ileostomy this increased to 500 ml. None of the patients in the laparoscopic group required a blood transfusion, whereas 35.5% in the laparoscopically assisted group needed blood transfusions. The overall complication rate was comparable; there was no mortality. The postoperative hospital stay was significantly shorter after the totally laparoscopic procedure.

*Morbidity and Mortality of Laparoscopic Pouch Formation*

Between October 2001 and January 2003 we performed 46 laparoscopic pouch operations, 22 for UC and 24 for familial adenomatous polyposis in our institution. Morbidity was 17% (8 patients with major complications), with a 0% mortality.

*Follow-Up Investigations after IPAA*

A standardized follow-up program was established in our institution for UC patients after IPAA with physical examination, pouchoscopy and contrast enema after 6–8 weeks prior to ileostomy enclosure. Thereafter, patients are examined 3, 6 and 12 months after IPAA, followed by annual control investigations for the next 4 years, then once every 2 years [35].

*Stool Frequency*

There is an increased stool frequency in the first year after IPAA with a mean frequency of 8.2 stools/24 h 3 months after surgery. Up to the second year there is a decrease of stool frequency down to 6.2/24 h without urgency which then remains stable in the long run [36].

*Quality of Life*

Quality of life is impaired when postoperative complications occur that cannot be adequately resolved over a limited period of time. On the other hand, patients with-

out complications and with good function after the ileoanal pouch procedure may achieve a quality of life comparable to that of healthy controls [36, 37]. Surgical experience, technical modifications concerning pouch design and fashioning of the pouch-anal anastomosis are important for further improving this complex procedure and for reducing the complication rate.

## Conclusion

Surgery for severe IBD has changed dramatically over the last decade. There is a clear trend towards earlier, but less invasive operations. When the indications are well reflected, most patients experience a substantial clinical benefit and improvement of quality of life after surgery. Most patients would have agreed to an earlier surgical procedure in retrospect if they had known the result of this procedure beforehand. This clearly indicates that gastroenterologists should probably consider involving an experienced surgeon earlier than practised to date.

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Review Article

Digestive Diseases

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# Intestinal Obstruction and Perforation – The Role of the Gastroenterologist

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**Key Words**
Small bowel · Large bowel · Obstruction · Perforation · Endoscopic stenting

**Abstract**
Intestinal obstruction belongs to highly severe conditions in gastroenterology, namely from the viewpoint of quick and correct diagnosis as well as at determining rational and effective therapy. Etiological multifactorial characteristics leading to processes resulting in mechanical or dynamic obstruction of the intestine, often referred to as paralytic ileus, are undoubtedly serious factors influencing the accuracy of diagnosis and therapeutic approach. Digestive endoscopy is a mandatory method in the diagnosis of intestinal obstructions. Diagnostic endoscopy, colonoscopy in the involvement of the large intestine or enteroscopy in the case of incomplete obstruction of the small intestine are the methods indicated in the majority of obstructive intestinal lesions. Besides their diagnostic importance, they also enable an effective therapeutic approach which may immediately follow the diagnostic intervention. Besides endoscopy that – due to the nature of performance – belongs to invasive methods, the diagnosis of obstructive intestinal processes is unthinkable without the use of non-invasive imaging methods. Abdominal ultrasound examination, a widely applied method, provides – under optimal examination conditions – information, e.g., about the width of the intestinal lumen or about the intestinal wall thickness; however, the specificity of investigation is not always sufficient. Both specificity and sensitivity of exploration are increased by a plain X-ray of the abdomen supplementing the ultrasound examination. Better results are achieved when the abdominal cavity is inspected by means of spiral CT examination that is nowadays not fashionably but highly effectively applied in the modification of the so-called CT enteroclysis or CT colonography. The usage of magnetic resonance (e.g. virtual colonography) is similar, but its efficacy is lower than that of CT examination. From a gastroenterologist's perspective, endoscopic examination is the fundamental diagnostic and therapeutic method. However, endoscopic examination is initially limited by the cardiopulmonary state of the patient – in a number of cases, first the cardiopulmonary condition must be stabilized, dysbalance of water and mineral state must be restored, and only then can endoscopic investigation be carried out. The application of enteroscopy in small intestine disorders is only suitable in cases where air must be aspirated from the region of the stomach and mainly small intestine as it happens, for example, in acute intestinal pseudo-obstruction. The success of complex conservative therapy in these states is reached in 80% of the cases. In acute and complete intestinal obstruction, a surgical treatment performed in time is the only method. In these cases, the importance of identification of obstruction and timing of the intervention performance from the viewpoint of the patient's survival is explicitly the principal and life-saving concern. In acute intestinal obstructions developing in patients with malignant affection of the intestine, it is necessary to choose – according to the obstruction location and general state of the patient – either urgently performed surgery or palliative endoscopic intervention

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which is the reduction of the intestinal lumen of the growing tumor mass and following insertion of a drain. This method also concerns lesions localized in the left half of the abdominal cavity, i.e. in the region of the rectosigmoid and descending part of the colon. Most patients in whom acute intestinal obstruction developed on the basis of malignant disease are risk and polymorbid subjects, and acute surgical intervention may be either impracticable or highly stressing. In such cases it is therefore helpful to insert a drain and to bridge the obstructed area after restoring the cardiopulmonary state including adjustment of the aqueous and mineral environment. Later, the performance of an elective surgical intervention is safer. Another alternative before inserting a drain is the dilatation of the stenotic site by means of a balloon, followed by stenting. Up until today, various types of intestinal drains have been introduced – they have always been self-expanding metallic stents. Just the application of self-expanding stents in patients with malignant intestinal obstruction and the endoscopic possibility of dilatations of benign intestinal obstructions with dilatation balloons are the most significant therapeutic contributions of digestive endoscopy in these states.



