SURGERY
Part II

PUBLIC HEALTH MINISTRY OF UKRAINE
KHARKIV NATIONAL MEDICAL UNIVERSITY

SURGERY

Part II

SURGICAL GASTROENTEROLOGY AND PROCTOLOGY
Textbook for medical students

ХІРУРГІЯ

Частина ІІ

ХІРУРГІЧНА ГАСТРОЕНТЕРОЛОГІЯ І ПРОКТОЛОГІЯ
Навчальний посібник для студентів медичних закладів

Kharkiv
KhNMU
2018

UDK 617
S94

Approved
by the Scientific Council of KhNMU.
Minutes No1 at 25.01.2018

Autors: I. A. Kryvoruchko, V. M. Lisovyi, V. V. Boyko, O. A. Tonkoglas

Рецензенти: *М. М. Велігоцький*, заслужений діяч науки і техніки України, лауреат Державної премії України в галузі науки і техніки, доктор медичних наук, професор, завідувач кафедри торакоабдомінальної хірургії ХМАПО МОЗ України;
Ю. В. Іванова, доктор медичних наук, головний науковий співробітник ДУ «Інститут загальної та невідкладної хірургії ім. В.Т. Зайцева НАМНУ».

S94 Surgery. Part II. Surgical gastroenterology and proctology: textbook for medical students / I. A. Kryvoruchko, V. M. Lisovyi, V. V. Boyko, O. A. Tonkoglas. – Kharkiv : KhNMU, 2018. – 290 p.

The textbook is completed in accordance with the student's study program. It subsequently existing and new data on the etiology, pathogenesis, diagnosis, comprehensive treatment of surgical diseases of the abdominal cavity and prevention of postoperative complications.

For the 4th year students of higher medical institutions which study by English. The textbook will be to useful students of other courses.

UDK 617

S94 Хірургія. Частина ІІ. Хірургічна гастроентерологія і проктологія: навч. посібник для студентів мед. закладів / І. А. Криворучко, В. М. Лісовий, В. В. Бойко, О. А. Тонкоглас. – Харків : ХНМУ, 2018. – 290 стор.

Навчальний посібник доповнено відповідно до програми навчання студентів. В ньому послідовно відображаються існуючі та нові дані щодо етіології, патогенезу, діагностики, комплексного лікування хірургічних захворювань органів черевної порожнини та профілактики післяопераційнихускладнень.

Для студентів 4-х курсів вищих медичних закладів, що навчаються англійською. Посібник буде корисним також студентам інших курсів.

УДК 617

CONTENTS

Chapter 1

OPERATION ON THE STOMACH AND DUODENUM

1.1. ANATOMY AND PHYSIOLOGY

The stomach and duodenum may be considered logically as a unit, since many physiologic functions and certain disorders are either shared by these two segments of the gut, or interact on each other.

For gross description, the stomach can be divided into fundus, body and antrum (*Fig. 1.1*). The cardia is located at the esophagogastric junction.The pylorus is the boundary between the stomach and the duodenum, which may be palpated as a thick ring of muscle and is externally marked by the prominuent vein (prepyloric vein).The incisure, approximately 5–6 cm proximal to the pylorus on the lesser curvature, is called the angular incisure.The fundus is the dome of the stomach that lies cephalad to the esophagogastric junction.

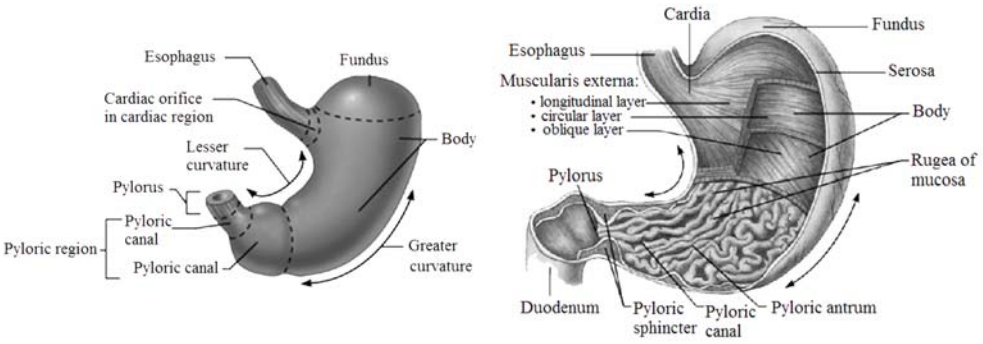


Figure 1.1. *The stomach and duodenum*

The area distal to a line drawn from the angular incisure to the greater curvature and proximal to the pylorus is the gastric antrum.The body of the stomach is the capacious central part, lying between the fundus and the antrum.

The cardiac gland area is the small segment located at the esophagogastric junction. Histologically, it contains principally mucus-secreting cells, although a few parietal cells are sometimes present. The oxyntic gland area is the portion containing parietal cells and chief cells that secrete acid peptic juice. The pyloric gland area constitutes the distal 30% of the stomach and contains the G-cells that secrete a hormone, gastrin. Mucous cells, which secrete relatively alkaline mucus, are common in both the oxyntic and pyloric gland areas.

Blood supply. Blood supply of the stomach is particularly rich and the wall of the stomach contains a rich submucosal vascular plexus. The left gastric artery (a branch of celiac trunk) and right gastric artery (a branch of the common hepatic artery) supply the area of the lesser cuvature and connects each other. The greater curvature is supplied by the right gastroepiploic artery. The mid portion of the greater

curvature corresponds to a point at which the gastroduodenal artery and the left gastroepiploic artery. The fundus of the stomach along the greater curvature is supplied by the short gastric arteries, branches of the splenic. The gastroduodenal artery may send small branches to the area of the pylorus. In 60% of persons, a posterior gastric artery arises off the middle third of the splenic artery and terminates in branches on the posterior surface of the body and the fundus.

The blood supply to the duodenum is from the superior and inferior pancreaticoduodenal arteries provide blood supply to the superior portion of duodenum.

Venous blood from the stomach drains into the coronary, gastroepiploic, and splenic veins before entering the portal vein.

Nerve supply. The parasymapthetic nerves to the stomach are from the vagal nerve. About 90% of the vagal fibers are sensory a afferent, the remaining 10% are efferent. The efferent fibers of the vagal nerves stimulate the motility of the stomach and the secretion of acid, pepsin and gastrin. As a rule, 2 major vagal trunks pass through the esophageal hiatus in cose approximation to the esophageal muscle. In the region of the gastroesophageal junction, each trunk bifurcates. The left or anterior vagal trunk sends to the liver a division at travels in the lesser momentum. The bifurcation of the right or posterior trunk gives rise to fibers that enter the celiac plexus and supply the parasympathetic innervation to the remainder of the gastrointestinal tract. Both trunks, after giving rise to their extra gastric divisions, send some fibers directly onto the surface of the stomach. "The anterior vagal trunk supply innervation to the anterior wall of the stomach (anterior nerves of Latarjet), the posterior vagal trunk supply innervation to the posterior wall of the stomach (the posterior nerves of Latarjet)".

The sympathetic nerve fibers pass along the arterial vessels from the celiac plexus to the stomach.

GASTRIC SECRETION

The output of gastric juice in a fasting subject varies between 500 and 1500 ml/d. After each meal, about 1000 ml are secreted by the stomach.

The components of gastric juice are as follows:

1. Pepsinogen. Pepsinogen is synthesized in the chief cells of the oxyntic gland area (and to a lesser extent in the pyloric area) and are stored as visible granules. Cholinergic stimuli are the most potent for secretions of pepsinogen, gastrin and secretin. The precursor zymogen is activated when pH falls below 5.0 a process that entails severance of a polypeptide fragment from the forger molecule. Pepsin sheaves peptide bonds, especially those containing phenylalanine, tyrosine, or leucine. Its optimal pH is about 2.0 Pepsin activity is abolished at pH greater that 5.0, and the molecule is irreversibly denatured at pH greater than 1.0.

2. Electrolytes. The unique characteristic of gastric secretion is its high concentration of hydrochloric acid, a product of the parietal cells. As the concentration of H2-rises during secretion, the concentration of Na drops in a reciprocal fashion. K remains relatively constant at 5–10 m Eq/L. Chloride concentration remains near 150 mEq/L, and gastric juice maintains its isotonicity and varying secretory rates.

3. Mucus. Mucus is a heterogeneous mixture of glycoproteins manufactured in the mucous cells of the oxyntic and pyloric gland areas. Mucus provides a weak barrier to the diffusion of H_2 and protects the mucosa. It also acts as a lubricant and impedes diffusion of pepsin.

4. Intrinsic factor. Intrinsic factor, a mucoprotein secreted by the parietal cells, binds with vitamin B_{12} of dietary origin and greatly enhances absorption of the vitamin. Deficiency in intrinsic factor may decrease vitamin B_{12} absorption from gut and result in megaloblastic anemia.

5. Blood group substances. 75% of people secrete blood group antigens into gastric juice. The trait is genetically determined and is associated with a lower incidence of duodenal ulcer than in nonsecretor.

The onset of secretion is accompanied by striking morphologic changes in the apical membranes. Resting parietal cells are characterized by an unfolding of the apical membrane, called the secretory canaliculus, with is lined by short microvilli. Multiple membrane-bound tubulovesicles and mitochondria are present in the cytoplasm. With stimulation, the secretory canaliculus expands, the microvilli become long and narrow and filled with microfilaments, and the cytoplasmic tubulovesicles disappear. The proton pump mechanism for acid secretion is located in the tubulovesicles in the resting state and in the secretory canaliculus in the stimulated state.

The basal lateral membrane contains the receptors for secretory stimulants and transfers HCO_3 out of the cell to balance the H_2 output at the apical membrane. Active uptake of Cl^- and K^+ conduction also occur at the basal lateral membrane. Separate membrane bound receptors exist for histamine (H_2-receptor), gastrin, and acetylcholine. The intracellular second messengers are thought to be cAMP for histamine and CaCl + for gastrin and acetylcholine.

Acid secretion at the apical membrane is accomplished by a membrane – bound H^+/K^+-ATPase (the proton pump); H_2 is secreted into the lumen in exchange for K^+.

The regulation of acid secretion may be described by considering separately those factors that enhance gastric acid production and those that depress it. The interaction of these forces is what determines the levels of secretion observed during fasting and after meals.

Gastric secretion may be classified as spontaneous secretion (interdigestive secretion), and stimulated secretion. Spontaneous acid secretion, occurring without. Stimulated acid secretion is usually described as the result of 3 phases that are exeied simultaneously after a meal.

1. *Cephalic phase.* Stimuli, such as sight, smell, taste, or even thought of appetizing food, the vagal nuclei of the brain lead to increased vagal efferent activity. The vagal stimuli release acetylcholine that has a direct effect on the parietal cells to increase acid output. The effect is entirely vagal mediated and is abolished by vagotomy.

2. *Gastric phase.* Food in the stomach (principally protein hydrolysate and hydrophobic amino acids) stimulates gastrin release rome the antrum. Gastric distention has a similar but less intense effect. Gastrin effects on the parietal cells to increase acid secretion.

3. *Intestinal phase.* The role of the intestinal phase in the small bowel releases a humoral factor, may name enter-oxyntin, which evokes acid secretion from the stomach. pH below 2.5 in the antrum inhibits the release of gastrin, then remove gastrin stimulus for acid secretion. When the pH-reaches 1.0, gastrin release is almost completely blocked. If the normal relationship of parietal cell mucosa to antral mucose is changed to that acid does not flow past the site of gastrin production, serum gastrin may increase to high levels, with marked acid stimulation. Somatostatin in gastric antral cells serves a physiologic role as an inhibitor of gastrin release.

Fat in the intestine (duodenum) is the most effective inhibitor, which affect gastrin release and acid secretion. The intestine may participates in controlling acid secretion by liberating some hormones, secretin, or a still unidentified hormone that inhibit both the release of gastrin and its effects on the parietal cells, and blocks acid secretion. The most remarkable physiological action of gastrin is its ability to stimulate gastric acid secretion. In addition to this action, gastrin also stimulates pepsin secretion, increase the gastric mucosal blood flow, and stimulate pancreatic enzyme secretion.

Gastrin is synthesized, stored by G cells in the pyloric glands of antral mucosa, and released from G cells. Carrying by the blood, gastrin stimulates the receptors in various organs of the gut. Gastrin has been shown to exist in a variety of sizes.

The initial form of gastrin was composed of 17 linearly arranged L-amino acids with a molecular weight of around 2100 (G-17), which is known as little gastrin. Minigastrin (G-14) consists of the 14 C-terminal amino acid residues of G-17. G-17 can be split enzymatically from big gastrin, which consists of 34 amino acids (G-34) and is the predominant from in circulation. Big-big gastrin has been shown to possess the full physiologic action of the parent molecule. This material is now available as pentagastrin.

With the development of specific and sensitive radioimmunoassay technique, it has been possible to measure directly the concentration of serum gastrin. Depending on the laboratory and technique, the normal basal level of serum gastrin is 50–100 picograms/ml (pg/ml).The level over 200 pg/ml can almost always be considered high. Many patients with Zollinger-Ellison syndrome have serum gastrin levels greater than 1,000–10,000 pg/ml.

1.2. DEFINITION OF ULCER

Ulcers are crater-like sores (generally 1/4 inch to 3/4 inch in diameter, but sometimes 1 to 2 inches in diameter) which form in the lining of the stomach (called gastric ulcers), just below the stomach at the beginning of the small intestine in the duodenum (called duodenal ulcers) or less commonly in the esophagus (called esophageal ulcers).

In general, ulcers in the stomach and duodenum are referred to as peptic ulcers.

It is known that the stomach is a bag of muscle that crushes and mixes food with the digestive "juices" – hydrochloric acid and pepsin. If the lining of the stomach (or duodenum) is damaged in one place or another, the acid and pepsin go to work on the lining as they would on food, breaking it down as though to digest it.

An ulcer is the result of an imbalance between aggressive and defensive factors (*Fig. 1.2*).

Aggressive factors:	Defensive factors:
• H. pylori;	• Mucus, bicarbonate layer;
• Drugs (NSAIDs);	• Blood flow, cell renewal;
• Acid, pepsin;	• Prostaglandins;
• Bile salts.	• Phospholipid.

Figure 1.2. *Pathogenesis of ulcers*

On one hand, too much acid and pepsin can damage the stomach lining and cause ulcers. On the other hand (and more commonly), the damage comes first from some other causes, making the stomach lining susceptible to even an ordinary level of gastric acid.

The stomach defends itself from hydrochloric acid and pepsin by creating a mucus coating (that shields stomach tissue), by producing bicarbonate and by circulating blood to the stomach lining to aid in cell renewal and repair. If any of these functions are impaired it can lead to the formation of an ulcer.

The primary cause of ulcers is the bacterium called Helicobacter pylori (H. pylori) (*Fig. 1.3*). H. pylori is a spiral-shaped bacterium found in the stomach. Unlike other bacterium, H. pylori is able to twist through the layer of mucous that protects the stomach cavity and attach to cells on the surface of the stomach wall, where it produces urease, an enzyme that generates ammonia.

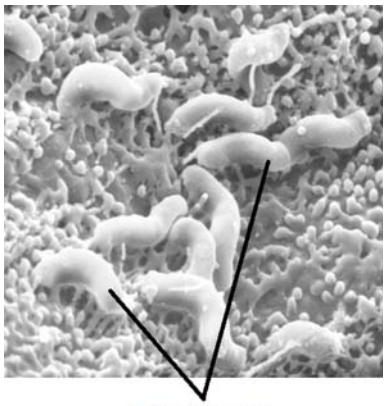


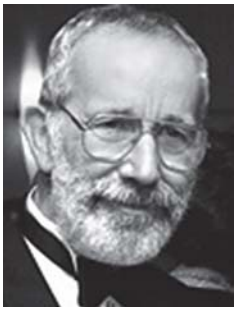
Figure 1.3. *Transmission electron micrograph of Helicobacter pylori*

On October 3, 2005, Sweden Karolinska Medical School announced to grant Australian scientists Barry J. Marshall and J. Robin Warren the Nobel Prize in Physiology or Medicine 2005 for their discovery of pylori Helicobacter pylori, a bacterium caused gastritis and gastric ulcer. Owing to their discovery in 1912, the chronic and incorrigible gastric ulcer could be cured by simply administering antibiotics and other drugs (*Fig. 1.4*).

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, or piroxicam interfere with the stomach's ability to produce mucus and bicarbonate (a chemical produced in the stomach that neutralizes and breaks down the hydrochloric acid and pepsin into substances less harmful). NSAIDs also affect blood flow to the stomach, hinder cell repair and cause the stomach's defense mechanisms to fail.

Lifestyle factors such as smoking, drinking caffeine, consuming alcohol and stress are also associated with ulcers.

The Nobel Prize
in Physiology
or Medicine
(2005)



Barry J. Marshall

J. Robin Warren

Helicobacter pylori Research Laboratory, QEII Medical Centre;
University of Western Australia, Nedlands, Australia

Figure 1.4. *Barry J. Marshall and J. Robin Warren*

Smoking slows the healing of ulcers and makes them likely to recur.

Caffeine stimulates acid secretion in the stomach, thus aggravating the pain of an existing ulcer.

Studies on alcohol consumption and ulcers have been less conclusive, although alcoholic cirrhosis has been linked to an increased risk of ulcers, and heavy drinking has been shown to delay the healing of ulcers.

Although emotional stress is no longer thought to be a cause of ulcers, people with ulcers often report that emotional stress increases ulcer pain. However, physical stress increases the risk of developing gastric ulcers.

1.3. GASTRIC ULCERS

Modified Johnson Classification

For many years ulcers of the stomach and duodenum were classified as a single disease. As a result some of their differing features cancelled out and were concealed in consideration of peptic ulcer as a whole. They are now generally recognized as distinct entities, and considered by many to have different pathogeneses.

Dragstedt's theory that duodenal ulcers are caused by neurogenic acid hypersecretion, and gastric ulcers by acid hypersecretion of hormonal origin, ignores the fact that less than 50 per cent of gastric ulcer subjects are acid hypersecretors.

In the classification of gastric ulcers proposed by H. D. Johnson (1965), gastric ulcer associated with duodenal ulcer represents a separate entity often featuring increased acid secretion, like prepyloric gastric ulcer (*Table 1.1*).

Table 1.1 – The types of gastric ulcers

Type	Location	Acid hypersecretion
I	Lesser curvature, incisura	No
II	Body of stomach, incisura, and duodenal ulcer (active or healed)	Yes
III	Prepyloric	Yes
IV	High on lesser curve, near gastroesophageal junction	No
V	Anywhere (medication induced)	No

Type 1. This is an ulcer in the body of the stomach without abnormality of the duodenum, pylorus or prepyloric region (*Fig. 1.5*).

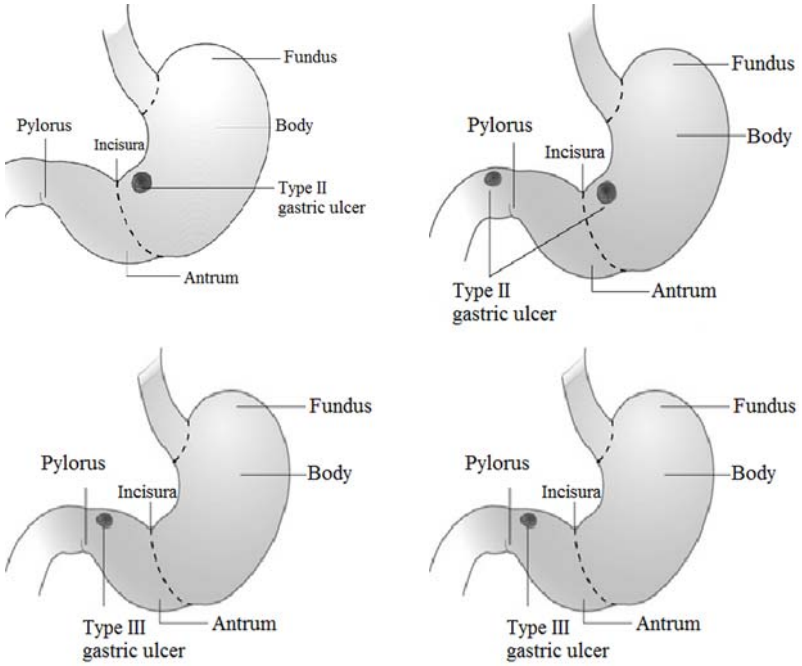


Figure 1.5. *The types of gastric ulcer (modified Johnson classification)*

Type 2. This is an ulcer in the body of the stomach combined with, and probably secondary to, an ulcer or its scar in the duodenum or at the pylorus. Although patients with ulcers of this type usually exhibit well-marked or even gross acid hypersecretion, in many the rate of secretion is low. These ulcers have a bad prognosis. They are very resistant to medical treatment and have a strong tendency to bleed.

Type 3. This is a gastric ulcer close to the pylorus. Lesions in this position which were combined with duodenal ulcers, or with a Type 2 ulcer proximal to them, were all classified as Type 3. Patients with prepyloric gastric ulcers, like those with duodenal ulcers, usually have acid hypersecretion.

Type 4. This is an ulcer in the body near gastroesophageal junction of the stomach.

Hypersecretion ulcers. Type 2 and 3: Gastric ulcers occurring as a complication of duodenal ulcers, and juxtapyloric gastric ulcers, both tend to occur – as do duodenal ulcers – in, hypersecreting individuals, though the onset of pyloric obstruction often modifies these findings in late cases. However, though antral ulcers, like duodenal ulcers, may be caused by hypersecretion, other factors must be considered in ulcers of Type 2.

Hyposecretion ulcers. Type 1: excessive hormonal stimulation may occur in the presence of gastric retention and may help to promote a gastric ulcer of Type 2 as a complication of a duodenal ulcer. Many researchers have shown that prepyloric ulcers occur in patients whose acid secretion averages more than that of healthy people. The mean secretion rate for patients with gastric ulcers of any kind, however, is below normal, for this average has been influenced by the consistently low rate of acid secretion in patients with primary ulcers in the body of the stomach.

Several factors may promote ulcers in persons with acid hyposecretion: 1) associated hyposecretion of mucus, 2) prolonging of the acid attack when gastric retention is present and 3) local slowing of the already-critical rate of mucus secretion which must result when submucosal arteriovenous shunts are opened.

Clinical features

The symptoms and complications of gastric ulcer closely resemble those of duodenal ulcer. The complications would be discussed separately in this chapter.

The principal symptom is epigastric pain. Epigastric tenderness is a variable finding. Compared with duodenal ulcer, the pain in gastric ulcer tends to appear earlier after eating, often within 30 minutes. Vomiting, anorexia, and aggravation of pain by eating are also more common with gastric ulcer. However, the overlap of symptoms between the 2 diseases is so great that historical information does not permit an accurate diagnosis without barium X-ray examination.

If gastric ulcer is accompanied by signs of active or old duodenal ulcer, gastric analysis may show hypersecretion. If gastric ulcer is unrelated to duodenal disease, basal and maximal acid secretion will be low or normal. Achlorhydria is defined as no acid after pentagastrin stimulation. Achlorhydria is incompatible with the diagnosis of peptic ulcer and suggests a malignant gastric ulcer.

Standard gastric analysis. The standard gastric analysis consists of the following: 1) measurement of acid production by the unstimulated stomach under basal fasting conditions; the result is expressed as H+ secretion in mEq/h and is termed the basal acid output (BAO); 2) measurement of acid production during stimulation by histamine (0.04 mg/Kg) or rentagastrin given (6 ug/Kg).The result is expressed as H_2 secretion in mEq/h and is termed the maximal acid ouput (MAO).Usually the normal upper limit of BAO is 6 mEq/h in man,and 4 mEq/h in women, MAO is 40 mEq/h in man, and 30 mEq/h in women.

Both BAO and MAO is more high that the normal upper limits in the most patients with duodenal ulcer, while it is normal or little lower than normal in the patients with gastric ulcer.

The term achlorhydria denotes no acid (pH>6.0) after maximal stimulation. Achlorhydria is incompatible with a diagnosis of benign peptic ulcer. In whom X-ray examination have demonstrated gastric ulcer, this finding would indicate the presence of underlying gastric cancer.

In Zollinger-Ellison synderome, basal acid secretion is often greater than 15 mEq/h, and the ratio of BAO to MAO is characteristically 0.6 or greater. But confirmation of the diagnosis requires direct measurement of elevated serum gastrin levels by immunoassay.

Hollander insulin gastric analysis. Hollander test involves the intravenous administration of regular insulin and measurement of gastric acid secretion. The intravenous injection of regular insulin in dose of 0.2 u/Kg may cause hypoglycemia (blood sugar less than 50 mg %). The hypoglycemia stimulates vagal activity, which results in acid secretion by gastric parietal cells. The procedure is based on the assumption that increased acid found after insulin hypoglycemia is entirely the result of vagal impulses arising from central nervous system stimulation .The Hollander test was used principally to test for completeness of vagotomy postoperatively.

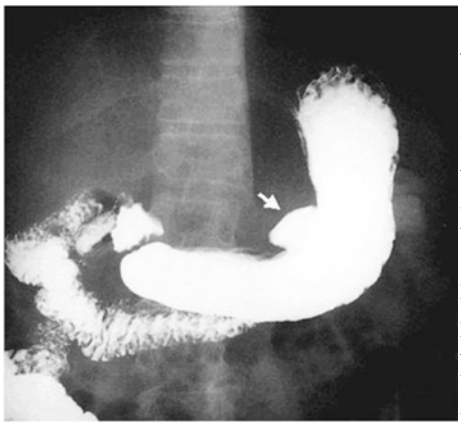


Figure 1.6. *X-ray: gastric ulcer, type I (arrow)*

Upper gastrointestinal X-ray (*Fig. 1.6*) will show an ulcer niche usually on the lesser curvature in the pyloric area. In the absence of a tumor mass, the following suggest that the ulcer is malignant 1) the deepest penetration of the ulcer is not beyond the expected border of the gastric wall; 2) the meniscus sign is present, a prominent rim of radiolucency surrounding the ulcer, caused by heaped-up edges of tumor; and 3) ulcer niche is greater than 2 cm in diameter. Coexistence of duodenal deformity or ulcer favors a diagnosis of benign ulcer in the stomach.

Gastroscopy and biopsy. Gastroscopy should be performed as part of the initial work-up of patients with gastric ulcer to attempt to find malignant lesions (*Fig. 1.7*).

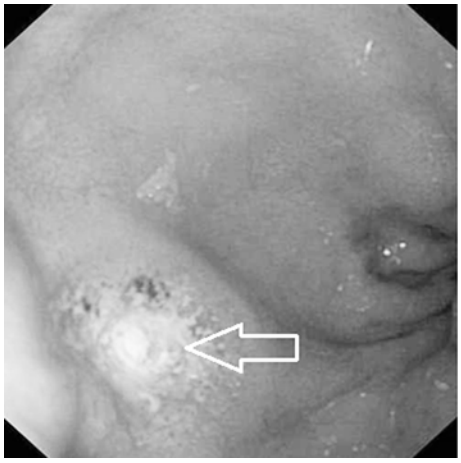


Figure 1.7. *Gastroscopy: gastric ulcer, type I (arrow)*

The rolled-up margins of the ulcer can be distinguished from the flat edges characteristic of a benign ulcer. Multiple (preferably 5–6) biopsy specimens and brush biopsy should be routinely obtained from the edge of the lesion.

The characteristic symptoms of gastric ulcer are often clouded by numerous nonspecific complaints. Atrophic gastritis, chronic cholecystitis, irritable colon syndrome, and undifferentiated functional problems are needed to be distinguishable from peptic ulcer through X-rays, and gastroscopy. These examinations should be always required before making the diagnosis of gastric ulcer. Besides these, one must always consider whether the noncharacteristic complain or a ulcer niche seen on X-ray represent an ulcerated malignant tumor rather than a simple benign ulcer.

1.4. DUODENAL ULCERS

Duodenal ulcers may occur in any age group but are most common in the young and middle-aged (20–35 years). They appear in men more often than women. About 95% of duodenal ulcers are situated within 2 cm of the pylorus, in the duodenal bulb.

Physiologic abnormalities found in patients with duodenal ulcer include the following: 1) increased numbers of parietal and chief cells, resulting in increased acid and pepsin secretion; 2) increased sensitivity of parietal cells to stimulation by gastrin; 3) increased gastric response to a meal; 4) decreased inhibition of gastric release

from the antral mucosa in response to acidification of gastric contents; 5) increased rate of gastric emptying, including decreased inhibition of emptying in response to a specific acid load in the duodenum; and 6) decreased bicarbonate production in the duodenum. Not all abnormalities are found in every patient, and other unknown factors must be important in some cases.

Another theoretic cause of peptic ulcer is decreased resistance of the duodenal mucosa to the action of gastric acid and pepsin. Several other clinical factors are known to be associated with enhanced susceptibility to duodenal ulcer. The disease is more common in individuals with blood group O and in those who fail to secrete blood group antigens A, or B in their gastric juice. Antral gastritis associated with Helicobacter pylori infection is present in a majority of patients with duodenal ulcer. Chronic liver disease, chronic lung diseases and chronic pancreatitis have all been implicated as increasing the possibility of duodenal ulceration.

Clinical features

Pain, the presenting symptom in most patients, is usually located in the epigastrium and is variably described as aching, burning, or gnawing. The daily cycle of the pain is often characteristic. The patient usually has no pain in the morning until an hour or more after breakfast. The pain is relieved by the noon meal, only to recur in the later afternoon. Pain may appear again in the evening, and in about half of cases it arouses the patient during the night. Food, milk, or antacid preaparations give temporary relief. When the ulcer penetrates the head of the pancreas posteriorly, back pain is noted; concomitantly, the cyclic pattern of pain may change to a more steady discomfort, with less relief from food and antacids. Varying degrees of nausea and vomiting are common. Vomiting may be a major feature even in the absence of obstruction.

The abdominal examination may reveal localized epigastric tenderness to the right of the midline, but in many instances no tenderness can be elicited.

The activity of duodenal ulcer and its accompanying symptoms typically remit and recur at intervals of several years. Relapses last for 2–4 months, but the variation is great.

Gastric analysis. Both basic acid output (BAO) and maximal acid output (MAO) are increased.

Upper gastrointestinal series. The changes induced by duodenal ulcer consist of duodenal deformities and an ulcer niche.

Gastroduodenoscopy. It is useful in evaluating patients with an uncertain diagnosis and peptic ulcer those with bleeding from the upper intestine, and those who have obstruction of the gastroduodenal segment and for assessing response to therapy (*Fig. 1.8*).

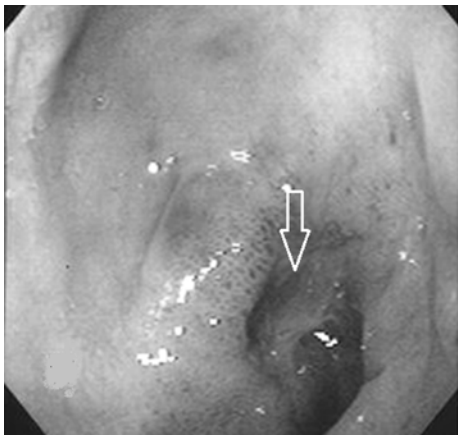


Figure 1.8. *Gastroduodenoscopy: duodenal ulcer (arrow)*

1.5. ULCER PENETRATION

Ulcer penetration refers to penetration of the ulcer through the bowel wall without free perforation and leakage of luminal contents into the peritoneal cavity. Surgical series suggest that penetration occurs in 20 percent of ulcers, but only a small proportion of penetrating ulcers become clinically evident. Penetration occurs in descending order of frequency into the pancreas, gastrohepatic omentum, biliary tract, liver, greater omentum, mesocolon, colon, and vascular structures.

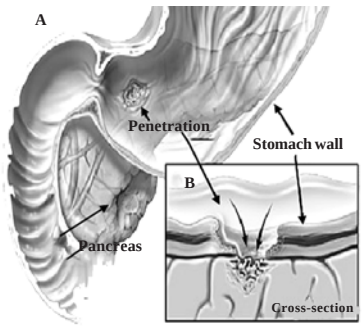


Figure 1.9. T*he scheme of penetration of gastric ulcer*

Antral and duodenal ulcers can penetrate into the pancreas. Penetration can also involve pyloric or pre pyloric ulcers penetrating the duodenum, eventually leading to a gastroduodenal fistula evident as a "double" pylorus. A long-standing ulcer history is common but not invariable in patients who develop penetration.

The scheme of penetration of stomach ulcers is presented in picture (*Fig. 1.9*).

Clinical features

Intense persistent pain. Penetration often comes to attention because of a change in symptoms or involvement of adjacent structures. The change in symptom pattern may be gradual or sudden; it usually involves a loss of cyclicity of the pain with meals, and loss of food and antacid relief. The pain typically becomes more intense, of longer duration, and is frequently referred to the lower thoracic or upper lumbar region.The diagnosis of penetrating ulcer is suspected clinically when an ulcer in the proper region is found. Mild hyperamylasemia can develop with posterior penetration of either gastric or duodenal ulcer, but clinical pancreatitis is uncommon. Penetration can be associated with a wide array of uncommon complications including perivisceral abscess (evident on CT or ultrasonography), erosion into vascular structures leading to exsanguinating hemorrhage (aortoenteric fistula), or erosion into the cystic artery .

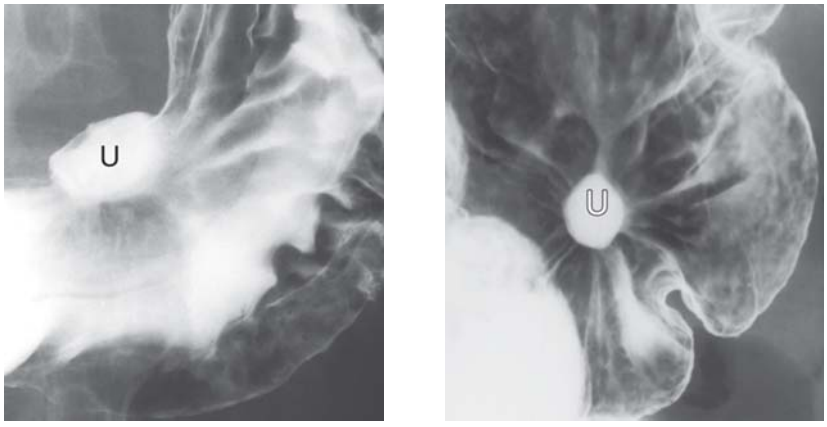


Figure 1.10. *X-ray: gastric ulcers (barium collects in ulcer crater)*

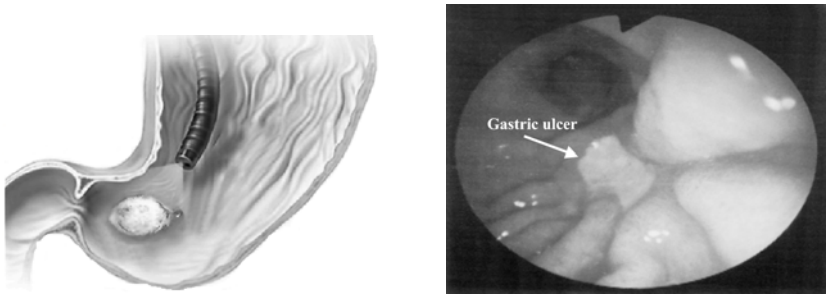


Figure 1.11. *Endoscopic view of ulcer*

Rare biliary tract complications include erosion into the biliary tree with choledochoduodenal fistula, extra hepatic obstruction, or hematobilia. Fistulization into the pancreatic duct has also been reported with penetrating duodenal ulcer fistulae are seen with greater curvature gastric ulcers, particularly marginal ulcers. Typical features of this complication include pain, weight loss, and diarrhea; feculent vomiting is an uncommon, but diagnostic symptom. A duodenocolic fistula can also occur.

Diagnosis confirmed by X-ray (*Fig. 1.10*), endoscopy (*Fig. 1.11*), CT or MRI.

1.6. PYLORIC STENOSIS

Pyloric stenosis is a narrowing of the outlet stomach (*Fig. 1.12*). Stenosis of pyloric part of the stomach and duodenum due to ulcers arise as a result of scarring and morphological changes around an ulcer. Narrowing, disturbance of the coordinated motility of pylorus as a result of ulcer creates an obstacle to the normal movement of stomach content to the duodenum.

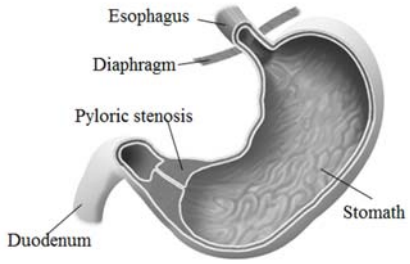


Figure 1.12. *Pyloric stenosis*

The pyloric orifice is 0,5–0,7cm in diameter. The mucosa of pyloric part of stomach is thickened with rough folds. Muscular fibers are hypertrophied and solid.