## Definition

*Intestinal obstruction* is caused by mechanical blockage or insufficient peristalsis and may be complete or partial. The condition can also be classified by the level of obstruction – small bowel or colon [25].

The synonym of this condition is *ileus*. The term *functional obstruction* is a possible alternative, but it is slightly confusing, because 'functional' could imply a psychological component to some, as in functional bowel disorder, 'obstruction' implies an anatomic impediment to flow.

Motor paralysis and paresis describe the physiologic malfunction of the bowel – *paralytic ileus* (adynamic ileus).

*Pseudo-obstruction* is often used in describing a chronic abnormality of function simulating mechanical obstruction but without anatomic cause [26, 29]. Acute colonic pseudo-obstruction (Ogilvie's syndrome) is a sudden massive idiopathic bowel dilatation [21].

The special sort of ileus in which severe transmural inflammation produces atony of the colonic muscle is *toxic megacolon*.

In the toxic megacolon the mucosal barrier is disrupted, resulting in systemic toxemia [2]. The term 'obstruction' is a synonym that implies that the process is intraluminal with the inability of intestinal contents to pass through the digestive tract. The term *closed-loop* obstruction is used if the lumen is obliterated at two sites. In partial obstruction, the passage continues but is impaired [20].

## Causes of Mechanical Obstruction – Extrinsic and Intrinsic Lesions

*Extrinsic Lesions*

Extrinsic masses can compress the bowel or mesentery and cause obstruction.

Adhesions

Adhesions are the most common cause of small intestine obstruction in adults. Adhesions may occur after abdominal surgery, infection or radiation.

Congenital Bands

Congenital bands behave clinically in much the same way as adhesions, but they may occur in association with malrotation, but very often in the absence of any known cause.

Hernias
- External
- Internal
- Pelvic hernias
- Diaphragmatic

Hernias may cause either simple obstruction or closed-loop obstruction. Strangulation is common in incarcerated hernias, because blood supply is compromised by the hernial ring.

Volvulus
- Gastric
- Midgut
- Cecal
- Sigmoid

Volvulus of the small intestine is relatively frequent in newborns but rare in adults. Volvulus of the stomach is often associated with large defects in the diaphragm or large paraesophageal hernias. Volvulus involves the sigmoid colon in 70–80% of the cases, and the cecum in 10–20% of the cases [28].

*Intrinsic Lesions*

Tumors

Benign and malignant tumors may narrow or obstruct the lumen. Malignant obstruction may be primary or metastatic. Primary malignancies of the small bowel are most often carcinoids, lymphomas or adenocarcinomas.

Inflammatory and Ischemic Processes

Most frequent etiologic agents are blunt abdominal trauma, hematomas as a result of severe thrombocytopenia or vascular fragility (Henoch-Schönlein purpura).

Intussusception and Congenital Defect

A leading segment of the bowel invaginates into an accepting segment. Intrinsic bowel lesion – e.g. Meckel diverticulum or tumor – usually initiates the process [23].

- Malrotation/volvulus
- Mesenteric cysts
- Annular pancreas
- Hirschsprung's disease
- Intestinal atresia

Intraluminal Objects

- Meconium ileus
- Barium impaction
- Fecal impaction
- Gallstone ileus
- Foreign bodies

## Causes of Adynamic Obstructions

Reflex Inhibition

- Laparotomy
- Renal transplantation
- Abdominal trauma

Inflammatory Processes

- Perforation or penetration
- Peritonitis
- Acute pancreatitis, acute cholecystitis
- IBD
- Celiac disease

*Abdominal Injury and Abdominal Irradiation*

Ischemic Processes

- Venous thrombosis
- Arterial insufficiency
- Mesenteric arteritis

Infection Processes

- Bacterial peritonitis
- Diverticulitis
- Appendicitis

Retroperitoneal Processes

- Pyelonephritis
- Retroperitoneal hemorrhage
- Pheochromocytoma
- Ureteropelvic stones

Drugs

- Opiates
- Chemotherapeutics
- Anticholinergic
- Phenothiazines

Metabolic Abnormalities

- Diabetes mellitus
- Uremia
- Septicemia
- Electrolyte dysbalances
- Pulmonary failure
- Porphyria

*Pathophysiology of Bowel Obstruction*

The pathophysiology of bowel obstruction is characterized by proximal colon dilatation; it occurs above the obstruction, mucosal edema, and impairs venous and arterial blood flow. Ischemia of the bowel wall can lead to bowel perforation. An important factor is the increase of bowel mucosal permeability with bacterial translocation, systematic toxicity, dehydration and electrolyte imbalances [29].

## Diagnostic Procedures

Diagnostic procedures include the history and evaluation of symptoms, laboratory (biochemical) examinations, gastrointestinal tests and endoscopy [28]. Diagnostic procedures are similar in small and large intestine obstructions.