During decompensation stage the muscular layer of stomach becomes thinner and the pyloric orifice narrows to a few millimeters. Microscopically atrophy of mucosa and muscular fibers, vessels sclerosis is seen.

Clinical stages of stenosis are distinguished:

1. Compensation stage.
2. Subcompensation stage.
3. Decompensation stage.

Clinical features

The first signs of stenosis can be seen eight-ten years after the onset of the peptic ulcer disease, there is mainly narrowing, rigidity and disturbance of the activity of the pylorus, which creates a barrier for transition of stomach content to the duodenum.

At the **compensation** stage, the hypertrophy of the wall of stomach develops. Thereupon gastric content does pass through the narrowed area of stomach but passes slowly. In this stage, patient usually complains of a feeling of discomfort in the epigastric area after food intake with periodic vomiting of sour gastric contents. X-ray – on an empty stomach in the stomach is determined 200–300 ml of fluid; the stomach is of normal size or slightly enlarged. The evacuation of barium suspension is timely or slowed down to 6–12 hours.

At the **subcompensation** stage muscular layer of stomach becomes thinner. Evacuation disorders are increased. In this stage of the disease patients usually complain of permanent feeling of discomfort in epigastric region, nausea and vomiting. Vomiting becomes systematic (once or twice on a day). When examined at this stage, the symptom of "splash noise" is often detected, diagnosed on an empty stomach or a few hours after eating. X-ray: the tone of the stomach is reduced, its capacity is increased, the peristalsis is sluggish. An empty stomach in the stomach with more than 500 ml of liquid. Evacuation of the barium suspension is slowed down to 10–12 hours.

At the **decompensation** stage, the clinical signs appear quickly. There are disturbances in the general condition of the patient, considerable loss of weight (30–40%), acutely expressed dehydration, hypoproteinemia, hypocalcaemia, azotemia and alkalosis. In case of prolonged disease, as a result of progression of disturbances of metabolism, there can be convulsive syndrome (gastric tetany). Vomiting in this stage is not always considered to be a typical sign, in fact patients often stop eating, and the stomach considerable increases in size and atrophy of wall is seen. In such patients, it is possible to define the contours of the stretched stomach in the epigastric region, which has slow peristalsis. 1.5–2 litres of food with a putrid smell are removed with a gastric tube. There can be considerable disturbances of electrolyte metabolism. X-ray: there is an increase in the size of the stomach and its lowering, a decrease in tone, a sluggish peristalsis. Evacuation is dramatically slowed down to 24 hours or more.

In the decompensated stage of stenosis, the stomach is not completely absorbed from food. Vomiting becomes systematic, pain is permanent. The severity in the epigastric region disappear only after vomiting or rinsing of the stomach. The general condition deteriorates sharply, exhaustion and dehydration increase, seizures and symptoms of azotemia (weakness, headache, loss of appetite, thirst, stench from the mouth, oliguria, seizures, etc.) appear. Determined constant "noise splash" on an empty stomach, develops a humoral syndrome: hypochloremia, hyperazotemia, alkalosis; there is a thickening of the blood.

As a result of repeated and profuse vomiting, in which hydrochloric acid is removed from the body, and with it a chlorine component, chlorine ions are drawn from the blood to form hydrochloric acid. The released sodium ions enter into a compound with bicarbonates, alkalosis develops. Alkalosis, azotemia, a violation of calcium metabolism contribute to an increase in the excitability of the neuromuscular system. With increased muscular excitability, positive are: **Khvostek's** sign – reduction of facial muscles of the face when struck by a hammer in the projection of

the trunk of the facial nerve or its branches; **Goffman's** sign – unbearable pain when tapping a hammer in the region of the exit of branches of the trigeminal nerve; **Trusso's** sign – convulsive evidence of fingers under pressure on the median nerve on the shoulder or forearm in the form of "hand of an obstetrician"; **Bechterew's** sign is the flexion of the fingers when striking the back surface of the foot in the region of III and IV metatarsus. Sometimes there is diplopia due to cramps in the eye muscles; myotonia – the patient cannot flex and unbend the hands and feet. With the growth of the hypochloraemia clinic, painful tonic spasms of skeletal muscles arise, spontaneous reduction of the fingers in the form of the "hand of an obstetrician" (**Poole's** sing), tonic convulsions of the whole body with opisthotonus and trismus. In severe cases, a deep coma develops.

The methods of investigations

Laboratory studies

• CBC count (leukocytosis with left shift is found in most cases.); biochemical parameters of blood, blood and urine analysis; coagulogramm; Ht (hematocrit, parity of volumes of uniform elements and plasmas of blood); blood group, rhesus-factor (Rh-factor);

• Serum gastrin levels (gastrin levels greater than 1000 pg/mL are suggestive of gastrinoma).

• H. pylori infection testing:

‣ Serum H. pylori antibody detection: Antibodies (immunoglobulin G [IgG]) to H. pylori can be measured in serum, plasma, or whole blood

‣ Urea breath tests: Urea breath tests are used to detect active H. pylori infection by testing for the enzymatic activity of bacterial urease. In the presence of urease produced by H. pylori, labeled carbon dioxide (heavy isotope, carbon-13, or radioactive isotope carbon-14) is produced in the stomach, absorbed into the bloodstream, diffused into the lungs, and exhaled.

‣ Fecal antigen tests: Fecal antigen testing is used to identify active H. pylori infection by revealing the presence of H. pylori antigens in stools. This test is more accurate than antibody testing and less expensive than urea breath tests.

• Hypochloremia is a relatively rare but severe and life-threatening complication of peptic ulcer of the stomach and duodenum, found in 0.5–1.5% of cases.

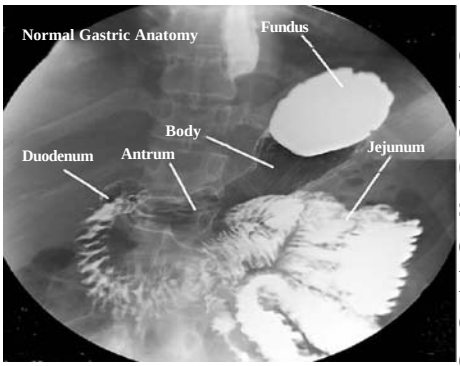


Figure 1.13. *X-ray: normal gastric anatomy*

X-ray examination (*Fig. 1.13*). In the compensation stage, the size of stomach is normal, its peristalsis is deep, increased, evacuation of contents occurs in not more than 6 hours. In the stage of subcompensation the size of stomach increases, peristalsis is decreased; evacuation takes up to 12 hours. During decompensation stage the stomach is considerably dilated like a sack and deformed, the contrast stays for long (more than 24–48 hours) (*Fig. 1.14*).

Gastroscopy with biopsy is a very informative method of examination of such patients. By this method it is possible to determine the reason and degree of stenosis and also the state of mucosa of the stomach (*Fig. 1.15*).

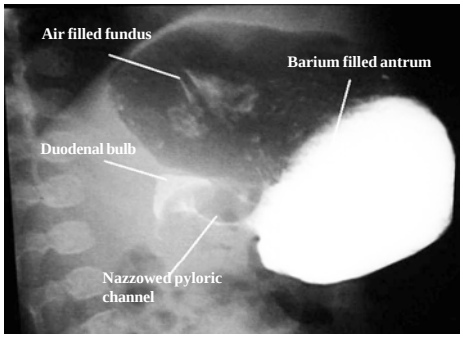


Figure 1.14. *Pyloric stenosis is seen in newborns within the first months. There is a 4:1 male ratio and is due to hypertrophied musculature at the pylorus*

Differential diagnosis

Functional gastrostasis is more frequently seen in women. In that there, is absence of some organic changes in the area of pyloric part of stomach or in a duodenum, which can be exposed during gastroscopy.

Carcinoma of the stomach as a rule also does not cause special difficulties. A diagnosis is finally confirmed by histological examinations of the biopsy material taken during endoscopy.

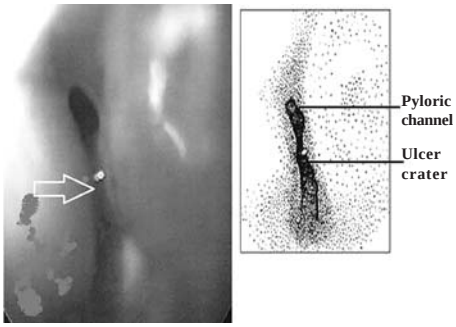


Figure 1.15. *Gastroscopy examination degree of stenosis*

Conservative and surgical treatment. Treatment for chronic ulcers involves conservative therapy and surgical intervention according to the indications.

Conservative treatment of peptic ulcers, basically, includes three components:

• Antibiotic usually includes amoxicillin or clarithromycin, sometimes tetracycline.

• Antimicrobial drug usually includes metronidazole.

• Proton pump inhibitors (omeprazole, rabeprazole, etc.) or bismuth preparations.

This treatment regimen is used for 7–14 days and allows achieving destruction of Helicobacter in 90% of patients. The patient should know that he must perform the prescribed treatment in full. Patients are also assigned physiotherapeutic treatment and recommended sanatorium treatment in sanatoria with medicinal mineral waters.

Particular qualities:

1. Rare; most uncomplicated ulcers heal within 12 weeks.
2. If don't, change medication, observe addition 12 weeks.
3. Check serum gastrin (antral G-cell hyperplasia or gastrinoma).
4. Esofogogastrodoudenscopy: biopsy all 4 quadrants of ulcer (rule out cancer) if refractory.

Absolute indications for surgical treatment are urgent: perforation of the ulcer, profuse bleeding, not docking conservatively, and delayed: decompensated stenosis of the outlet of the stomach, unstable hemostasis or recurrent bleeding.

Relative indications: refractory ulcers to conservative therapy or often recurrent (more than 2 times a year for complex treatment), with complications in the

history, as well as ulcers in the cardia, large curvature and in the pyloric part of the stomach, which can not be conservatively treated during 1 weeks.

Surgical treatment of peptic ulcer

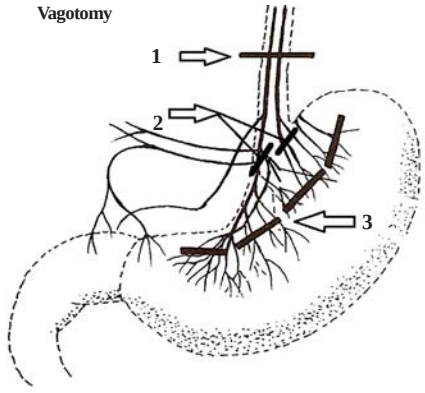
In 1811, Theodor Billroth successfully performed the first gastric resection with gastroduodenostomy for gastric carcinoma complicated with pyloric obstruction in Vienna. In 1812, von Rydigier performed the same procedure firstly for peptic ulcer. By 1940, the term "subtotal gastrectomy" was interpreted as denoting removal of the distal two-thirds or three-fourths of the stomach.

After resection of the stomach, the continuity of the gut can be restored by anastomosis of the remaining portion of the stomach to the duodenum (gastroduodenostomy, or Billroth I anastomosis) or by anastomosis, there are different choices for gastrojejunostomy, the surgeon may bring the jejunal loop up to the gastric remnant either anterior to the transverse colon (Moynihan's operation, and V. Eishlsberg's operation) or posteriorly through a hole in the transverse mesocolon (Hoffmeister's operation, and Ploy's operation).

For duodenal ulcer, Billroth II anastomosis may be preferable, because the recurrent rate of Billroth I is higher than Billroth II. Billroth I is the first choice for gastric ulcer. When creating a Billroth II anastomosis, which kind of gastrojejunostomy should be elected is depended on surgeon's personal experiences since another method is satisfactory.

Physiologically, subtotal gastrectomy removes the antrum which is the major source of gastrin secretion. As result, it decreases the gastric acid secretion stimulated by gastrin. The procedure removes the part of the parietal cell mass by excision of the half aråa of the gastric body. As result, it decreases the gastric acid secretion stimulated directly by vagus nerve.

In 1943 and 1949, Drapanas reported his idea that pathogenesis of duodenal ulcer was associated with increased acid secretion and vagus section would be beneficial experience about vagotomy. After long period of development, vagotomy has been accepted in widely use in the western. In general, vagotomy includes three basic types, truncal vagotomy, selective vagotomy and superselective vagotomy (*Fig. 1.16*).



Fugure 1.16. *Types of vagotomy:*
1 – truncal vagotomy;
2 – selective vagotomy;
3 – superselective vagotomy

Truncal vagotomy. Truncal vagotomy consists of resection of 2 cm segment of each vagal trunk as it enters the abdomen on the distal esophagus. Resection of truncal vagus causes a great reduction of gastric acid secretion, but it also greatly suppresses gastric motility due to vagal enervation of the entire stomach, and produces the disturbances of the remainder of the abdominal viscera due to denervating these organs, which often

present as diarrhea and gallstones. The method of drainage must be performed for-delayed emptying of the stomach. Because the denervation of the vagal fibers in other abdominal viscera is still a big problem, this operation is not used very often.

The most common types of surgery for ulcers are vagotomy, antrectomy and pyloroplasty. Vagotomy involves cutting the vagus nerve that transmits messages from the brain to the stomach. This interruption reduces acid secretion. Antrectomy removes the lower part of the stomach (antrum) which produces a hormone that stimulates the stomach to secrete digestive juices. This enlarges the opening into the duodenum and small intestine (pyloris), enabling contents to pass more freely from the stomach. Pyloroplasty may be performed with a vagotomy.

Selective vagotomy. In selective vagotomy, each abdominal vague is transected at a point just beyond its bifurcation into gastric and extra gastric divisions. Thus, the hepatic branch of the anterior vagus and the celiac branch of the posterior vagus are maintained. The drainage procedure is still necessary in selective vagotony. Two kinds of drainage procedures can be chosen, pyloroplasty and gastrojejunostomy.

The pyloroplasty, originally introduced by Heiineke (1816) and Mikulicz (1811), can provide a large gastric outlet and enhance emptying of the stomach. There are multiple techniques for pyloroplasty, Heineke-Mikulicz technique and Finney technique are most commonly in use today. If gastroenterostomy is chosen for delayed emptying of the stomach, the anastomosis should be performed in the distal antrum, immediately proximal to the pylorus.

Superselective (highly selective) vagotomy. The newer operation was developed for the treatment of peptic ulcer. The technique spares the main nerves of Latarjet but divides al vagal branches that terminate on the proximal two-thirds of the stomach. The denervation of the vagal fibers is limited to only the proximal stomach (roughly to the area of parietal cells mass) with preservation of the innervation of the antrum. Since antral innervation is preserved, gastric emptying is relatively unimpaired, and a drainage procedure is unnecessary. Physiologically, all types of vagotomy eliminate direct vogal stimulation of the parietal cells, as the result, gastric acid secretion stimulated by vagus is decreased; gastric acid secretion stimulated by gastrin is also decreased since gastrin release from antrum is diminished resulting from vagus resection. Basal and postprandial serm gastrin levels are increased because of the rise in gastric pH. Basal and stimulated acid secretion is both reduced to about one-tired of preservation of the entire gastric reservoir capacity. The principal disadvantage is recurrent ulceration in about 10% of patients. The reason mainly is incomplete vagotomy, which lead to great emphasis on this procedure. In addition to the problems of surgical technique, variations in the vagus at the esophageal hiatus and adjacent to the abdominal esophagus and on the stomach make complete interruption of al vagal fibers impossible in some patients.

Antrectomy and vagotomy. This operation entails a distal gastrectomy of 50% of the stomach, with the line of gastric transection carried high on the lesser curvature to conform to the boundary of the gastrinproducing mucosa. Excision of the antrum removes gastric acid secretion stimulated by gastrin; vagotomy eliminates

direct vagal stimulation of the parietal cells. The procedure combines gastrectomy and vagotomy in both surgical technique, and effects to peptic ulcer. The procedure of antrectomy and vagotomy is associated with a low incidence of marginal ulceration and a generally good overall outcome.

The terms antrectomy and hemigastrectomy are loosely synonymous. The proximal remnant may be reanastomosed to the duodenum (Billroth I anastomosis, *Fig. 1.17*) or to the side of the proximal jejunum (Billroth II anastomosis, *Fig. 1.18*).

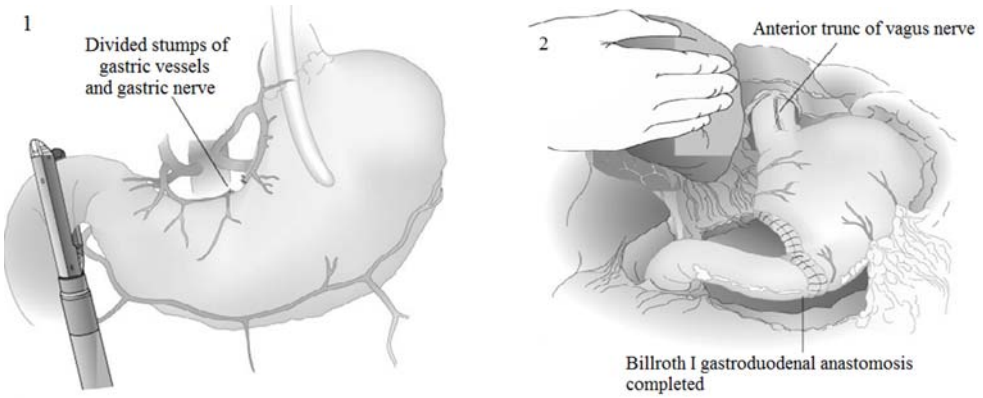


Figure 1.17. *Billroth I procedure*

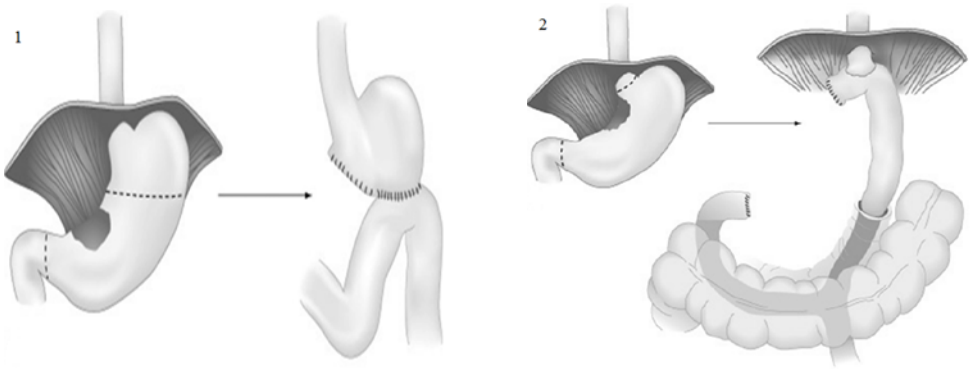


Figure 1.18. *Billroth II (1) and R-Y limb gastrectomy (2) procedures*

The Billroth I technique is most popular, but there is no conclusive evidence that the results are superior. When creating a Billroth II anastomosis, the surgeon may bring the jejunal loop up to the gastric remnant either anterior to the transverse colon or posteriorly throgh a hole in the transverse mesocolon. Since either method is satisfactory, or antecolic anastomosis is elected in most cases because it is simpler.