*Clinical symptoms* are relatively typical; in patients with 'high' obstruction it is vomiting, very frequently abdominal pain connected with abdominal distension, absolute constipation, signs of peritonism and hypotension, tachycardia and oliguria.

In patients with large bowel obstruction, malignant lesions are the most frequent etiological factor of the

obstruction. Carcinomas are the cause of obstruction in 60–65%, diverticulitis in 20% and volvulus in 5%.

Clinical symptoms of the large colon obstruction are similar to those of patients with small bowel obstruction – abdominal pain, vomiting, dehydration and sepsis. Symptoms of peritonism can be found very often.

*X-ray examination* – supine abdominal X-ray can give information about the colon distention and air or liquid in the colonic lumen. 'Free' air in the abdominal cavity is a typical sign in patients with colon perforation [20].

Plain abdominal radiography can demonstrate the absence of rectal gas and distended colon in cases with closed-loop obstruction with large bowel obstruction. Sigmoid volvulus is presented radiographically as a 'bent inner tube' and cecal volvulus as a 'coffee bean'.

*Abdominal sonography* is effective in some cases and can describe the changes of lumen diameter and thickness of the bowel wall [12]. Ultrasound can be a useful adjunct to the plain film when CT is not practicable or desirable.

*CT scan* sensibility for high-grade obstruction is about 90%, for low-grade obstruction approximately 50% [6, 16]. CT is superior in comparison with abdominal X-ray, ultrasonography and MRI for locating the site of obstruction and diagnosis of bowel ischemia [15, 18].

A new effective diagnostic approach is *CT enteroclysis* [4], which, as a diagnostic procedure of the small bowel obstruction, is the gold standard for detecting low-grade obstruction and predicting the site of obstruction. However, enteroclysis is contraindicated if bowel ischemia is suspected. CT enteroclysis offers a novel technique for diagnostically challenging cases.

An essential diagnostic method is *endoscopy*. Endoscopical methods can locate obstructive lesions. The procedure must be performed without air insufflation and without biopsy, especially in cases where bowel perforation is suspected.

*Endoscopy* is a mandatory examination in obstructions of the small bowel and colon, with high efficacy as diagnostic procedures, but can be used as a therapeutic modality as well.

*Enteroscopes* are available to examine the more distal small bowel as a diagnostic procedure [20] and desufflation of the small bowel (e.g. early postoperative bowel obstruction) can be used as a therapeutic procedure [11].

*Colonoscopy* is indicated in examination of the rectum, colon and ileocecal valve and in desufflation of the colon, tumor mass ablation, stent insertion or colonic stricture dilatation [7, 24].

## Therapy

Acute complete bowel obstruction is a surgical emergency. The effect of endoscopical therapy in uncomplicated obstruction is dependent on the patient's cardiorespiratory status stabilization which is the first step of therapy in acute colonic disorders [10].

Together with nasogastric tube insertion, the correction of the fluid and electrolyte dysbalances [10] and eradication of the sources of sepsis by using broad-spectrum antibiotics (third-generation cephalosporins, metronidazole or amoxiclav) are mandatory therapeutic approaches. Uncomplicated obstruction can be treated conservatively in 80% of the cases, providing there are signs of resolution within 24 h.

Endoscopical bowel decompression together with fasting, nasogastric tube insertion and regular changes of patient position are indicated in bowel obstruction [5]. In patients with pseudo-obstruction, colonoscopic decompression is successful in more than 80% of the cases and further colonoscopy successfully treats the majority of recurrences [16]. After 24 h, the clinical situation has to be reviewed and a decision made if there is a need for further surgical intervention.

The rates of colonic perforation in patients with acute colonic pseudo-obstruction vary from 3.0 to 15% [24]. The cecum is the most common site of perforation. Perforation leads to increased mortality which can be between 43 and 46% [26]. Perforation leads to surgery, which is associated with increased mortality as well. It is extremely important to decide the correct timing between conservative and surgical therapy as a prevention of perforation. Endoscopical therapy is indicated in patients with benign bowel stricture [22], but this situation sometimes leads to acute colonic obstruction. Recent balloons are flexible and well suited to placement in the tortuous colon. Newer balloons with controlled radial expansion can be expanded in a controlled fashion.

The optimal time for inflation and number of dilatation procedures are still not known. Savary dilators can be used in patients with anastomotic strictures. These dilators predominantly exert their force in the axial direction and this may lead to a greater risk of complications and lower effect than balloons [27].

Endoscopical therapeutic procedures in patients with tumor colonic obstruction are tumor mass ablation [30] and stenting of the colon [1, 2, 19]. Metallic stents have been used since the beginning of 1990s (this method was first described by Spinelli in 1992). Endoscopical placement of self-expanding metallic stents over placement by

interventional radiology has its advantages; the endoscopical technique is able to pass some stents directly by the working channel of the endoscope. This advantage is especially useful when the obstruction is proximal to the rectosigmoid region or in patients with angulated rectosigmoid anatomy [8, 13]. However, both techniques, endoscopical and radiological, can usually be used effectively [2].

Endoscopic stenting can be performed with the therapeutic endoscope with a minimal working channel of 4.2 mm in diameter. Three stents are recommended – colonic Z stents with a 25-mm diameter in the body, enteral Wallstent (22-mm diameter) and BARD Memotherm stent (30-mm diameter). Technical success is, of course, dependent on the experience of the endoscopist, the optimal is success rate being 90–95% insertions. The limitation is the inability to pass a guide-wire through the stricture or anatomic difficulties [3, 9]. Clinical success is defined as successful bowel decompression and stool defecation [14].

Early complications after the procedure are stent migration, bowel perforation and bleeding [25]. Late complications are similar and stent migration is the most frequent. This complication can be asymptomatic or symptomatically patients can have tenesmus. Proximal stent migration is very rare. Stenting is the first method of choice in patients with tumor localization in the left colon, especially in the rectosigmoid junction or in the rectum [27]. Surgical resection or bypass operation is indicated in patients with proximal colon obstruction. Patients with total colonic obstruction are frequently ill with severe medical conditions. In these patients the self-expanding metallic stent insertion can help in the medical stabilization and later performed colon resection, when the tumor and stent are resected en bloc at the time of resection with greater safety [17].

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Review Article

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# Intestinal Obstruction and Perforation – The Role of the Surgeon

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**Key Words**
Intestinal obstruction · Perforation · Small bowel obstruction · Large bowel obstruction

**Abstract**
Intestinal obstruction and perforation are always a challenge for the surgeon, not only in respect to the surgical option offered to the patient, but also to the ability to accurately diagnose and stage the disease. The understanding of the underlying pathophysiological mechanism is also very important in order to classify each patient in order to receive the more appropriate treatment. Mechanisms of obstruction and perforation, methods of diagnosis as well as prevention and treatment of the disease were reviewed.



## Introduction

Obstruction of the small and large intestine seems to be a major health problem all over the world. Fifty years ago the most common cause of small bowel obstruction was external hernia. Nowadays, postoperative adhesions comprise more than half of small bowel obstructions, due to the increased number of surgical procedures and early elective hernia repair [1]. On the other hand, although many improvements have been achieved concerning large bowel obstruction and pseudo-obstruction, the main cause, i.e. malignancy, still remains unchanged. In the past 20 years, the rate of morbidity and mortality for elective colon operations has dropped significantly, but mortality for emergency colon operations is still twice as high compared to elective ones [2].

The mechanism of obstruction (mechanical vs. functional), the presence of vascular compromise, the level of obstruction (proximal or distal), the rate of progression of obstruction and the location of the responsible pathologies are of great importance in intestine's obstruction classification. Correct and immediate diagnosis in small and large bowel is of great importance as far as morbidity and mortality are concerned. Many pathophysiologic consequences implicate in clinical manifestation of this situation. Symptoms such as colicky pain, tenderness, peritonitis, signs of dehydration, abdominal distention and auscultation may indicate bowel obstruction. Laboratory tests are not helpful to identify obstruction. Radiological exams (X-rays, CT) and digital exams are essential not only for diagnosis confirmation, but also for locating the obstruction area.

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Although many partial obstructions can be treated conservatively or endoscopically, surgery still remains the cornerstone of treatment. The time of operation, indications, and the specific surgical procedures are related directly to the nature of the problem. Perforation can be due to several causes, malignant or benign pathologies, and leads to local or generalized peritonitis. Radiological, laboratory and clinical findings are essential in establishing the diagnosis. Surgery is the gold standard in the treatment of perforations.

In the present article, small and large intestine obstruction and perforation will be described separately with special references in the new advances in diagnosis and treatment of these pathologies [3].

## Small Bowel Obstruction

The causes of small bowel obstruction (SBO) can be divided into three groups, extraluminal causes (hernias, adhesions, carcinomas and abscesses), obstructions intrinsic to the wall (tumors, tuberculosis, actinomycosis, malrotation, cysts, diverticula, hematomas, strictures, etc.), and in intraluminal causes as enterolith, gallstone, foreign bodies, etc. At the beginning of the 20th century, hernias were the leading cause of small intestinal obstruction, but with routine elective hernia repair, adhesions secondary to previous surgery became by far the most common cause [4].

Postoperative adhesions are responsible for more than 70% of all causes of SBO, particularly after pelvic procedures because small intestine is more mobile in the pelvis [5].

Tumors are the second leading cause accounting for about 20% of SBO, especially metastatic lesions from intra-abdominal primary tumor (e.g. ovarian, gastric, colonic, etc), and rarely from extra-abdominal primary tumors (e.g. breast, lung, melanoma, etc). Large intestine malignant neoplasm may present with small intestine obstruction. Hernias are the third leading cause (ventral, inguinal, and internal) and inflammatory bowel diseases (Crohn's disease) is the fourth cause, resulting from acute inflammation and edema [6]. Intra-abdominal abscesses may present as SBO (local ileus). Other miscellaneous causes (enterolith, gallstone, foreign bodies, diverticula, and polyps), while very rare (<2%), should be considered in the differential diagnosis (table 1) [7, 8].