• Least common (5% of all gastric ulcers).

• Ulcers 2–5 cm from cardia can be treated with distal gastrectomy, extending resection along the lesser curvature and Billroth I (Pauchet–Shoemaker's procedure).

• Ulcers closer to GEJ, tongue-shaped resection high onto lesser curve (Csende's procedure with Roux-en-Y reconstruction) (*Fig. 1.19*).

Giant Gastric Ulcer

• Giant gastric ulcer: >3 cm; 30% malignancy risk.

• Subtotal gastrectomy with Roux-en-Y (high morbidity and mortality).

• Kelling-Madlener procedure: less aggressive, antrectomy, Billroth I reconstruction, bilateral truncal vagotomy, leave ulcer, multiple biopsies, cautery of ulcer.

Surgical treatment of penetration ulcer

1. Reduce gastric acidity:

• Antisecretory drugs (proton pump inhibitors, H2 receptor antagonists etc.): reduce histamine production, which also blocks effects of acetylcholine, and gastrin.

• Antibiotics to get rid of H. pylori infection.

• Discontinue smoking.

2. Surgery (*Figs. 1.18–1.19*):

• Last resort.

• Most applicable to complications that don't respond to drug therapy.

• Procedure involves reduction of acid secretion while ensuring gastric drainage.

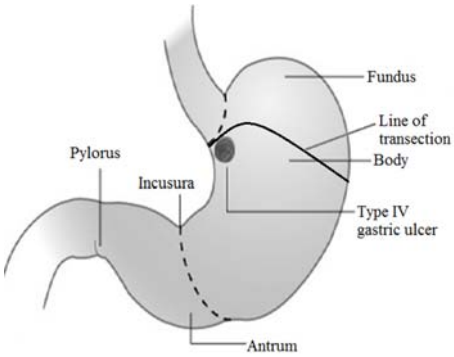


Figure 1.19. *Csendes resection (line of transection; Roux-en-Y anastomosis)*

Duodenal ulcers

The main task of routine surgical treatment for peptic ulcer is the creation in the postoperative period of conditions for the elimination of aggression factors in the gastroduodenal region with a simultaneous decrease in mortality and the maximum reduction of side effects. With ulcer of the duodenum - this effect on the acid-producing zone, the effectiveness of the operation is determined by the level of suppression of gastric secretion; with gastric ulcer – the effect on the zone of ulcerative infiltrate, which further allows normalizing trophic disorders and creating conditions for stabilizing histostructural changes in the gastric mucosa. In the structure of surgical interventions in duodenal ulcer, the most justified in the dominance of the nervous mechanism of acid regulation are selective proximal vagotomy, selective or truncal vagotomy (*Fig. 1.20*) with removal of the ulcerous substrate or its excretion in the lumen of the digestive tract and various variants of duodeno- or pyloroduodenoplasty in depending on the performed vagotomy.

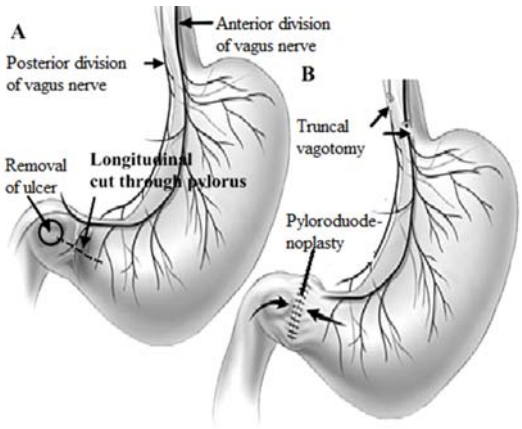


Figure 1.20. R*emoval of ulcer (A), pyloroplasty and truncal vagotomy (B)*

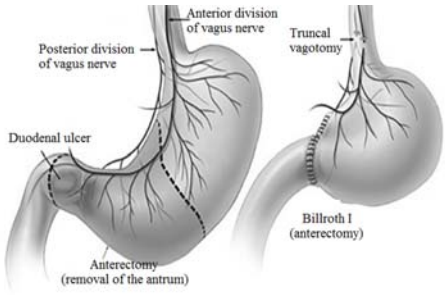


Figure 1.21. *Antrectomy with Billroth I and truncal vagotomy*

The prevalence of the humoral link of the regulatory mechanisms, which is expressed by the hyperplasia of the gastrin-producing cells of the antral part of the stomach and the simultaneous decrease in the amount of somatostatin-producing cells, serves as an indication for performing subdiaphragmatic truncal vagotomy with antrumectomy as an operation that acts simultaneously on two mechanisms of acid regulation in the stomach: the nervous and humoral (*Fig. 1.21*).

Surgical treatment of ulcerative stenosis of the outlet stomach

Preparation of patients for operation: correction of metabolic disturbances, such patients must receive transfusion of fluids up to 2,5–3 1 per day which contain the ions K+, Na+, Ca++, amino acid and glucose; plasma, albumin. Twice daily decompression and washing of stomach with anti-ulcer therapy is done. Effective preoperative preparation in such patients requires 5–7 days, sometimes even more.

The choice of operation method depends on many factors: degree of stenosis, secretory and motility functions of stomach, age of patient, presence of accompanying diseases etc. In the compensated and subcompensated stages of stenosis and when functions of stomach are preserved, it is possible to perform organsaving drainage operations or minimal resection of stomach. With increase in the signs of stenosis and disturbance of basic functions of stomach, the volume of operation must be increased to resection by the Billroth's methods.

Stomach resections and vagotomy:

• Billroth I – gastro-duodenoanastomosis end-to-end.

• Billroth II – gastro-jejunoanastomosis end-to-side with blind closure of duodenum.

• Selective or highly selective vagotomy – denervation of parietal gastric cells.

Postoperative complications:

• Gastric atony ~ 50%.
• Alkaline gastritis.
• Recurrent ulcers ~ 2%.
• Diarrhea ~ 16%.
• Dumping syndrome ~ 14%.
• Bilious vomit ~ 10%.
• Anemia ~ 12%.
• B12 deficiency ~ 14%.
• Folate deficiency ~ 32%.

Postvagotomy complications:

• Diarrhea ~ 2%.
• Dumping syndrome ~ 2%.
• Bilious vomiting < 2%.

1.7. POSTOPERATIVE COMPLICATIONS OF SURGERY FOR PEPTIC ULCER

Postoperative complications after gastrectomy

In our clinics, we use to the following classification of postresection syndromes:

I. Functional disorders.

II. Organic disorders.

Functional disorders include: dumping syndrome, functional syndrome leading and withdrawal hinge syndrome, hypo- and hyperglycemic syndrome, and post-resection dystrophy; to **organic** – disorders due to mechanical causes (operation defects): a) mechanical syndrome of the resulting loop, b) anastomoses; 2) disorders, which are based on inflammatory processes: a) cholecystitis, b) hepatitis, c) pancreatitis, d) enterocolitis, e) peptic ulcers of stump of the stomach and jejunum. In addition, we single out early and late postoperative complications.

Early complications: postoperative hemorrhage, duodenal stump leakage, anastomosis leakage, obstruction, and gastric retention may develop in the immediate postoperative period.

Postoperative hemorrhage. Within 24 hours after operation, small volume of dark red or coffee grounds' gastric juice may be sucked from nasogastric tube. The volume usually is less than 100–300 ml/d. It should disappear during the second to third days after operation. Massive blood sucked from nasogastric tube, or severe melena is the indication of postoperative hemorrhage, which may be due to bleeding at the suture line of gastrojejunostomy of gastroduodenostomy, or may be due to failure to control bleeding from ulcer if lesion is left in the place. Most patients with this complication can be cured by nonoperative managements including prolonged fasting, hemostatic, and blood transfusion. But reoperation is indicated if blood loss is more than 1500 ml in 24 hours, or shock occurs.

Duodenal stump leakage. Blowout of the duodenal stump is the most common cause of death after Billroth II gastrectomy. This complication can be minimized by resorting to catheter drainage of the duodenum if the duodenal closure is not satisfied due to duodenal scarring and intiammation. Equally important is selection of vagotomy with drainage procedure in preference to gastric rescction in patients with a badly damaged or inflamed duodenum. Obstruction of the afferent limb of the gastrojejunostomy may contribute to this complication by increasing intraluminal pressure in the duodenum.

The clinical picture is characterized by sudden severe upper abdominal pain during the third to sixth days after surgery. The pain often radiates to the shoulder, and the patient develops abdominal rigidity, high fever, and leukocytosis.

Immediate reoperation is mandatory. A sump device should be placed in the region of the leaking duodenal closure. Spontaneous closure usually occurs if the patient survives the acute phase; if it does not, the fistula should be surgically closed after the patient has been stable for 4–6 weeks.

Anastomosis leakage. Anastomosis leakage usually occurs during the fifth to seventh days after operation, and it may occur at the gastrojejunstomy (Billroth II

anastomosis) or at gastroduodenostomy (Billroth I anastomosis). Both result in peritoneal spoilage with gut contents and are associated with peritonitis. Leakage form the suture line is most commonly caused by ischemia or by problems of suture technique. Nonoperative managements are considered firstly. Some patients may need reoperation to repair leakage.

Postoperative obstructions. According to the anatomic position, postoperative obstruction can be divided into anastomotic obstruction, afferent loop obstruction and efferent loop obstruction.

Anastomotic obstruction. Anastomotic obstruction occurs following Billroth I gastrectomy (gastroduodenostomy). The diameter of anastomosis between the remaining portion of the stomach and the duodenum is limited by the lumen of the duodenum. The problems of surgical suture and tissue edema may cause the obstruction of the anastomosis. The clinical features are the gastric stasis and vomiting after eating, the vomitus usually does not contain bile. Barium X-ray examination may demonstrate the diagnosis. If conservative treatment for short period does not relief obstruction, reoperation and re-anastomosis is indicated.

Afferent lop obstruction. Afferent loop obstruction occurs only after Billroth II gastrectomy (gastrojejunostomy). It may occur as an acute complete obstruction, or as a chronic incomplete problem. Obstruction can result from sharp angulation or kink at the gastrojejunstomy, inflammation secondary to an anastomotic leak, fat necrosis. If the transected edge of the stomach is sewn to the jejunum on a line that is not parallel to the antimesenteric border of the jejunum, the anastomosis is likely to twist and obstruct.

Acute complete obstruction of the afferent loop is a closed-loop obstruction, characterized by sudden and severe epigastric pain, frequent vomiting without bile, and severe tenderness of right upper quadrant. In chronic incomplete obstruction of the afferent loop, bile and pancreatic juices distend the partially obstructed afferent part, especially after eating. The feature is that abdominal pain and vomiting with bile occur at 15–30 minutes after eating. The meal itself is usually niot vomited because it enters the efferent part of loop without difficulty. Chronic incomplete obstruction of the afferent loop is also termed afferent loop syndrome.

All patients with acute complete obstruction should undergo emergency operation. But medical management may be considered for afferent loop syndrome. Reoperation is indicated if symptoms are severe and persistent. The afferent and efferent parts of loop may be anastomosed side to side. A Billtroth II anastomosis can be converted to a Billroth I anastomosis or a Roux-en-Y gastrojejunostomy.

Efferent loop obstruction. Obstruction of the efferent part of gastrojejunostomy may be due to the same causes responsible for the afferent part obstruction. In addition, obstruction of the efferent part of loop may be due to herniation of small bowel through the space behind the gastrojejunostomy unless this space is obliterated. The clinical manifestations are the presentation of high jejunum obstruction, and vomitus contains bile. Emergency operation should be considered if symptoms do not relief.

Gastric retention. An occasional patient is unable to tolerate oral feedings when they are started 4 or 5 days after surgery. If this condition is due to edema of

the stump, resolution will usually occur if the stomach is decompressed for several more days. If improvement is slow, balloon dilatation by an endoscopy may be helpful.

Late complications. Late complications may occur at several months or years after operation.

Anastomotic ulcer. Anastomotic ulcer is recurrent ulcers, which is nearly always locates immediately adjacent to the anastomosis on the intestinal side (marginal ulcer). More than 90% develops after Billroth II subtotal gastrectomy for duodenal ulcer, and it is unusual after gastrectomy for gastric ulcer.

The usual complaint is upper abdominal pain, which is often aggravated by eating and improved by antacids. About a third of patients with anastomotic ulcer will experience massive gastrointestinal hemorrhage. The common cause of anastomotic ulcer after gastrectomy is inadequate gastric resection. Another common cause found in patient received Billroth II gastrectomy is too long afferent loop, which produces considerable absorption of alkaline pancreatic and biliary secretions before these juices reach the anastomosis. H_2 receptor blocker (cimetidine) or proton pump blocker (omeprazole, etc.) will cause most marginal ulcers to heal, but recurrences are common, re-gastrectomy will be indicated in the most cases.

Dumping syndrome. Early dumping syndrome occurs within 10–20 minutes of eating and seems to be most common after milk with sugar or a carbohydrate meal. "Symptoms of the dumping syndrome" are noted to some extent by most patients who have an operation that impairs the ability of the stomach to regulate its rate of emptying . The sudden emptying of hyperosmotic material into jejunum may bring about a large inflow of extracellular fluid into the jejunum. This rapid fluid shift may result in decreased blood volume, increased splanchnic blood flow, decreased blood pressure, and increased hematocrit. Patients may experience palpitation, weakness, sweating , dyspnea, naused and vomiting, diarrhea, abdominal cramps, even syncope. The degree of severity varies widely, and not all symptoms are reported by all patients. The patient must lie down for 30–40 minutes until the discomfort passes. Within several months to one year, however, dumping correlates loosely with the size of the gastrointestinal anastomosis, and preoperative psychology instability.

Diet therapy to reduce jejunal osmolality is successful in all but a few cases. The diet should be low in carbohydrate and high in fat and protein content. Meals should be taken dry, with restricting all intake of fluid during meals. Anticholinergic drugs may be of help in some patients. If dumping symptoms are refractory to dietary and drugs therapy, further surgery may be considered. Good results have been reported following conversion of Billroth II into Billroth I anastomosis and with the insertion of a reversed 10 cm segment of small intestine at the gastric outlet.

The late dumping syndrome occurs in 2–4 hours after eating. This condition mimics early dumping syndrome, but the clinical features are caused by hypoglycemia. The etiology may be the same as early dumping syndrome. After eating, large amount of food flow into jejunum rapidly, resulting in rapid absorption of sugar and hyperglycemia. Hyperglycemia stimulates more insulin, which produce hypoglycemia. The patient obtains relief by eating sugar immediately after the symptoms of hypoglycemia occurs.

Alklige reflux gastritis. Reflux of duodenal juices into the stomach is an invariable and usually innocuous situation after operations that interfere with pyloric function, but in some patients, it may cause marked gastritis. Bile salts may destroy gastric mucosal barrier. The principal symptoms are:

1. Persistent epigastric burning pain, which is getting worse after meal, antacids do not relief pain.

2. Vomiting with bile.

3. Weight loss, stools may be positive when tested for occult blood, but melena or hematemesis is rare. The diagnosis is depended on endoscopic and biopsy demonstration of an edematous inflamed gastric mucosa. Since a minor degree of gastritis is found in most patients after gastrectomy, the endoscopic linings are to some degree nonspecific. There appears to be a correlation between the amount of bile reflex and a way to select patients for corrective operation.

Roux-en-Y gastrojejunostomy with a 40 cm efferent jejunal loop is the treatment of choice. About 75–95% of patients experience a satisfying result.

Nutritional disturbances

Weight loss and malabsorption. Some patients gain weight when gastrectomy relieves ulcer discomfort, but on the average, a 5–10% of patients have weight loss. The major factors than can contribute to malnutrition after gastrectomy are as follows; small gastric reservoir after the most area of stomach is removed, a decreased fat absorption caused by uncoordinated mixing of food and pancreatic enzymes in the bowel, and blind loop syndrome. Diet therapy and oral nutritional support may be needed in the patients.

Anemia. Anemia after gastrectomy is due to a nutritional deficiency of iron, vitamin B_{12} or folate. Iron deficiency plays the most important role in the development of chronic anemia, but anemia may be the result of any combination of iron, vitamin B_{12}, and folate deficiencies. Before this diagnosis is accepted, the patient should be checked for blood loss, marginal ulcer, or an unsuspected tumor. Iron deficiency anemia develops in about 30% of patients within 5 years after gastrectomy. It is caused by failure to absorb food iron bound in an organic molecule. Inorganic iron, ferrous sulfate or ferrous gluconate, is indicated for treatment and organic molecule. Inorganic iron, ferrous sulfateor, ferrous gluconate is indicated for treatment and is absorbed normally after gastrectomy. Megaloblastic anemia is due to deficiency absorption of vitamin B_{12}, which is the result of a deficiency of the intrinsic factor after gastrectomy. Vitamin B_{12} can be given to cure megaloblastic anemia.

Steatorrhea. Steatorrhea is the loss in the stool of more than 7% of the total amount of fat ingested, which is occasionally seen after Billroth II gastrectomy. In this situation, bypass of duodenum may interfere with mixing of bile and pancreatic lipase with ingested fat. Some patients have afferent loop stasis; overgrowth of bacteria in the afferent limb may cause the blind loop syndrome, resulting in malabsorption and steatorrhea.

Bone Disease. Bone disease usually occurs in 5–10 years after gastrectomy, and is more commonly observed in women than men. Osteomalacia and osteoporosis

are common findings. Malabsorption of vitamin D or calcium rather than their decreased dietary intake is responsible for these postoperative bone diseases.

Postoperative complications after vagotomy

Postvagotomy diarrhea. The daily frequency of bowel movements is increased in about two thirds of patients who have had a truncal vagotomy. But only about 5–10% of patients who have severe diarrhea and require treatment with antidiarrheal agents at some time. The diarrhea may occur two or three times every week or may be episodic, in which case the onset is unpredictable after symptom free intervals of weeks to months. An attack may consist of only one or 2 watery movements or, in severe cases, may last for a few days. Other patients may continually produce 3–5 loose stools per day.

Postvagotomy diarrhea is probably due to increased gastric emptying (following the drainage procedure) and the effects of vagal denervation on intestinal motility, but the pathophysiology has not been fully understood. This complication may be avoided by parietal cell vagotomy.