**Table 1.** Small bowel obstruction causes in adults

| |
|---|
| *Extrinsic lesions* |
| Adhesions |
| Postoperative |
| Primary |
| Neoplasms |
| Benign |
| Malignant |
| Intra-abdominal carcinomatosis |
| Extraintestinal tumor |
| Hernias |
| Internal (paraduodenal, diaphragmatic, etc.) |
| External (inguinal, umbilical, etc.) |
| Intra-abdominal abscess |
| *Intestinal wall, intrinsic lesions* |
| Neoplasms |
| Primary |
| Metastatic |
| Inflammatory |
| Crohn's disease |
| Infectious diseases |
| Actinomycosis |
| Tuberculosis |
| Diverticulitis |
| Congenital |
| Malrotation |
| Intestinal wall cysts |
| Duplication |
| Miscellaneous lesions |
| Hematoma |
| Ischemia |
| Stricture |
| Post-radiation enteritis |
| Endometriosis |
| Intussusception |
| *Intraluminal causes* |
| Enterolith |
| Gallstone |
| Foreign body |
| Trichopilimma |

*Diagnosis*

In the majority of patients, a thorough history and physical examination are very important to establish the diagnosis and treatment. The above should be complemented with abdomen X-rays, although more sophisticated exams (US, CT, MRI, endoscopy, or laparoscopy) may be necessary in cases with uncertain diagnosis. The main symptoms of SBO are colicky abdominal pain, nausea and vomiting (more common in higher obstruction),

abdominal distention and failure to pass feces and flatus [2, 4, 7].

Physical examination may reveal important signs, including tachycardia, hypotension, severe dehydration, and fever. In the early stages, peristaltic waves can be observed, and the auscultation may demonstrate hyperactive bowel sounds, but in the late stages minimal or no bowel sounds are present. Other findings include tenderness, palpable mass, rebound, and localized pain (local peritonitis). Physical examination may include rectal and stool exam and careful examination for incarcerated hernias, in the groin, femoral triangle and in obturator foramen [1–3].

Most of the patients with SBO have a simple mechanical blockage in luminal contents flow without disturbance of intestinal wall viability. In rarer cases intestinal strangulation may occur. Strangulation obstruction involves a closed-loop obstruction with compromised vascular supply of a particular intestinal segment leading to infarction, which is associated with higher morbidity and mortality rates. Tachycardia, fever, leukocytosis, and constant abdominal pain present the most common symptoms of strangulation obstruction [1, 6].

*Laboratory and Radiologic Examinations*

Laboratory examinations are not helpful in the actual diagnosis. The most common findings in routine patients' laboratory measurements are elevated hematocrit due to dehydration, serum electrolytes (sodium, potassium, bicarbonate) and creatinine changes and leukocytosis (particularly in patients with strangulation), although elevated white blood cell count does not always denote strangulation [9].

Various serum determinations (amylase, electrolytes, ALP and ammonia) have been tried to find an association with the strangulated obstruction, with no result. The present studies indicate that serum *D*-lactate, CK-BB isoenzyme and intestinal fatty acid binding protein may be associated with strangulated obstruction.

Radiological studies confirm the clinical suspicion and define more accurately the site of obstruction. Plain abdomen X-rays present 60% accuracy in defining the cause and site of SBO. Most common findings are dilated small intestine loops, colonic distention, multiple air-fluid levels, and foreign bodies or gallstones. In more complicated cases, further diagnostic evaluations may be necessary [10, 11].

In these cases, CT scanning proved to be beneficial, although this exam seems to be less sensitive in patients with partial SBO. CT has dramatically improved the management of patients with suspected obstruction, although its accuracy varies [12].

Multi-slice or helical CT has better outcomes. Intravenous contrast is needed in every case because it highlights the abdominal viscera and lesions of the bowel or surrounding area, and allows examination of the bowel's wall, particularly in cases where strangulation is suspected. Thin slices are useful when the site of obstruction is estimated [13].

In full obstructions it is of great importance to accurately determine the cause and the site of the obstruction, even if the cause is extrinsic (tumor, abscess, etc). Barium studies and particularly *enteroclysis* may be helpful in the assessment of obstruction, as it can precisely demonstrate the level and cause of the obstruction in patients with low-grade intermittent SBO and uncertain diagnosis. There are doubts about the diagnostic value of ultrasound, while MRI appears not to be better diagnostically compared to CT scan [14–16].

Richards et al. [17] tried to detect mesenteric ischemia associated with altered small intestine's basic electric rhythm with a non-invasive technique using a superconducting quantum interference magnetometer. This procedure may be useful in strangulated obstruction diagnosis and is at present under clinical evaluation and assessment.

*Treatment*

Conservative Treatment

Patients with SBO are usually dehydrated, and depleted of electrolytes. These patients require intravenous replacement of body fluids and electrolytes. The appropriate replacement is intravenously with the patient monitored. Serial blood measurements (electrolytes, hematocrit and white blood cells) must be performed in order to assess the adequacy of resuscitation and the patient's general condition. In some cases, intravenous fluid replacement may require central venous catheter and Swan-Ganz catheter. In complicated patients with increased white blood cells number, antibiotics prophylaxis or treatment may be useful [18].

Additionally with body fluid and electrolyte replacement, the patient's SBO support requires nasogastric suction with a nasogastric (Levin) tube, which empties the stomach and reduces the risk of gastric fluid pulmonary aspiration. Several prospective studies demonstrate no significant difference concerning the non-operative treatment or the morbidity-mortality rates after surgical interference, with or without nasogastric decompression [19].

Conservative treatment may be successful in patients with partial SBO. Resolution of the symptoms and patient's discharge have been reported in 65–80% of the patients. The small intestine's distention in abdominal X-rays during conservative treatment with a nasogastric tube is an indication for immediate surgical intervention [20]. Choi et al. [21] suggest that the use of Gastrographin in adhesive SBO is safe and reduces the need for surgery when conservative treatment fails. These authors treated patients with partial obstruction (contrast reaches the colon within 24 h) conservatively, and suggest that Gastrographin helped in the conservative treatment of the patients.

Adhesion Prevention

Intestinal obstruction due to abdominopelvic adhesions has developed into a serious health problem worldwide. Research towards reduction of possible adhesion etiopathogenic factors as well as prevention of adhesion formation has shown that various individual factors such as nutritional status, disease state like diabetes and the presence of concurrent infectious processes, affect adhesion formation. In addition, various clinical techniques and agents seem to decrease the incidence of postoperative adhesions [22, 23].

Surgical techniques that inhibit adhesions include limiting trauma to intra-abdominal structures [24], meticulous hemostasis [25] (free blood provides a source of fibrin and thromboplastin that activate the clotting cascade), delicate handling of the bowel [24], tissues moistening [26] and use of minimally invasive surgery when possible. All these maneuvers have been shown to protect against adhesion formation and should always be followed.

On the other hand, despite the fact that many pharmacological agents have been tried against adhesions, several points need to be clarified before the enthusiasm for the development of the ideal adhesion barrier becomes scientific certainty [27]. This 'adjuvant' therapy points either to the various causes of the inflammatory process (NSAIDs [28], glucocorticoids and antihistamines [29], progesterone/estrogen [27], anticoagulants [27], fibrinolytics [30], antibiotics) or directly to adhesion formation. The latter fall into two main categories: macromolecular solutions (crystalloids, 32% dextran 70, hyaluronic acid, HA-PBS/Sepracoat, carboxymethylcellulose) and solid barriers [27] (autologous peritoneal transplants, PTFE, oxidized-regenerated cellulose, HA-CMC [31]).

Surgical Treatment

Patients with complete SBO require surgical intervention, although some authors suggest that many patients can be managed conservatively with nasogastric suction and fluid-electrolyte replacement. Several studies indicate that a 12- to 24-hour delay of the surgical treatment seems to be safe, although the incidence of strangulation of other complications may increase. During that period, conservative means can be used in severe patients' (with fever, tachycardia, tenderness and leukocytosis) resuscitation.

The nature of the problem indicates the appropriate operation in patients with SBO. In patients with a history of cancer and intra-abdominal widespread metastasis, conservative treatment may be more useful in those cases where operation is contraindicated. In non-complicated cases, tumor resection or bowel bypass may solve the problem temporarily or permanently. In SBO, due to Crohn's disease, conservative treatment may be useful, whereas bowel resection is indicated in strictures or fistulas. Intra-abdominal abscess causing SBO needs drainage. The operation type depends on the nature of SBO. In complicated cases where bowel viability is questionable, the obstructed segment is released and placed in warm saline gausses for 15–20 min, then re-estimated, and if there is still doubt, partial bowel resection should be performed [32].

Several authors suggest that SBO estimation should start laparoscopically, because most of the cases are due to secondary adhesions. Laparoscopic treatment of SBO seems to be effective and in selected patients leads to a shorter hospital stay. Several criteria have been proposed for patient selections. Appropriate for laparoscopic intervention patients include those with mild abdominal distention, proximal obstruction, and partial and anticipated single band obstruction. Advanced, complete or distal SBO is a contraindication for laparoscopic treatment. As already reported, patients with adhesions, widespread carcinomatosis, or inducing distention after nasogastric suction should be managed with open laparotomy [33, 34].

Recent studies support the role of minimal invasive procedures in SBO treatment. Endoscopical stent placement in cancer obstructions seems to temporarily release obstruction, and become a good alternative in patients with widespread carcinomatosis, where surgical treatment is contraindicated and conventional management has no effect.

## Large Bowel Obstruction

Along the colon, many segments are completely intraperitoneal, while others are partially retroperitoneal, which means that the colon is more fixed and its parts have different mobility depending on the laxity of the mesocolon. The causes for large bowel obstruction are quite different to those of the small intestine. The main causes are the following: tumor (benign or malignant: 8–29%), ulcerative colitis, large diverticula, adhesions, enterolith, intra-abdominal abscess and volvulus. Because of its anatomic difference (different mobility) from small intestine, volvulus is a specific for colon obstruction cause. The main risk of volvulus is the infarction of the segment involved, via torsion of the supplying vessels that interrupts the in- and outflow in the colon wall, or via torsion of colon or/and ileum (in cecal volvuli), creation of a closed loop and strangulation. In both cases, fatal arterial obstruction is the final result. The most common volvulus sites are cecum and sigmoid colon, and rarely transverse colon [35].

*Diagnosis*

As already referred to, malignancy seems to be the most common cause of colonic obstruction. This pathology rarely requires immediate operative treatment, so in the majority a preoperative evaluation should take place. Diagnosis can be achieved through contrast enema or colonoscopy. The value of contrast enema is in the diagnosis of pseudo-obstruction in which barium has not only diagnostic but also therapeutic use. Colonoscopy, on the other hand, is useful in identifying tumors and taking biopsies [1, 4].

Radiological studies confirm the clinical suspicion and define more accurately the site of obstruction. Most common findings are colonic distention and multiple air-fluid levels. In more complicated cases, further diagnostic evaluations may be necessary. In these cases, CT scanning proved to be beneficial, ultrasound does not offer much, while MRI appears not to be better diagnostically compared to CT scan [2, 7, 16].