Necrosis of gastric lesser curvature. Necrosis of gastric lesser curvature is a rare early complication seen in patients with superselective vagotomy. It may be caused by devascularization and injury achieved incidentally in the process of denervation the lesser curvature. If this complication is suspected, gastroscopy may be used for a prompt diagnosis. Emergency reoperation and excision of necrotic area of the stomach are indicated.

Gastric retention. The mechanism of gastric retention after vagotomy is different from that after gastrectomy. But this complication occurs only in truncal and selective vagotomy without drainage procedure. Gastric emptying is brought about in large part by contraction of the antral musculature. The vagal denervation of the stomach including the antrum produces delayed gastric emptying. After drainage procedures (pyloroplasty and gastrojejunostomy) have been added in vagotomy, gastric retention did not occur commonly. Superselective vagotomy has been developed also for avoidance of delayed gastric emptying by preservation of the vagal innervation of the antrum.

Stress upper gastrointestinal mucosal injurer (SUGMI)

The term "stress ulcer" has been used classically for long time to refer to a heterogeneous group of acte upper gastrointestinal ulcers or acute mucosal injury that develop following physiolgically stressful illnesses, such as shock, sepsis, burns, and central nervous system tumors and trauma, or occurs in the patients who are critically ill for long periods. It may also develop following some drugs ingestion (aspirin, cortisone). This pathological conditions were termed variedly, for example, acute gastritis, Curling's ulcer (following burns), or Cushing's ulcer (following central nervous system tumors and trauma). But none of these including stress ulcers can exactly present and describe the pathological and clinical features for these conditions. The term "stress upper gastrointstinal mucosal injuries" may be more preferable. The reasons are the following (1) although the lesions are found most commonly in the stomach, but they are not limited within the gastric mucosa, the duodenum, the lower

portion of the esophagus and the upper portion of the jejunum may be evolved, so "upper gasrointestinal mucosal" has to be used; (2) lesions may be superficial erosions, or acute ulcer deep into the muscular layer not correct; (3) lesions usually occur in the streased patients or lesions result stress condition, so term "stress" should not be abandoned.

Gastroduodenal endoscopy performed early in traumatized or burned patients has shown acute gastric erosions in the majority of patients within 72 hours of the injury. Such studies illustrate how frequently the disease process remains subclinical; clinically apparent lesions develop in about 20% of susceptible patients. In fact, the real incidence of SUGMI would be higher than the incidence of massive hemorrhage and acute perforation, because it is difficult to be found if SUGMI occurs without complication of massive hemorrhage or perforation.

Hemorrhage is the major clinical problem and usually is the first manifestation in severe stressed patients, although perforation occurs in about 10% of cases Acute gastroduodenal perforation is the second common symptom. Clinically evident bleeding is usually seen 3–5 days after the injury, and massive bleeding generally does not appear until 4–5 days later.

Physical examination is not contributory except to reveal gross or occult fecal blood or signs of shock.

SUGMI should be considered whenever acute gastrointestinal bleeding or perforation occurs after major trauma or during the course of critically ill. Gastroscopy is the most important diagnostic procedure available. It is usually possible to demonstrate acute, superficial, bleeding gastric erosions if gastroscopy is performed during the period of bleeding. Upper gastrointestinal X-ray series are rarely helpful since the erosion lesions are quite superficial. The diagnosis of perforated ulcer is depended on the clinical features (the sudden severe epigastric pain, and signs of peritonitis).

Initial management should consist of gastric lavage with iced Normal Saline solution, antacids, H_2 – receptor antagonists and proton pump inhibitors. Blood transfusion may be indicated in some patients.

In the sickest patients, if facilities and trained personnel are available, the selective infusion of vasoconstriction agents (e.g., vasopressin) into the left gastric artery through a percutaneously placed catheter should probably be attempted before operation is considered.

Emergency laparotomy should be considered if the nonoperative management fails to control the bleeding. Surgical treatment consists of subtotal gastrectomy, or vagotomy and pyloroplasty with suture of the bleeding points. Most experts recommend a high subtotal gastrectomy excising as much ulcerated parietal cell mucosa as possible, if the patient's condition permits. When it occurs, rebleeding is nearly always from lesions left behind at the initial procedure. Rarely, total gastrectomy has had to be used because of the extent of erosions and severity of bleeding.

1.8. ENDOCRINE DISEASES THAT CAUSE PEPTIC ULCERS

1.8.1. PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism causes hypercalcemia (elevated blood calcium levels) through the excessive secretion of parathyroid hormone (PTH), usually by an adenoma (benign tumors) of the parathyroid glands. Its incidence is approximately 42 per 100,000 people. It is almost exactly three times as common in women as men.

The parathyroid glands are four pea-sized glands located on the thyroid gland in the neck (*Fig. 1.22*). Occasionally, a person is born with one or more of the parathyroid glands embedded in the thyroid, in the thymus, or located elsewhere around this area. In most such cases, however, the glands function normally.

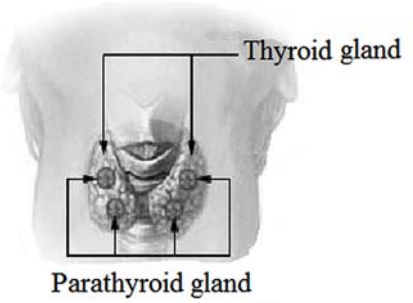


Figure 1.22. *Thyroid and parathyroid gland*

Though their names are similar, the thyroid and parathyroid glands are entirely different glands, each producing distinct hormones with specific functions. The parathyroid glands secrete PTH, a substance that helps maintain the correct balance of calcium and phosphorus in the body. PTH regulates the level of calcium in the blood, release of calcium from bone, absorption of calcium in the intestine, and excretion of calcium in the urine.

When the level of calcium in the blood falls too low, the parathyroid glands secrete just enough PTH to restore the blood calcium level.

Signs and Symptoms

The signs and symptoms of primary hyperparathyroidism are those of hypercalcemia. They are classically summarized by the mnemonic "stones, bones, abdominal groans and psychic moans".

• "Stones" refers to kidney stones, nephrocalcinosis, and diabetes insipidus (polyuria and polydipsia). These can ultimately lead to renal failure.

• "Bones" refers to bone-related complications. The classic bone disease in hyperparathyroidism is osteitis fibrosis cystica, which results in pain and sometimes pathological fractures. Other bone diseases associated with hyperparathyroidism are osteoporosis, osteomalacia, and arthritis.

• "Abdominal groans" refers to gastrointestinal symptoms of constipation, indigestion, nausea and vomiting. Hypercalcemia can lead to peptic ulcers and acute pancreatitis.

• "Psychic moans" refers to effects on the central nervous system. Symptoms include lethargy, fatigue, depression, memory loss, psychosis, ataxia, delirium, and coma.

• Left ventricular hypertrophy.

• Increased all-cause mortality.

Diagnosis

Blood tests – hyperparathyroidism is diagnosed based upon levels of blood calcium and parathyroid hormone. In most people with hyperparathyroidism, both levels are higher than normal. Occasionally, a person may have an elevated calcium level and a normal or minimally elevated PTH level. Since PTH should normally be low when calcium is elevated, a minimally elevated PTH is considered abnormal and indicates hyperparathyroidism.

Bone density testing – bone density testing is usually recommended for people with hyperparathyroidism. This test can help determine if the bones have become weakened as a result of abnormal blood calcium levels. Dual x-ray absorptiometry (DXA) testing is the most commonly used method for measuring bone density. This test is described in detail separately.

Kidney stone testing – testing for "silent" kidney stones is not recommended when you are first diagnosed with hyperparathyroidism. Testing is recommended, however, if you have had a kidney stone previously. Testing usually involves an ultrasound or CT scan of the kidneys. Further testing is not needed after the initial screening unless a person develops signs or symptoms of a stone.

Causes

The most common cause of primary hyperparathyroidism is a sporadic, single parathyroid adenoma resulting from a clonal mutation (~ 97%). Less common are parathyroid hyperplasia (~ 2.5%), parathyroid carcinoma (malignant tumor), and adenomas in more than one gland (together ~ 0.5%).

Primary hyperparathyroidism is also a feature of several familial endocrine disorders: multiple endocrine neoplasia type 1 and type 2A (MEN type 1 and MEN type 2A), and familial hyperparathyroidism.

Complications

The classic bone disease in hyperparathyroidism is osteitis fibrosis cystica, which results in pain and sometimes pathological fractures. Other bone diseases associated with hyperparathyroidism are osteoporosis, osteomalacia, and arthritis.

Treatment

Treatment is usually surgical removal of the gland(s) containing adenomas.

Medications

Medications include estrogen replacement therapy in postmenopausal women and bisphosphonates. Bisphosphonates may improve bone turnover. Newer medications termed "calcimimetics" used in secondary hyperparathyroidism are now being used in Primary hyperparathyroidism. Calcimimetics reduce the amount of parathyroid hormone released by the parathyroid glands. They are recommended in patients in whom surgery is inappropriate.

Surgery

Surgery is often recommended for people whose blood calcium is moderately elevated. Surgery is also recommended for people who are excreting a significant amount of calcium through their urine and for people with signs of impaired kidney function or decreased bone density.

It is also recommended if the person is less than 50 years old or if periodic follow-up would be difficult (e.g., if a person lived a great distance from a healthcare provider or travels to places where it is difficult to find medical care).

Traditional surgery. The surgery is usually performed while the person is under anesthesia. An incision is made in the lower neck measuring 5 to 10 cm (2 to 5 inches). All four parathyroid glands are examined; usually, at least one abnormal-appearing gland is removed while the normal-appearing glands are left in place.

Minimally invasive surgery. Minimally invasive surgery can be performed in cases where one abnormal parathyroid gland has been located by a pre-operative imaging study.

The surgery can be performed under local nerve block, and is an alternative when one abnormal gland has been localized pre-operatively. This procedure is also a good alternative for patients who are at high-risk for general anesthesia. During the surgery, a small incision (2 to 4 cm or 0.1 to 1.1 inches) is made in the neck and the abnormal tissue is removed. The patient's blood level of PTH is tested before and immediately after removal to confirm that the PTH level drops significantly after the abnormal tissue is removed.

The advantage of minimally invasive surgery compared to traditional surgery is that it requires a smaller incision, less time under anesthesia, and a shorter hospital stay. This procedure is only available for people with certain characteristics and it requires an experienced surgeon and medical center.

Effectiveness of surgery. With an experienced endocrine surgeon, surgical treatment is effective in curing hyperparathyroidism in about 95 percent of patients. The complication rate associated with surgery is very low.

Complications could include temporary or permanent damage to the other parathyroid glands resulting in low calcium levels and/or temporary or permanent hoarseness. Patients are hospitalized for a short time after surgery, usually for less than two days.

Occasionally, some abnormal parathyroid tissue goes undetected and is not removed during the first operation. In this case, high calcium levels and symptoms of hyperparathyroidism persist after surgery. Imaging studies are required to locate the abnormal parathyroid tissue. In some patients, parathyroid glands may be present in unusual locations, such as in the chest or in other regions of the neck. A second surgical procedure is usually required to remove remaining abnormal tissue.

Follow up care after surgery. Six to eight weeks after surgery, most clinicians recommend a blood test to measure the blood level of calcium and PTH. These tests are then repeated once per year to ensure that they remain normal and that abnormal tissue has not regrown. A bone density test may be recommended one year after surgery to guide treatment of bone loss (osteopenia or osteoporosis).

1.8.2. ZOLLINGER–ELLISON SYNDROME

Zollinger–Ellison syndrome (ZES) is a rare disorder characterized by one or more tumors in the pancreas, duodenum, or both. The tumors cause the stomach to

make too much acid, leading to peptic ulcers in the duodenum. The tumors are sometimes cancerous and spread to other areas of the body.

Causes ZES

ZES is caused by tumors called gastrinomas, which release the hormone gastrin.

Normally, cells in the stomach produce and control gastrin so only the right amount is released. Gastrin travels through the bloodstream to signal other cells in the stomach to release gastric acid to help break down food. Gastrinomas release abnormal amounts of gastrin, resulting in excess gastric acid in the stomach and duodenum. The excess acid eventually causes sores called peptic ulcers to form in the lining of the duodenum.

Scientists are unsure what causes the majority of gastrinomas, which appear sporadically. About 25 percent of gastrinoma cases are caused by an inherited genetic disorder called multiple endocrine neoplasia type 1 (MEN1). MEN1 can cause a variety of hormone-releasing tumors such as prolactinomas and insulinomas. Prolactinomas form in the pituitary gland in the brain and cause excess prolactin – a hormone that influences milk production, fertility, and bone strength. Insulinomas form in the pancreas and cause excess insulin – a hormone that helps control blood glucose. Signs and symptoms of MEN1 include increased hormone levels in the blood, kidney stones, diabetes, muscle weakness, and weakened bones and fractures.

Anyone can get ZES, but the disease is more common among men 30 to 50 years old. People with MEN1 have a 20 to 61 percent chance of developing ZES. Children who have a parent with MEN1 have a 50 percent chance of inheriting the MEN1 gene and are, therefore, also at increased risk of ZES.

Symptoms of ZES

ZES symptoms are similar to those of peptic ulcers and include:

- burning abdominal pain;
- nausea and vomiting;
- weight loss;
- diarrhea;
- severe gastroesophageal reflux – a condition where gastric acid and food from the stomach backs up into the esophagus

Diagnostics ZES:

- assessing symptoms;
- measuring stomach acid and the amount of gastrin circulating in the blood;
- conducting imaging tests to look for gastrinomas.

A doctor may suspect ZES if diarrhea accompanies peptic ulcer symptoms or if treatment for peptic ulcers fails. Most peptic ulcers are caused by bacteria called *Helicobacter pylori (H. pylori)* or the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen. Peptic ulcers in the absence of *H. pylori* infection or NSAIDs usage or severe peptic ulcers that bleed or cause perforation of the duodenum are possible indicators of ZES. A MEN1 diagnosis in the patient or the patient's family or the presence of MEN1 signs and symptoms strongly suggests ZES.

Multiple ulcers in the duodenum – seen during upper gastrointestinal (GI) endoscopy – may cause a doctor to suspect ZES. Upper GI endoscopy, however, rarely reveals gastrinomas, which grow in tissue layers beneath the visible surface.

A procedure called somatostatin receptor scintigraphy (SRS) – sometimes called OctreoScan – is used to find gastrinomas in the duodenum, pancreas, and other parts of the body. SRS uses a radioactive compound called a radiotracer that, when injected into the bloodstream, selectively labels tumor cells. The labeled cells light up when scanned with a device called a gamma camera.

Other imaging procedures used to find gastrinomas include the following:

Angiography is sometimes used to find tumors in the pancreas.

Endoscopic ultrasonography is sometimes used to look for tumors in the pancreas.

A computerized tomography (CT) scan takes hundreds of cross-sectional X-ray images in a few seconds. A computer assembles the images to produce three-dimensional views of internal organs and tissues. While not good at finding tumors in the pancreas or duodenum, this technique is more useful in finding gastrinomas that have spread to the liver.

Treatment

ZES is treated with medications to relieve ulcer symptoms and surgery, if appropriate, to remove tumors. Chemotherapy is sometimes used when tumors are too widespread to remove with surgery.

A class of drugs called proton pump inhibitors effectively reduces gastric acid secretion in the stomach and includes: esomeprazole; lansoprazole; pantoprazole; omeprazole.

Reducing stomach acid allows peptic ulcers to heal and relieves ZES symptoms.

Surgical removal of gastrinomas is the only cure for ZES. Some gastrinomas behave like cancers and spread to other parts of the body, especially the liver and bones. Finding and removing all gastrinomas is often challenging.

Gastrinomas that cannot be surgically removed are sometimes treated with chemotherapy drugs, including: streptozotocin; 5-fluorouracil; doxorubicin.

The outcome for people with ZES largely depends on the nature and extent of the gastrinomas. About 25 percent of gastrinoma cases are considered cancerous, with an estimated 10-year survival rate of around 30 percent. The remaining cases are considered slow-growing, with an estimated 10-year survival rate of around 95 percent. If peptic ulcer symptoms are well controlled, however, most patients – even those with tumors that spread – will feel well until the late stages of the disease.

1.9. BEZOARS AND FOREIGN BODIES

Bezoars are tightly packed collections of partially digested or undigested material stuck in the stomach or other parts of the digestive tract. Foreign bodies are small ingested objects that can also get stuck in the digestive tract and sometimes perforate (pierce) it.

• Masses of indigestible materials can get stuck in various parts of the digestive tract.

• Most bezoars and foreign bodies cause no symptoms.

• The diagnosis is based on X-rays and sometimes on a visual examination of the digestive tract by using a flexible viewing tube (endoscopy).

• Most bezoars and foreign bodies pass without treatment, but some need to be broken down manually or removed surgically.

The stomach is a common collection site for hardened, partially digested or undigested masses of food or other materials (bezoars) or for foreign objects (bodies). Reasons include the curved shape of the stomach and the narrow opening (pyloric sphincter) that the stomach's contents must pass through to enter the first segment of the small intestine (duodenum). Bezoars or foreign bodies larger than 3/4 of an inch (about 2 centimeters) in diameter are rarely able to pass out of the stomach.

Bezoars may consist of partially digested hair, fiber from fruits or vegetables, even hardened blocks of drugs (such as antacids), which accumulates most often in the stomach but sometimes elsewhere in the digestive tract (*Fig. 1.23, 1.24*).

Figure 1.23. *Bezoar from the craw of a chicken*

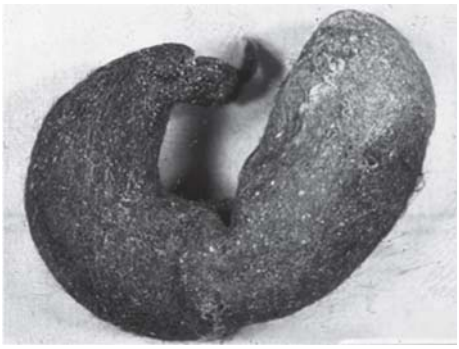


Figure 1.24. *Trichobezoar from a human*

These hairballs or foodballs cannot pass through narrow openings or spaces and thus get stuck in the digestive tract. Foreign bodies are sometimes swallowed by children and even adults, especially intoxicated adults. If these indigestible objects are small, they pass through the digestive system until they are excreted with stool. However, larger objects or sharp ones, such as fish bones, may get stuck in the esophagus or stomach or, less often, in other parts of the digestive tract. Sometimes foreign bodies are swallowed purposely, as when smugglers swallow balloons filled with illegal drugs to get through customs.