Laboratory examinations are not helpful in the actual diagnosis. The most common findings in routine patient laboratory measurements are serum electrolyte disturbances (sodium, potassium, bicarbonate), creatinine changes and leukocytosis (particularly in patients with strangulation). Various serum determinations (amylase, electrolytes, ALP and ammonia) have been tried to find an association with the obstruction, with no result, while fibrinogen and d-dimers seems to increase in cases of colonic necrosis [3].

Diagnosis of colonic obstruction caused by ulcerative colitis is difficult and needs not only radiological, but also pathologic and laboratory definition. No matter which is the cause, diagnosis of colon obstruction can be achieved in most of the cases, with abdominal X-rays, enema contrast studies, colonoscopy and CT. The final diagnosis can be defined intra- or postoperatively [36].

*Treatment*

Colon obstruction treatment is rarely conservative. In most of the cases, the cause of obstruction should be removed or bypassed, with surgical or endoscopic procedures. According to Ballantyne et al. [37], sigmoid volvulus is responsible for 6.1% of colon obstructions. Sigmoidoscopic decompression by insertion of a rectal tube or endoscopicaly relieves the obstructions in uncomplicated cases (absence of necrosis or perforation). The recurrence rate after endoscopic or conservative treatment varies from 40 to 85% or more in different series, which indicates surgical treatment (resection of the involved colon) to be a definitive therapy [38].

There are doubts about the appropriate surgical treatment of obstructive colon malignancies. Many surgeons suggest resection of the lesion and primary anastomosis at the same time, while others support other methods as for example intraoperative colonic irrigation primary to anastomosis [39]. These techniques have significant complication rates when they are performed in patients with acute or chronic obstruction: wound infection rate is 12%, severe anastomotic leakage rate 6%, morbidity rate 14% and total mortality rate is 8%. The decision for the type of operation depends on the surgeon, on prognostic factors and staging of malignancy, on the existence of intraperitoneal microcarcinomatosis and on parameters associated with the patient's general situation and other health problems. An effective alternative to primary anastomosis is colostomy, which is indicated particularly in high mortality risk patients and in cases where tumor resection is impossible. Bypass may be useful in cases where it is not easy to perform either colostomy or primary anastomosis [3, 7, 38].

Treatment of acute colorectal obstruction by using metallic stents is a recent advance that has been mainly for preoperative decompression. Despite limited reports in the literature, endoscopic stent placement for colonic obstruction relief seems to be a highly feasible and safe method [40]. Successful stent implantation is achieved in 85–100% of the patients, depending on the center's experience. Colonic stent can be also placed under fluoroscopic guidance or with a combination of these two methods.

These techniques offer a highly effective therapeutic option, with a high success rate and rapid colon decompression [41]. Complication rates after endoscopic stent placement varies from 14 to 49%. The most common complication is colonic perforation, which in most cases is microperforation without inflammatory reaction of the surrounding tissues treated conservatively. In severe perforation with signs and symptoms of peritonitis, immediate surgical treatment is required. In cancer patients, stent placement is a good alternative which relieves symptoms and increases quality of life [42].

*Small and Large Intestine Pseudo-Obstruction*

Pseudo-obstruction still remains a severe diagnostic problem, which increases the number of unnecessary operations. Repeated laparotomies lead to more adhesions increasing the incidence of mechanical obstruction.

Small Bowel Pseudo-Obstruction

Pseudo-obstruction is more common in the small bowel. A variety of diseases associated with small bowel pseudo-obstruction exist (table 2), although their etiologies can be divided into two major groups: (a) degeneration of the intestine's smooth muscles and (b) degeneration of myenteric and submucosal nerve plexes, which lead to disturbance of normal bowel contraction [43].

The clinical presentation varies, although there are some common symptoms as nausea, vomiting, abdominal distention, crampy pains, obstipation, constipation and pseudo-diarrhea. The most common laboratory findings are leukocytosis and electrolytic changes. There are no specific diagnostic or predictive laboratory exams. A differential diagnosis of the form of bowel obstruction can be achieved with a combination of the patient's history and radiological exams. Abdominal X-ray indicates distention of the bowel, while enteroclysis may identify areas of dismotility [43, 44]. Patients with pseudo-obstruction present a prolonged transit time of barium to colon compared to those with mechanical bowel obstruction. Endoscopists have tried to evaluate pseudo-obstruction manometrically with the use of multilumen long intestinal tubes for recording contractions. Another method for pseudo-obstruction diagnosis is the radioactive labeling and evaluation of radionuclide motility. Patients with disturbances of intestinal motility have a prolonged radionuclide transit time. Abdominal CT scan gives only indirect information and diagnosis of pseudo-obstruction is achieved with difficulty and indirectly by absence of other intestinal pathologies [45].

**Table 2.** Causes of pseudo-obstruction

| |
|---|
| Electrolyte alterations |
| Uremia |
| Hypokalemia |
| Hypomagnesemia |
| Hypocalcemia |
| Drugs and pharmaceutical agents |
| Phenothiazines |
| Tricyclic antidepressants |
| Antiparkinson drugs |
| Clonidine |
| Endocrine disorders |
| Diabetes |
| Hypothyroidism |
| Hypoparathyroidism |
| Neurologic disorders |
| Parkinson's disease |
| Hirshsprung's disease |
| Chagas' disease |
| Shy-Drager syndrome |
| Other situations |
| Scleroderma |
| Dermatomyositis |
| Lupus erythematosus |
| Amyloidosis |
| Ceroidosis |
| Non-tropical sprue |
| Spinal cord trauma |
| Paraplegia |
| Brain injury |

Treatment of small bowel pseudo-obstruction can be either conservative or surgical. Laparotomy is common prior to pseudo-obstruction diagnosis, but after diagnosis should be avoided. Several strategies have been proposed for conservative pseudo-obstruction treatment, as for example indomethacin (prostaglandin inhibitor) and cisapride (prokinetic agent with activity in esophagus, stomach and intestine). Early reports for cisapride treatment indicate a decrease in intestinal transit time in patients with chronic idiopathic pseudo-obstruction. Cholinergic drugs as fisostigmine, prostigmine and neostigmine have been used with success in pseudo-obstruction treatment. Surgical treatment in not necessary if the diagnosis is achieved. In cases where the patients undergo operation, three categories of pseudo-obstruction are identified which have different treatments: (a) *esophageal,* predominantly treated with dilation, (b) *gastroduodenal,* predominantly treated with vagotomy, antrectomy and gastrojujenostomy, and (c) *small intestine,* predominantly treated

with gastrostomy or jujenostomy. Prior to surgical treatment, decompression with a nasogastric tube should be performed, combined with intravenous alimentation for restoration of fluids and calories in these patients [46, 47].

Large Bowel Pseudo-Obstruction (LBPO)

LBPO is also known as Ogilvie's syndrome. Ogilvie [48] first described 2 patients with colonic distention without mechanical obstruction, suggesting that it may be due to imbalance between parasympathetic and sympathetic colon innervation. The clinical features of LBPO are similar to those of LBO, with predominant symptoms of abdominal distention, nausea, vomiting, fever, pain and obstipation, although flatus and liquid stools may not be inhibited. Laboratory findings include leukocytosis and electrolytic disorders [49, 50].

Diagnosis can be achieved with several radiological and endoscopical exams. Abdomen X-ray presents enormous colonic distention and dilation, while CT scan presents no obvious obstruction. Colonoscopy is the appropriate diagnostic and therapeutic treatment [51]. Absence of obstruction can be well established while decompression of cecum reduces distention. Colonoscopic decompression is indicated when the cecum diameter exceeds 12 cm. Other authors suggest a long tube placement through the rectum for continuing large bowel decompression. In rare cases where colon function and motility cannot be re-established, surgical decompression of the colon (colostomy or cecostomy) should be performed [52–54].

*Small and Large Bowel Perforation*

Intestinal perforation has a variety of causes. The main causes can be divided into three groups: (a) benign conditions, as appendicitis, Meckel diverticula, diverticulitis, volvulus, intussusception, ulcerations, etc.; (b) malignant disease, as small bowel and colon tumors, and (c) other situations, as foreign bodies, iatrogenic injuries (after colonoscopy, or endoscopical polypectomy), inflammatory bowel diseases, etc. [55].

Diagnosis of intestinal perforation is not difficult, because it leads to local or generalized peritonitis and presents with acute abdomen. A patient's history may not indicate an obvious cause for perforation, but physical examination results in diagnosis of acute abdomen. Common symptoms and signs of intestinal perforation are fever, nausea, severe pain (localized or all over the abdomen), and contraction of abdomen, rebound, vomiting, dizziness, paleness, tachycardia, hypotension and absence of enteral sounds. The patient's condition worsens with time. Common findings from laboratory examinations are leukocytosis (>16,000) with granulocyte domination, alterations in fluid and electrolyte balance, arterial blood gases and pH alterations [56, 57].

Diagnosis of intestinal perforation is achieved radiologically. Abdomen X-ray with the patient standing can present free air in the abdominal cavity and especially subdiaphragmatic. An X-ray can also demonstrate intestinal distention or air-fluid levels. CT scan is useful in establishing the diagnosis, demonstrating free air or liquid in the abdominal cavity pointing in some cases to the perforated part of the bowel. US has also significant diagnostic value by presenting free air and liquid in the abdomen. No further diagnostic procedures need to be developed, as perforation diagnosis is a more clinical challenge than radiological evidence [58, 59].

Patients with intestinal perforation should be resuscitated first. When admitted to hospital, most of them are suffering from shock. Intravenous fluids and electrolytes, antibiotics and analgesics should be administrated before operation. A nasogastric tube (Levin) helps in gastric decompression. The treatment of perforation is operative, while conservative means have a supportive role [60].

The type of operation is based on perforation etiology. The primary goal is to remove all contaminated material from the abdominal cavity, preventing further contamination. Definitive treatment is based on etiology, local conditions and the patient's general status. A one-stage operation is preferable if it is possible [56, 60]. If a tumor is present its removal is of great importance. In inflammatory diseases, partial enterectomy or colectomy may be performed. In cases of foreign bodies, the material is removed and the intestine is sutured, while in iatrogenic injuries an attempt must be made to suture the bowel. In cases of minimal contamination, a primary anastomosis should be performed, otherwise a two-stage restoration takes place, with primary stoma creation and restoration of the intestinal continuity the second time [61, 62].

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