Food or other materials can collect in anyone but do so more often under certain circumstances. People, who have undergone surgery to their digestive tract, particularly if they have had part of their stomach or intestines removed, are particularly prone to bezoars and foreign bodies becoming stuck. People with diabetes sometimes develop a condition in which the stomach does not empty properly, resulting in problematic collections of food.

Symptoms and diagnosis

Most bezoars and foreign bodies cause no symptoms.

A small blunt object that is swallowed may produce the sensation of something being stuck in the esophagus. This feeling may persist for a short time even after the object has passed into the stomach. A small sharp object that is swallowed may become lodged in the esophagus and cause pain, even though the person is able to swallow normally. When the esophagus is completely blocked, the person is unable to swallow anything, even saliva, and drools and spits constantly. The person may try to vomit, but nothing comes up. If a sharp object pierces the esophagus, consequences may be serious.

Sometimes bezoars or foreign bodies lead to blood in the stool. If they are partially or completely obstructing the stomach, the small intestine, or, rarely, the large intestine, they cause cramps, bloating, loss of appetite, vomiting, and sometimes fever. If a sharp object has pierced the stomach or intestines, stool spills into the area around the intestines, causing severe abdominal pain, fever, fainting, and sometimes shock. Such a leakage is a medical emergency because it can cause peritonitis. If a person has swallowed a drug-filled balloon, the balloon may rupture, which can then lead to an overdose of the drug.

Often, an obstructing object can be seen on X-rays of the abdomen. Sometimes, endoscopy (a visual examination of the digestive tract using a flexible tube called an endoscope is performed to determine the nature of the obstructing object and to exclude a tumor as the cause. Rarely, CT and ultrasound scans are used to identify the problem.

Treatment

Most bezoars and foreign bodies require no treatment. Even a small coin is likely to pass without problem. A doctor advises the person to check the stool to see when the object is excreted. Sometimes a doctor recommends that the person consume a liquid diet to help excrete the object.

To help break down a bezoar, a doctor may prescribe a regimen of cellulose or meat tenderizer, which is dissolved in a liquid and taken by mouth for several days. Sometimes doctors use forceps, a laser, or other instruments to break up bezoars so that they can pass through or be removed more easily.

When a doctor suspects that a blunt foreign body is stuck in the esophagus, the drug glucagon may be given intravenously to relax the esophagus and allow the object to pass through the digestive tract. Other drugs such as metoclopramide taken by mouth can help bezoars or blunt foreign objects pass through the digestive tract by causing muscles to contract.

Doctors can remove some objects that are stuck in the esophagus with forceps or a basket passed through an endoscope.

Because sharp objects may pierce the wall of the esophagus, they must be removed, either by endoscopy or surgery. Batteries are also removed from the esophagus because they can cause internal burns. When an object suspected of being a drug-filled balloon is detected, it is removed to prevent the drug overdose that can occur if such a balloon ruptures.

1.10. MALLORY–WEISS SYNDROME

Mallory–Weiss syndrome or gastro-esophageal laceration syndrome refers to bleeding from tears (*a Mallory–Weiss tear*) in the mucosa at the junction of the stomach and esophagus, usually caused by severe retching, coughing, or vomiting. It is often associated with alcoholism and eating disorders and there is some evidence that presence of a hiatal hernia is a predisposing condition.

In 1929, Kenneth Mallory and Soma Weiss first described a syndrome characterized by esophageal bleeding caused by a mucosal tear in the esophagus as a result of forceful vomiting or retching. The initial description was associated with alcoholic bingeing; however, with the advent of endoscopy, Mallory–Weiss tears have been diagnosed in many patients with no antecedent history of alcohol intake. Although the tear typically occurs after repeated episodes of vomiting or retching, it may occur after a single incident.

Causes

Many underlying disorders that cause vomiting and retching result in a Mallory–Weiss tear.

- Gastrointestinal disease.
- Infectious gastroenteritis.
- Gastric outlet obstruction.
- Ulcers.
- Hiatal hernias.
- Malrotation.
- Volvulus.
- Inflammatory conditions of the stomach and intestine.
- Pregnancy: Some women develop hyperemesis gravidarum, a syndrome characterized by persistent severe vomiting and retching, in the first trimester of pregnancy. Gastric dysrhythmias and prolonged small-bowel motility cause the development of hyperemesis gravidarum. Some women lose as much as 10% of their body weight during this period.
- Hepatitis: acute inflammation of the liver causes vomiting in 10–20% of patients.
- Cirrhosis.
- Cholecystitis.
- Biliary cirrhosis.
- Renal disease: vomiting is often associated with diseases affecting the kidneys, including the following:
  - urinary tract infections;
  - kidney stones;
  - uteropelvic junction (UPJ) obstruction;
  - renal failure.
- Increased intracranial pressure: Intracranial lesions that cause hydrocephalus or increased intracranial pressure may lead to vomiting in children. Most common causes of hydrocephalus include tumors, cysts, and congenital abnormalities. Other causes of increased intracranial pressure consist of trauma, infections (e.g., meningitis), medications, and pseudotumor cerebri.
- Iatrogenic causes: complications of endoscopy may cause esophageal tears and are almost always associated with a patient who is retching or struggling during

the procedure. The use of polyethylene glycol lavage, when used for ingestions, severe constipation, or preparation for colonoscopy, may cause severe vomiting.

- Other causes:
  - severe diabetic ketoacidosis;
  - toxins;
  - drugs (e.g., chemotherapeutic agents).

Pathophysiology

Any disorder that initiates vomiting may result in the development of a Mallory–Weiss tear, which develops as a linear laceration at the gastroesophageal junction because the esophagus and stomach are cylindrical. The cylindrical shape allows longitudinal tears to occur more easily than circumferential tears. These tears have been postulated to occur either by a rapid increase in intragastric pressure and distention, which increases the forceful fluid ejection through the esophagus, or secondary to a significant change in transgastric pressure (i.e., difference in pressure across the gastric wall) because negative intrathoracic pressure and positive intragastric pressure leads to distortion of the gastric cardia, resulting in a gastric or esophageal tear.

Although most cases of Mallory–Weiss tears are self-limiting, patients with severe or recurrent episodes of bleeding that require intensive care therapy and interventional endoscopy have been reported. Typically these patients have underlying conditions, including portal hypertension and hepatic insufficiency. Although upper gastrointestinal bleeding is generally assumed to be secondary to varies in these patients, the physician must also be aware of the potential for Mallory–Weiss tears.

Presentation

Mallory–Weiss syndrome often presents as an episode of vomiting up blood (hematemesis) after violent retching or vomiting, but may also be noticed as old blood in the stool (melena), and a history of retching may be absent.

In most cases, the bleeding stops spontaneously after 24–48 hours, but endoscopic or surgical treatment is sometimes required and rarely the condition is fatal.

Diagnosis

Definitive diagnosis is by endoscopy (*Fig. 1.25, 1.26*).

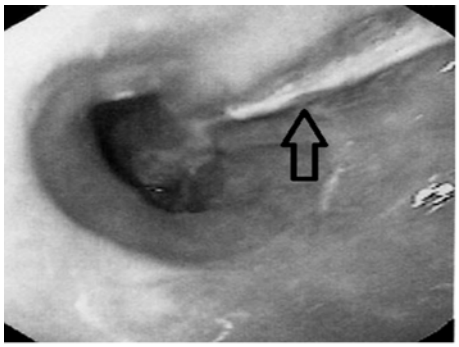


Figure 1.25. *Mallory–Weiss tear. Typical longitudinal mucosal tear with overlying fibrinous exudate extending from the distal esophagus to the gastric cardia (arrow)*

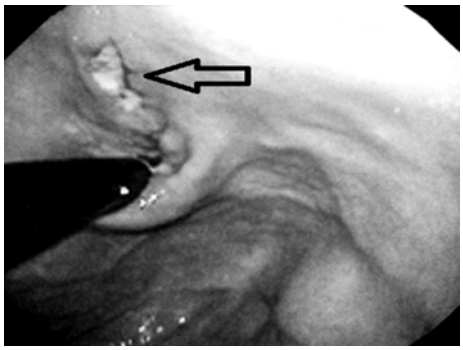


Figure 1.26. *Mallory-Weiss tear. Retroflexed view of the cardia showing the typical location of the tear with a clean base (arrow)*

Treatment

Treatment is usually supportive as persistent bleeding is uncommon. However cauterization or injection of epinephrine to stop the bleeding may be undertaken during the index endoscopy procedure.

Very rarely embolization of the arteries supplying the region may be required to stop the bleeding.

1.11. MENETRIE'S DISEASE

Menetrie's disease causes the ridges along the inside of the stomach wall – called rugae – to enlarge, forming giant folds in the lining of the stomach. The rugae enlarge because of an overgrowth of surface mucous cells of the stomach. In a normal stomach, rugae release protein-containing mucus. Enlarged rugae release too much mucus, causing a leakage of protein from the blood into the stomach. This shortage of protein in the blood is known as hypoproteinemia. Ménétrie's disease also causes a decrease in stomach acid resulting from a reduction in acid-producing parietal cells.

Menetrie's disease is rare and more common in men, usually appearing between the ages of 30 and 60.

People with Menetrier disease suffer from severe stomach pain, nausea, frequent vomiting, and other symptoms. They also have a higher risk of developing stomach cancer, also called gastric cancer.

Menetrie's disease is also called hypoproteinemic hypertrophic gastropathy.

Other conditions that can cause enlarged rugae but are **not** Menetrie's disease include:

- Zollinger–Ellison syndrome – a condition in which tumors in the pancreas cause the stomach to make too much acid.
- Syphilis – a type of sexually transmitted bacterial infection.
- Cytomegalovirus – a type of viral infection.
- Histoplasmosis – a type of fungal infection.
- Linitis plastica – a type of gastric cancer.
- Gastric lymphoma – a type of cancer originating in the stomach.

Causes

What causes Menetrie's disease is unclear; however, it is thought to be an acquired disorder with no known genetic component. Recent studies suggest people with Ménétrie's disease have stomachs that make abnormally high amounts of a protein called transforming growth factor-alpha (TGF-α). Growth factors are proteins in the body that tell cells what to do, such as grow larger, change shape, or divide to make more cells. A cause for the overproduction of TGF-α has yet to be found.

Symptoms

Possible signs and symptoms of Menetrie's disease include:

- severe pain in the top middle part of the abdomen;
- nausea and frequent vomiting;
- swelling of the face, abdomen, limbs, and feet;

• loss of appetite;
• extreme weight loss;
• malnutrition;
• low blood protein;
• anemia;
• diarrhea.

Diagnosis

Menetrie's disease is diagnosed through x rays, endoscopy, and biopsy of stomach tissue. Endoscopy involves looking at the inside of the stomach using a long, lighted tube inserted through the mouth. During a biopsy, the doctor removes a small piece of tissue and examines it with a microscope for signs of disease.

• Menetrie's disease causes the ridges along the inside of the stomach wall – called rugae – to enlarge, forming giant folds in the lining of the stomach.

• Menetrie's disease is rare and more common in men, usually appearing between the ages of 30 and 60.

• Recent studies suggest people with Menetrie's disease have stomachs that make abnormally high amounts of transforming growth factor alpha (TGF-α) – a protein that tells cells what to do.

• Menetrie's disease is diagnosed through x rays, endoscopy, and biopsy of stomach tissue.

• Treatment for Menetrie's disease may include medications to relieve nausea and pain and surgery to remove part or all of the stomach.

Treatment

Treatment may include medications to relieve nausea and pain. A high-protein diet is prescribed to offset the loss of protein from enlarged rugae. Part or all of the stomach may need to be removed if the disease is severe.

The anticancer drug cetuximab (Erbitux) blocks the action of TGF-α and is being investigated as a promising new treatment for Ménétrier disease.

1.12. OSLER–WEBER–RENDU SYNDROME

Osler–Weber–Rendu syndrome, also known as hereditary hemorrhagic telangiectasia (HHT), is an autosomal dominant disorder typically identified by the triad of telangiectasia, recurrent epistaxis, and a positive family history for the disorder. The major cause of morbidity and mortality due to this disorder lies in the presence of multiorgan arteriovenous malformations (AVMs) and the associated hemorrhage that may accompany them. The disease has a wide spectrum of presentations; patients may be asymptomatic or have multiple organ involvement presenting at any age.

Pathophysiology

The clinical manifestations of Osler–Weber–Rendu disease are caused by the development of abnormal vasculature, including telangiectasia, AVMs, and aneurysms. The genetic defect largely involves either one of two genes: ENG or ALK-1. Both of these genes transcribe proteins that are highly expressed on endothelial cells and play important roles in tissue repair and angiogenesis through their common function

as receptors for transforming growth factor beta. Defects in the endothelial cell junctions, endothelial cell degeneration, and weakness of the perivascular connective tissue are thought to cause dilation of capillaries and postcapillary venules, which manifest as telangiectasia. Most commonly, telangiectasias involve the mucous membranes, as well as the skin, the conjunctiva, the retina, and the gastrointestinal tract. AVMs are abnormal tortuous vessels with both arterial and venous components. The larger AVMs can cause left-to-right shunting and, if sufficiently large, may contribute to high-output heart failure. Loss of the muscular is layer and disturbance of the elastic lamina of vessel walls may also give rise to aneurysms in multiple organ systems. AVMs are found in the lungs, brain, and liver.

The disease is caused by genetic defects with an autosomal dominant inheritance. So far, two primary loci have been identified associated with Osler–Weber–Rendu syndrome: one on chromosome arm 9q33-34 (HHT1) and a second on chromosome arm 12q11-14 (HHT2). Two more genes have been implicated; MADH4 gene mutation in patients with a combined syndrome of Osler–Weber–Rendu syndrome and juvenile polyposis and an unidentified HHT3 gene linked to chromosome 5.

• Chromosome arm 9q33-34 (HHT1) harbors the endoglin gene, which encodes for a homodimeric integral membrane glycoprotein expressed at high levels on human vascular endothelial cells. Over 150 mutations of the endoglin gene have been reported in family members with Osler–Weber–Rendu syndrome. The vast majority of these mutations create premature stop codons and subsequently reduce levels of functional endoglin protein, the likely cause of Osler–Weber–Rendu syndrome type 1.

• Chromosome arm 12q11-14 (HHT2) contains the activin receptorlike kinase 1 (ALK1), which encodes for a surface receptor for the transforming growth factor (TGF)-beta superfamily of ligands. The TGF-beta multifunctional protein plays an important role in angiogenesis and vascular remodeling. Over 120 mutations have been reported in the ALK1 gene, yet unlike Osler–Weber–Rendu type 1, more than 50% of the mutations contributing to type 2 are missense substitutions.

• In patients with the HHT1 genotype, the prevalence of pulmonary AVMs and cerebral AVMs was shown to be higher than that of patients with the HHT2 genotype. Also, oral and nasal mucosal telangiectasia present earlier in life in patients with the HHT1 genotype. The prevalence of hepatic AVMs is higher in patients with HHT2 than in patients with HHT1. Patients with the HHT2 genotype also present earlier in life with dermal lesions.

Mortality/Morbidity

Patients are at risk for hemorrhage from both mucosal and visceral sites, as well as high-output cardiac failure, cerebral abscess, ischemic stroke, migraines and further sequel. Studies show that life expectancy appears to be significantly lower in patients with Osler–Weber–Rendu syndrome compared with the general population.1 The mortality of these patients revealed an early peak at age 50 years and a later peak at 60–79 years due to acute complications.

• Hemorrhage: recurrent epistaxis is observed in as many as 90% of patients. In one half of patients, the epistaxis becomes more serious with age, and blood transfusions

are required in 10–30% of patients. Patients with pulmonary AVMs and telangiectasis of the gastrointestinal tract are at risk for life-threatening hemorrhage of the lungs and gastrointestinal tract.

• CNS complications: cerebral abscess due to impaired function of pulmonary vasculature is the most common neurologic manifestation of Osler–Weber–Rendu syndrome. Also, patients with this disease suffer from strokes, which may be either hemorrhagic or ischemic. Ischemic strokes likely due to pulmonary AVMs are common, whereas hemorrhagic strokes due to cerebral AVMs are far less common. Of patients who have pulmonary AVMs, 2% per year are estimated to have a stroke and 1% per year are estimated to develop a brain abscess.

• High-output cardiac failure: due to the presence of large AVMs and blood loss, high-output cardiac failure may occur. This known complication of HHT has recently been linked with the onset of severe and recurrent epistaxis in a small sample of patients.

Clinical

Because Osler–Weber–Rendu syndrome is an autosomal dominant disease, a family history of telangiectasia and recurrent bleeding in other family members is usually present. Symptoms vary depending on the area of involvement. The main areas of involvement are nasal mucosa, skin, the gastrointestinal tract, pulmonary vasculature, and the brain.

Diagnostic criteria are based on 4 components. The diagnosis is considered definite if 3 criteria are present and is considered possible if 2 criteria are present. The diagnosis is unlikely if fewer than 2 criteria are present. The criteria are as follows:

• Nosebleeds – spontaneous and recurrent.

• Telangiectasia – multiple sites including the lips, oral cavity, fingers, and nose.

• Presence of internal lesions – gastrointestinal telangiectasia, pulmonary arteriovenous malformations (AVMs), hepatic AVMs, cerebral AVMs, spinal AVMs.

• Family history – a first-degree relative with Osler-Weber–Rendu syndrome according to these criteria.

Other symptoms that may be reported include the following:

Nasal mucosa: epistaxis is the most common manifestation of the disease and occurs in as many as 90% of affected patients. Bleeding may occur as often as every day or as infrequently as once a month. Patients with epistaxis usually present before the second decade of life. Blood transfusions are required in 10–30% of patients, and as many as 50% of patients require surgical treatment.

Gastrointestinal tract: recurrent painless gastrointestinal bleeding occurs in 10–40% of patients and generally occurs later in life than epistaxis. Patients may report abdominal pain that may be due to thrombosis of gastrointestinal AVMs.

Pulmonary vasculature: Pulmonary AVMs are present in 15–33% of patients with the disease. Dyspnea and exercise intolerance are often presenting symptoms; however, recent studies reveal that most patients with pulmonary AVM have no significant respiratory symptoms. Pulmonary AVMs may cause enough right-to-left shunting to cause cyanosis, hypoxemia, and secondary polycythemia. Pulmonary

AVMs also increase the incidence of infection due to septic emboli formation in the pulmonary vasculature.

Hemoptysis results from either telangiectasia of the trachea and bronchi or pulmonary arteriovenous (AV) fistulas. Patients usually present around the third or fourth decades of life.

Migraine headaches are present in 13–50% of patients with Osler–Weber–Rendu syndrome. Although the reason is unclear, the headaches are more prevalent in patients with pulmonary AVMs.

CNS involvement:

• Neurologic involvement occurs in 1–12% of patients with Osler–Weber–Rendu syndrome. A history of headache, seizures, and focal neurologic symptoms (e.g., paraplegia, paralysis) may be presenting symptoms.

• Stroke and brain abscess are more common in patients with Osler–Weber–Rendu syndrome compared with the healthy population. This is due to loss of the normal filtering function of the pulmonary vasculature in patients with pulmonary AVMs. These AVMs allow thrombotic and septic emboli to travel to the brain. Untreated patients have a 2% risk of stroke and a 1% risk of brain abscess per year.

Fatigue: fatigue may be elicited on history and may be due to an iron deficiency anemia caused by recurrent blood loss.

Visual disturbances: visual disturbances may be noted, possibly caused by intraocular hemorrhage. Patients may notice bloody tears, which are due to conjunctival telangiectasia.

Liver involvement: liver involvement (often asymptomatic) is reported in as many as 40% of patients. Symptoms may include right upper quadrant pain, jaundice, symptoms of high-output cardiac failure, and bleeding from esophageal varices. The complication of cardiac failure is caused by a large left-to-right shunt that can occur between the hepatic arteries and veins. Occasionally, patients with Osler–Weber–Rendu syndrome may present with atypical cirrhosis.

Physical

The areas involved dictate the signs that may be found on physical examination.

Skin

• The most obvious finding on physical examination is telangiectasias. These lesions may be found on the oral mucosa, nasal mucosa, skin, and conjunctiva.

• Cyanosis and clubbing may be present in patients with pulmonary AVMs. These signs develop due to right-to-left shunting.

• Liver involvement may cause jaundice.

• CNS: if a previous stroke, brain abscess, or intracerebral hematoma has occurred, patients may present with focal neurologic signs.

• Respiratory system: in the presence of pulmonary AVMs, the patient may be tachypnea, cyanotic, and have clubbing. A pulmonary bruit may be heard best on inspiration.

• Cardiovascular system: patients may be cyanotic because of right-to-left pulmonary shunting or pale because of anemia. Patients may have a hyperdynamic circulation if they have hepatic involvement and a large left-to-right shunt. Hyperdynamic circulation may be exacerbated by anemia.

• Gastrointestinal system:

‣ Examination of the oral mucosa reveals telangiectasias in 51–79% of patients.

‣ Rectal examination may reveal frank blood.

‣ Signs of liver involvement include jaundice, hepatomegaly, and a right upper quadrant bruit or thrill.

• Eyes: funduscopic examination may reveal retinal telangiectasias and hemorrhages. Bloody tears may be present because of conjunctival telangiectasias.

Investigations

Capillary microscopy (examining the capillary pattern of the fingernail; this can be useful in screening for HHT, as most patients have detectable abnormalities before development of other signs). CT, MRI scanning and angiography (for example, pulmonary and cerebral angiography) are used to identify lesions.

Diagnosis

The diagnosis is made if at least three of the following are present:

• Epistaxis.

• Telangiectasia.

• Visceral lesions.

• Appropriate family history.

Genetic testing can be undertaken to identify the specific mutation in the index case. This can then be used to investigate other family members.

Management

Optimal management is improved with early diagnosis, based on clinical findings.

Acute hemorrhage may require treatment including blood transfusion and attempts to stem the flow.

Surgical or laser ablation may be required as an emergency or elective procedure. AVMs may need embolization, ligation of the blood supply or resection.

Septoplasty of the nose may be required.

Liver transplantation or stereotactic intracranial radiosurgery may be indicated.

Prognosis

Usually there is no effect on lifespan unless there is severe hemorrhage, although cirrhosis may shorten life.

REFERENCES

1. Ambrogini E, Cetani F, Cianferotti L, et al. (2007). "Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial". J. Clin. Endocrinol. Metab. 92 (8) : 3114–21.

2. Bayrak–Toydemir P, McDonald J, Akarsu N, et al. (2006). "A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7". Am. J. Med. Genet. A 140 (20): 2155–62.

3. Bilezikian JP, Potts JT, Fuleihan Gel-H, et al. (2002). "Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century". J. Clin. Endocrinol. Metab. 87 (12) : 5353–6.

4. Bollerslev J, Jansson S, Mollerup CL, et al. (2007). "Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial". J. Clin. Endocrinol. Metab. 92 (5) : 1687–92.

5. Broulík PD, Pacovský V (1979). "The chloride phosphate ratio as the screening test for primary hyperparathyroidism". Horm. Metab. Res. 11 (10): 577–9.

6. Caroli A, Follador R, Gobbi V, Breda P, Ricci G (1989). "[Mallory-Weiss syndrome. Personal experience and review of the literature]" (in Italian). Minerva dietologica e gastroenterologica 35 (1): 7–12.

7. Cole SG, Begbie ME, Wallace GM, Shovlin CL (2005). "A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5". J. Med. Genet. 42 (7): 577–82.

8. Del Valle J, Scheiman JM. Zollinger-Ellison syndrome. In: Yamada T, ed. Textbook of Gastroenterology. Vol. 1. Philadelphia: Lippincott Williams & Wilkins; 2003: 1377–1394.

9. Gawrieh S, Shaker R (2005). "Treatment of actively bleeding Mallory-Weiss syndrome: epinephrine injection or band ligation?". Current gastroenterology reports 7 (3): 175.

10. James, William D.; Berger, Timothy G.; et al. (2006). Andrews' Diseases of the Skin: clinical Dermatology. Saunders Elsevier.

11. Jensen RT. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. Journal of Internal Medicine. 1998; 243(6): 477–488.

12. Khan AA, Bilezikian JP, Kung AW, et al. (2004). "Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial". J. Clin. Endocrinol. Metab. 89 (7).

13. Lawler FH, Janssen HP (1983). "Chloride : phosphate ratio with hypercalcemia secondary to thiazide administration". The Journal of family practice 16 (1): 153–4.

14. Lebrin, Franck; Srun S., Raymond K, Martin S., van den Brink S, Freitas C., Bréant C., Mathivet T., Larrivée B., Thomas J., Arthur H., Westermann C., Disch F., Mager J., Snijder R., Eichmann A., Mummery C. (April 2010). "Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia". Nature Medicine 16 (4).

15. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger–Ellison syndrome. New England Journal of Medicine. 1999; 341(9) : 635–644.

16. Palmer FJ, Nelson JC, Bacchus H (1974). "The chloride-phosphate ratio in hypercalcemia". Ann. Intern. Med. 80 (2): 200–4.

17. Rao DS, Phillips ER, Divine GW, Talpos GB (2004). "Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism". J. Clin. Endocrinol. Metab. 89 (11) : 5415–22.

18. Reeves CD, Palmer F, Bacchus H, Longerbeam JK (1975). "Differential diagnosis of hypercalcemia by the chloride/phosphate ratio". Am. J. Surg. 130 (2): 166–71.

19. Shovlin CL, Guttmacher AE, Buscarini E, et al. (Mar 2000). "Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)". Am J Med Genet 91 (1): 66–7.

20. Stefenelli T, Abela C, Frank H, et al. (1997). "Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up". J. Clin. Endocrinol. Metab. 82 (1): 106–12.

21. Vestergaard, P. and Mosekilde, L., BMJ Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. 2003 Sep 6; 327 (7414): 530–4.

22. Vestergaarde and Mosekilde, BMJ Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism.2003 Sep 6; 327(7414) : 530–4.

23. Warner JV, Nyholt DR, Busfield F, et al. (March 2006). "Familial isolated hyperparathyroidism is linked to a 1.7 Mb region on chromosome 2p13.3–14". J. Med. Genet. 43 (3).

Chapter 2

LIVER DISEASES

The liver is a vital organ present in vertebrates and some other animals. It has a wide range of functions, including detoxification, protein synthesis, and production of biochemical necessary for digestion. The liver is necessary for survival; there is currently no way to compensate for the absence of liver function.

This organ plays a major role in metabolism and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification. It lies below the diaphragm in the abdominal-pelvic region of the abdomen. It produces bile, an alkaline compound which aids in digestion, via the emulsification of lipids. The liver's highly specialized tissues regulate a wide variety of high-volume biochemical reactions, including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions.

Medical terms related to the liver often start in *hepato-* or *hepatic* from the Greek word for liver, *hēpar*.

2.1. ANATOMY AND PHYSIOLOGY

The **liver**, the largest gland in the body, has both external and internal secretions, which are formed in the hepatic cells. Its external secretion, the **bile**, is collected after passing through the bile capillaries by the bile ducts, which join like the twigs and branches of a tree to form two large ducts that unite to form the hepatic duct. The bile is either carried to the gall-bladder by the cystic duct or poured directly into the duodenum by the common bile duct where it aids in digestion. The internal secretions are concerned with the metabolism of both nitrogenous and carbohydrate materials absorbed from the intestine and carried to the liver by the portal vein. The carbohydrates are stored in the hepatic cells in the form of glycogen which is secreted in the form of sugar directly into the blood stream. Some of the cells lining the blood capillaries of the liver are concerned in the destruction of red blood corpuscles. It is situated in the upper and right parts of the abdominal cavity, occupying almost the whole of the right hypochondriac, the greater part of the epigastrium, and not uncommonly extending into the left hypochondriac as far as the mammillary line. In the male it weighs from 1.4 to 1.6 kilogm, in the female from 1.2 to 1.4 kilogm. It is relatively much larger in the fetus than in the adult, constituting, in the former, about one-eighteenth, and in the latter about one thirty-sixth of the entire body weight. Its greatest transverse measurement is from 20 to 22.5 cm. Vertically, near its lateral or right surface, it measures about 15 to 17.5 cm, while its greatest antero-posterior diameter is on a level with the upper end of the right kidney, and is from 10 to 12.5 cm. Opposite the vertebral column its measurement from before backward is reduced to about 7.5 cm. Its consistence is that of a soft solid; it is friable, easily lacerated and highly vascular; its color is a dark reddish brown, and its specific gravity is 1.05.

To obtain a correct idea of its shape it must be hardened *in situ*, and it will then be seen to present the appearance of a wedge, the base of which is directed to the right and the thin edge toward the left. Symington describes its shape as that "of a right-angled triangular prism with the right angle rounded off".

Lobes. The right lobe (*lobus hepatis dexter*) is much larger than the left; the proportion between them being as six to one. It occupies the right hypochondrium, and is separated from the left lobe on it's upper surface by the falciform ligament; on it's under and posterior surfaces by the left sagittal fossa; and in front by the umbilical notch. It is of a somewhat quadrilateral form, it's under and posterior surfaces being marked by three fossæ: the porta and the fossæ for the gall-bladder and inferior vena cava, which separate its left part into two smaller lobes; the quadrate and caudate lobes. The impressions on the right lobe have already been described.

The **quadrate lobe** (*lobus quadratus*) is situated on the under surface of the right lobe, bounded in front by the anterior margin of the liver; behind by the porta; on the right, by the fossa for the gall-bladder; and on the left, by the fossa for the umbilical vein. It is oblong in shape, its antero-posterior diameter being greater than it's transverse.

The **caudate lobe** (*lobus caudatus; Spigelian lobe*) is situated upon the posterior surface of the right lobe of the liver, opposite the tenth and eleventh thoracic vertebræ. It is bounded, below, by the porta; on the right, by the fossa for the inferior vena cava; and, on the left, by the fossa for the ductus venosus. It looks backward, being nearly vertical in position; it is longer from above downward than from side to side, and is somewhat concave in the transverse direction. The **caudate process** is a small elevation of the hepatic substance extending obliquely lateral ward, from the lower extremity of the caudate lobe to the under surface of the right lobe. It is situated behind the porta, and separates the fossa for the gall-bladder from the commencement of the fossa for the inferior vena cava.

The **left lobe** (*lobus hepatis sinister*) is smaller and more flattened than the right. It is situated in the epigastric and left hypochondriac regions. It's upper surface is slightly convex and is molded on to the diaphragm (*Fig. 2.1*).

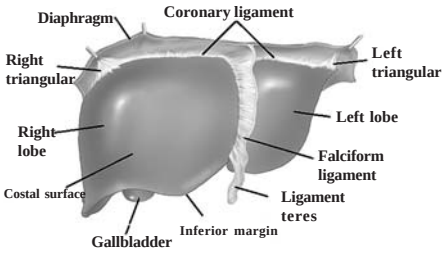


Figure 2.1. *Liver anatomy*

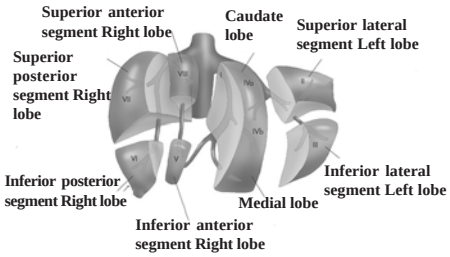


Figure 2.2. *Courinaud's system*

Hepatic nomenclature

• Courinaud's system of hepatic nomenclature provides the anatomic basis for hepatic surgical resection.

• Allows the radiologist to precisely isolate the location of lesions for the surgical team.

• 8 segments based on hepatic and portal venous segments (*Fig. 2.2*).

Hepatic artery. Enters the liver and then divides into two branches: right hepatic artery; left hepatic artery.

Portal veins. Enters the liver and then divides into two branches: right portal vein; left portal vein.

Right portal vein: larger of the two branches; divides into anterior and posterior branches.

Left portal vein: divides into medial and lateral branches.

Hepatic veins: 3 components – right, middle, left.

Physiology. The liver has many functions: metabolism, digestion, storage, detoxification.

Among the most important liver functions are:

Removing and excreting body wastes and hormones as well as drugs and other foreign substances. These substances have entered the blood supply either through production by metabolism within the body or from the outside in the form of drugs or other foreign compounds. Enzymes in the liver alter some toxins so they can be more easily excreted in urine.

Synthesizing plasma proteins, including those necessary for blood clotting. Most of the 12 clotting factors are plasma proteins produced by the liver. If the liver is damaged or diseased, it can take longer for the body to form clots. Other plasma proteins produced by the liver include albumin which binds many water-insoluble substances and contributes to osmotic pressure, fibrogen which is key to the clotting process, and certain globulins which transport substances such as cholesterol and iron.

Producing immune factors and removing bacteria, helping the body fight infection. The phagocytes in the liver produce acute-phase proteins in response to microbes. These proteins are associated with the inflammation process, tissue repair, and immune cell activities.

Other important but less immediate functions include:

Producing bile to aid in digestion. Bile salts aid in fat digestion and absorption. Bile is continuously secreted by the liver and stored in the gallbladder until a meal, when bile enters the beginning of the small intestine. Bile production ranges from 250 mL to 1 L per day depending of amount of food eaten.

Excretion of bilirubin. Bilirubin is one of the few waste products excreted in bile. Macrophages in the liver remove worn out red blood cells from the blood. Bilirubin then results from the breakdown of the hemoglobin in the red blood cells and is excreted into bile by hepatocytes. Jaundice results when bilirubin cannot be removed from the blood quickly enough due to gallstones, liver disease, or the excessive breakdown of red blood cells.

Storing certain vitamins, minerals, and sugars. The liver stores enough glucose in the form of glycogen to provide about a day's worth of energy. The liver also stores fats, iron, copper, and many vitamins including vitamins A, D, K, and B_{12}.

Processing nutrients absorbed from digestive tract. The liver converts glucose into glycogen, its storage form. This glycogen can then be transformed back into glucose if the body needs energy. The fatty acids produced by the digestion of

lipids are used to synthesize cholesterol and other substances. The liver also has the ability to convert certain amino acids into others.

Despite the wide variety of functions performed by the liver, there is very little specialization among hepatocytes (liver cells). Aside from the macrophages called Kupffer cells in the liver, hepatocytes all seem to be able to perform the same wide variety of tasks.

One of the liver's most interesting abilities is self-repair and the regeneration of damaged tissues. In clearing the body of toxins, the liver is damaged by exposure to harmful substances, demonstrating why this capability is important. It also gives hope that if a failing liver can be supported for a certain period of time, it might regenerate and allow the patient to survive and regain a normal life.

2.2. LIVER FIBROSIS

Cirrhosis is defined by its histological features, consisting of nodules of regenerating hepatocytes and the abnormal deposition of connective tissue in and around the nodules (fibrosis). Although the injury that initiated the process of regeneration and fibrosis may cease (and histological or laboratory evidence of inflammation and injury disappear), the fibrosis may be fixed and irreversible. By obliterating sinusoidal fenestrations, obstructing the space of Disse, and replacing vascular channels, fibrotic tissue increases resistance to blood flow. The resultant elevation of sinusoidal pressure causes shunting of portal flow around the liver, both exaggerating cellular dysfunction and creating the devastating consequences of portal hypertension. In addition, excess fibrosis prevents nutrient and metabolite exchange, further exacerbating the ramifications of the fibrotic response. Thus, liver fibrosis is a sine qua none of cirrhosis and directly responsible for many of its clinical features.

Many different diseases may result in the common "end stage" of cirrhosis. The spectrum of clinical abnormalities characterizing the cirrhotic stage of these diseases depends more on the extent of fibrosis, as well as the presence or absence of ongoing injury, than on the cause. Because so few of the underlying causes of cirrhosis are treatable, much attention has been focused on understanding, and potentially reversing, the generic process of fibrogenesis itself. However, it is unlikely that all diseases causing cirrhosis do so through the same initiating mechanism. For example, chronic hepatitis B, chronic ethanol abuse, and hemochromatosis may all result in cirrhosis. However, the liver in chronic hepatitis B characteristically demonstrates a lymphocytic infiltrate, whereas alcoholic liver disease is marked by hepatic infiltration with neutrophils, and infiltrates are absent in hemochromatosis. Furthermore, there are subtle differences in the specific content or location of deposited scar tissue in cirrhosis of different causes. Such differences may reflect differences in pathogenesis as well. If so, therapies successfully designed to limit fibrogenesis in one disease state may fail to work in another. One must bear this in mind when considering data obtained in any one model of hepatic fibrogenesis.

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires

liver transplantation. Our knowledge of the cellular and molecular mechanisms of liver fibrosis has greatly advanced. Activated hepatic stellate cells, portal fibroblasts, and myofibroblasts of bone marrow origin have been identified as major collagen-producing cells in the injured liver. These cells are activated by fibrogenic cytokines such as TGF-beta1, angiotensin II, and leptin. Reversibility of advanced liver fibrosis in patients has been recently documented, which has stimulated researchers to develop antifibrotic drugs. Emerging antifibrotic therapies are aimed at inhibiting the accumulation of fibrogenic cells and/or preventing the deposition of extracellular matrix proteins. Although many therapeutic interventions are effective in experimental models of liver fibrosis, their efficacy and safety in humans is unknown.

All chronic liver diseases (CLD) can lead to liver fibrosis. Over many years the principle causes of CLD have been chronic viral hepatitis B (CHB) and alcoholic liver disease (ALD). While rates of alcoholism and ALD are falling in many countries, hazardous drinking amongst young people is resulting in alarming rates of ALD in several northern European countries. Over the last few decades two other diseases have emerged to make a major contribution to the burden of CLD. Chronic hepatitis C (CHC) and non-alcoholic fatty liver disease (NAFLD) are recognized to have already had a major impact on CLD incidence. Hepatitis C virus (HCV) is transmitted in blood and blood products through unsafe injection practices and the therapeutic use of infected blood products. It is thought that the world prevalence of CHC is nearly 200 million people. In the developed world with rapidly increasing rates of obesity, NAFLD is considered to represent a major cause of significant fibrosis. Although it appears that only a minority of patients with NAFLD (maybe 20%) develop significant fibrosis, due to the vast prevalence of the at-risk overweight population, NAFLD may give rise to an epidemic of liver fibrosis.

The gold standard for the diagnosis of liver fibrosis is a biopsy with histological examination. The histological evaluation is performed on the JSHAK or METAVIR scale.

Depending on the location and prevalence, the following forms of liver fibrosis are distinguished:

• venular and perivennular (in the center of the lobules and walls of the central veins – characteristic of chronic alcoholic hepatitis);

• pericellular (around hepatocytes in chronic viral and alcoholic hepatitis);

• septal (concentric proliferation of fibrous tissue around the bile ducts – with viral hepatitis);

• portal and periportal (with viral, alcoholic, autoimmune hepatitis);

• periductal fibrosis (around the bile duct with sclerosing cholangitis);

• mixed (different forms of fibrosis are presented).

The fibrosis markers are divided into direct (biomarkers) reflecting the metabolism of the extracellular matrix, and indirect, indicative of hepatic insufficiency. Direct markers include carboxypeteral peptide procollagen type I, aminoterminal peptide procollagen III type, TIMP-1, 2, collagen type IV, hyaluronic acid, laminin, MMP-2.

Magnetic resonance ellastography is a direct method for determining the density of the liver, which makes it possible to determine F0 in comparison with healthy

volunteers, which so far has not been demonstrated by other methods of assessing fibrosis.

Antifibrotic therapy is inextricably linked with the etiological and pathogenetic treatment of chronic hepatitis. In most cases, drugs to eliminate the etiological factors of hepatitis are also antifibrotic drugs. An antifibrotic effect was detected in antiviral drugs, pentoxifylline, phosphatidylcholine, glucocorticosteroids, donators of nitric oxide, vitamin E, endothelin receptor antagonists, angiotensin receptor antagonists, angiotensin converting enzyme inhibitors, silymarin.

Now drugs with a directed antifibrotic effect are being studied:

• elimination of the damaging agent: interleukin 10, TNF inhibitors (anti-inflammatory effect), antioxidants (suppression of fibrotic processes in response to oxidative stress) etc.;

• suppression of the strabotic activity of stellate cells: interferons, hepatocyte growth factor, PPARγ agonists;

• maintenance of active antifibrotic activity of stellate cells: TGFβ1 antagonists (reduce matrix synthesis and enhance its decomposition), PDGF antagonists, nitric oxide, angiotensin-converting enzyme (ACE) inhibitors (suppression of Ito cell proliferation);

• the effect on the secretion of collagens by stellate cells of the liver: ACE inhibitors, polyhydroxylase inhibitors, interferon γ – reduce fibrosis, endothelin receptor antagonists (reduce fibrosis and portal hypertension);

• inhibition of apoptosis of Ito cells: hyylotoxin, NGF – neuronal growth factor (stimulate apoptosis);

• increased collagen matrix decomposition: metalloproteinases (MMP), antagonists of the tissue MMP inhibitor, TGF-β1 antagonists (reduce the activity of TIMP and increase the activity of MMP), relaxin (reduces the activity of TIMP and increases MMP activity).

Fibrosis is now called the cornerstone of chronic liver disease. It is he that determines the formation of liver cirrhosis, so early diagnosis and treatment of fibrosis are extremely relevant at the present time and are the task of future scientific research.

2.3. LIVER CIRRHOSIS

Cirrhosis is a liver disease caused by scarring of the liver over a long period of time (months to years). Term was 1st coined by Laennec in 1826 (*Fig. 2.3*).

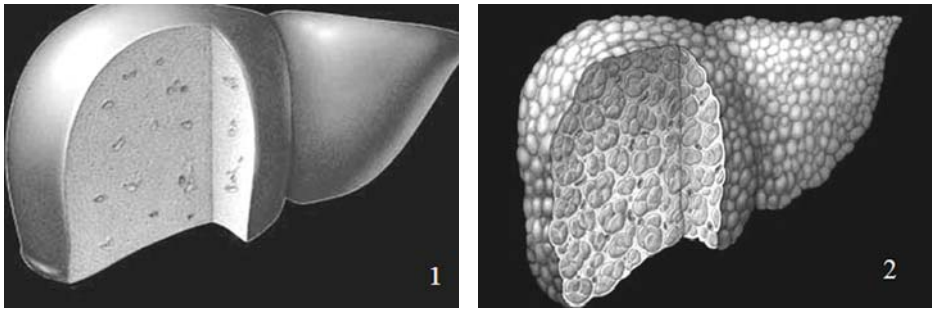


Figure 2.3. *Normal liver (1). Cirrothic liver (2)*

Cirrhosis is a result of late stage scarring in chronic liver disease. Cirrhosis occurs as a result of progressive damage to the liver tissue starting with subendothelial or pericentral fibrosis (hepatic fibrosis) and progresses to panlobular fibrosis with nodule formation (cirrhosis). Up until now it has been generally thought that once fibrosis is established it is irreversible. Until recently the clinical diagnosis of cirrhosis was made based upon the signs and symptoms of end stage liver disease.

Epidemiology

- Worldwide major health problem.
- Over 500,000 deaths per year (> 50% of liver disease in the US is directly related to alcohol consumption).
- Growing number of cases related to chronic hepatitis C.
- Direct correlation between alcohol consumption in any geographic area and the death rate from cirrhosis in that area.
- Over 20% were latent.
- 2 ~ 10% in postmortem examination.
- 4th leading cause of death in people between 35 and 54 years of age.

Etiology and pathophysiology

1. Cell necrosis occurs.
2. Destroyed liver cells are replaced by scar tissue.
3. Normal architecture becomes nodular.

Four types of cirrhosis:

1. Alcoholic (Laennec's) cirrhosis.
2. Postnecrotic cirrhosis.
3. Biliary cirrhosis.
4. Cardiac cirrhosis.

Alcoholic (Laennec's) cirrhosis:

- Associated with alcohol abuse.
- Preceded by a theoretically reversible fatty infiltration of the liver cells.
- Widespread scar formation.

Alcoholic liver disease. Alcoholic cirrhosis develops for between 10% and 20% of individuals who drink heavily for a decade or more. There is great variability in the amount of alcohol needed to cause cirrhosis (as little as 3–4 drinks a day in some men and 2–3 in some women. Alcohol seems to injure the liver by blocking the normal metabolism of protein, fats, and carbohydrates. Patients may also have concurrent alcoholic hepatitis with fever, hepatomegaly, jaundice, and anorexia. AST and ALT are both elevated but less than 300 IU/L with a AST: ALT ratio > 2.0, a value rarely seen in other liver diseases. Liver biopsy may show hepatocyte necrosis, Mallory bodies, neutrophilic infiltration with perivenular inflammation.

Postnecrotic cirrhosis:

- Complication of toxic or viral hepatitis.
- Accounts for 20% of the cases of cirrhosis.
- Broad bands of scar tissue form within the liver.

Chronic hepatitis C. Infection with the hepatitis C virus causes inflammation of the liver and a variable grade of damage to the organ that over several decades can lead to cirrhosis. Cirrhosis caused by hepatitis C is the most common reason for liver transplant. Can be diagnosed with serologic assays that detect hepatitis C antibody or viral RNA. The enzyme immunoassay, EIA-2, is the most commonly used screening test in the US.

Chronic hepatitis B. The hepatitis B virus causes liver inflammation and injury that over several decades can lead to cirrhosis. Hepatitis D is dependent on the presence of hepatitis B, but accelerates cirrhosis in co-infection. Chronic hepatitis B can be diagnosed with detection of HBsAG > 6 months after initial infection. HBeAG and HBV DNA are determined to assess whether patient will need antiviral therapy.

Non-alcoholic steatohepatitis (NASH). In NASH, fat builds up in the liver and eventually causes scar tissue. This type of hepatitis appears to be associated with diabetes, protein malnutrition, obesity, coronary artery disease, and treatment with corticosteroid medications. This disorder is similar to that of alcoholic liver disease but patient does not have an alcohol history. Biopsy is needed for diagnosis.

Biliary cirrhosis:

- Associated with chronic biliary obstruction and infection.
- Accounts for 15% of all cases of cirrhosis.

Primary biliary cirrhosis. May be asymptomatic or complain of fatigue, pruritus, and non-jaundice skin hyperpigmentation with hepatomegaly. There is prominent alkaline phosphatase elevation as well as elevations in cholesterol and bilirubin. Gold standard diagnosis is antimitochondrial antibodies with liver biopsy as confirmation if showing florid bile duct lesions. It is more common in women.

Primary sclerosing cholangitis (PSC). PSC is a progressive cholestatic disorder presenting with pruritus, steatorrhea, fat soluble vitamin deficiencies, and metabolic bone disease. There is a strong association with inflammatory bowel disease, especially ulcerative colitis. Diagnosis is best with contrast cholangiography showing diffuse, multifocal strictures and focal dilation of bile ducts, leading to a beaded appearance. Non-specific serum immunoglobulins may also be elevated.

Autoimmune hepatitis. This disease is caused by the immunologic damage to the liver causing inflammation and eventually scarring and cirrhosis. Findings include elevations in serum globulins, especially gamma globulins. Therapy with prednisone +/- azathioprine is beneficial. Cirrhosis due to autoimmune hepatitis still has 10-year survival of 20%+. There is no specific tool to diagnose autoimmune but it can be beneficial to initiate a trial of corticosteroids.

Hereditary hemochromatosis. Usually presents with family history of cirrhosis, skin hyperpigmentation, diabetes mellitus, pseudogout, and/or cardiomyopathy, all due to signs of iron overload. Labs will show fasting transferrin saturation of > 60% and ferritin > 300 ng/mL. Genetic testing may be used to identify HFE mutations. If these are present, biopsy may not need to be performed. Treatment is with phlebotomy to lower total body iron levels.

Wilson's disease. Autosomal recessive disorder characterized by low serum ceruloplasmin and increased hepatic copper content on liver biopsy. May also have Kayser-Fleischer rings in the cornea and altered mental status.

Alpha1-antitrypsin deficiency (AAT). Autosomal recessive disorder. Patients may also have COPD, especially if they have a history of tobacco smoking. Serum AAT levels are low. Recombinant AAT is used to prevent lung disease due to AAT deficiency.

Cardiac cirrhosis:

- Results from longstanding severe right-sided heart failure:
  - Galactosemia.
  - Cystic fibrosis.
  - Hepatotoxic drugs or toxins.
  - Certain parasitic infections.

The liver plays a vital role in synthesis of proteins (e.g., albumin, clotting factors and complement), detoxification and storage (e.g., vitamin A). In addition, it participates in the metabolism of lipids and carbohydrates.

Cirrhosis is often preceded by hepatitis and fatty liver (steatosis), independent of the cause. If the cause is removed at this stage, the changes are still fully reversible.

The pathological hallmark of cirrhosis is the development of scar tissue that replaces normal parenchyma, blocking the portal flow of blood through the organ and disturbing normal function. Recent research shows the pivotal role of the stellate cell, a cell type that normally stores vitamin A, in the development of cirrhosis. Damage to the hepatic parenchyma leads to activation of the stellate cell, which becomes contractile (called myofibroblast) and obstructs blood flow in the circulation. In addition, it secretes TGF-β1, which leads to a fibrotic response and proliferation of connective tissue. Furthermore, it disturbs the balance between matrix metalloproteinases and the naturally occurring inhibitors (TIMP 1 and 2), leading to matrix breakdown and replacement by connective tissue-secreted matrix.

The fibrous tissue bands (septa) separate hepatocyte nodules, which eventually replace the entire liver architecture, leading to decreased blood flow throughout. The spleen becomes congested, which leads to hypersplenism and increased sequestration of platelets. Portal hypertension is responsible for most severe complications of cirrhosis.

2.3.1. PATHOLOGY

World Health Organization divided cirrhosis into **3 categories** based on morphological characteristics of the hepatic nodules:

1. Micronodular.
2. Macronodular.
3. Mixed.

Micronodular cirrhosis:

- Nodules are <3 mm in diameter.
- Relatively uniform in size.
- Distributed throughout the liver.
- Rarely contain portal tracts or efferent veins.
- Liver is of uniform size or mildly enlarged.
- Reflect relatively early disease.

Macronodular and mixed cirrhosis:

- Nodules are >3 mm in diameter and vary considerably in size.
- Usually contain portal tracts and efferent veins.
- Liver is usually normal or reduced in size.
- Mixed pattern if both type of nodules are present in equal proportions.

2.3.2. MANIFESTATIONS OF LIVER CIRRHOSIS

Early cirrhosis manifestations

1. Onset usually insidious.
2. Gastrointestinal disturbances:

- anorexia;
- dyspepsia;
- flatulence;
- change in bowel habits;
- abdominal pain;
- fever;
- lassitude;
- poor growth;
- weight loss;
- enlarged liver or spleen.

Late cirrhosis manifestations

Two causative mechanisms:

1. Hepatocellular failure.
2. Portal hypertension

Jaundice

1. Occurs because of insufficient conjugation of bilirubin by the liver cells, and local obstruction of biliary ducts by scarring and regenerating tissue.
2. Intermittent jaundice is characteristic of biliary cirrhosis.
3. Late stages of cirrhosis the patient will usually be jaundiced.

Skin

- Spider angiomas (telangiectasia, spider nevi).
- Palmar erythema. Due to increased circulating estrogen.

Endocrine Disturbances

- Steroid hormones of the adrenal cortex (aldosterone), testes, and ovaries are metabolized and inactivated by the normal liver.
- Alteration in hair distribution:
  - decreased amount of pubic hair;
  - axillary and pectoral alopecia.

Hematologic Disorders

- Bleeding tendencies as a result of decreased production of hepatic clotting factors (II, VII, IX, and X).
- Anemia, leukopenia, and thrombocytopenia are believed to be result of hypersplenism.

Peripheral Neuropathy

- Dietary deficiencies of thiamine, folic acid, and vitamin B_{12}.

2.3.3. DIAGNOSIS

The gold standard for diagnosis of cirrhosis is a liver biopsy, through a percutaneous, transjugular, laparoscopic, or fine-needle approach. Histologically cirrhosis can be classified as micronodular, macronodular, or mixed, but this classification has been abandoned since it is non-specific to the etiology, it may change as the disease progresses, and serological markers are much more specific. However, a biopsy is not necessary if the clinical, laboratory, and radiologic data suggests cirrhosis. Furthermore, there is a small but significant risk to liver biopsy, and cirrhosis itself predisposes for complications due to liver biopsy.

Signs and symptoms

Some of the following signs and symptoms *may* occur in the presence of cirrhosis or as a result of the complications of cirrhosis. Many are nonspecific and may occur in other diseases and do not necessarily point to cirrhosis. Likewise, the absence of any does not rule out the possibility of cirrhosis.

Spider angiomata or spider nevi. Vascular lesions consisting of a central arteriole surrounded by many smaller vessels due to an increase in estradiol. These occur in about 1/3 of cases.

Palmar erythema. Exaggerations of normal speckled mottling of the palm, due to altered sex hormone metabolism.

Nail changes

Muehrcke's lines – paired horizontal bands separated by normal color due to hypoalbuminemia (inadequate production of albumin).

Terry's nails – proximal two-thirds of the nail plate appears white with distal one-third red, also due to hypoalbuminemia

Clubbing – angle between the nail plate and proximal nail fold > 180 degrees

Hypertrophic osteoarthropathy. Chronic proliferative periostitis of the long bones that can cause considerable pain.

Dupuytren's contracture. Thickening and shortening of palmar fascia that leads to flexion deformities of the fingers. Thought to be due to fibroblastic proliferation and disorderly collagen deposition. It is relatively common (33% of patients).

Gynecomastia. Benign proliferation of glandular tissue of male breasts presenting with a rubbery or firm mass extending concentrically from the nipples. This is due to increased estradiol and can occur in up to 66% of patients.

Hypogonadism. Manifested as impotence, infertility, loss of sexual drive, and testicular atrophy due to primary gonadal injury or suppression of hypothalamic or pituitary function.

Liver size. Can be enlarged, normal, or shrunken.

Splenomegaly (increase in size of the spleen). Due to congestion of the red pulp as a result of portal hypertension.

Ascites. Accumulation of fluid in the peritoneal cavity giving rise to flank dullness (needs about 1500 mL to detect flank dullness). It may be associated with hydrocele and penile flomation (swelling of the penile shaft) in men.

Caput medusae. In portal hypertension, the umbilical vein may open. Blood from the portal venous system may be shunted through the periumbilical veins into

the umbilical vein and ultimately to the abdominal wall veins, manifesting as caput medusa.

Cruveilhier-Baumgarten murmur. Venous hum heard in epigastric region (on examination by stethoscope) due to collateral connections between portal system and the remnant of the umbilical vein in portal hypertension.

Fetor hepaticus. Musty odor in breath due to increased dimethyl sulfide.

Jaundice. Yellow discoloring of the skin, eye, and mucus membranes due to increased bilirubin (at least 2–3 mg/dL or 30 mmol/L). Urine may also appear dark.

Asterixis. Bilateral asynchronous flapping of outstretched, dorsiflexed hands seen in patients with hepatic encephalopathy.

Other: weakness, fatigue, anorexia, weight loss.

Laboratory investigations

The following findings are typical in cirrhosis:

• *Aminotransferases* – Aspartate transferase (AST) and Alanine transferase (ALT) are moderately elevated, with AST > ALT. However, normal aminotransferases do not preclude cirrhosis.

• *Alkaline phosphatase* – usually slightly elevated.

• *Gamma-glutamintranspeptidase* – correlates with levels of process activity. Typically much higher in chronic liver disease from alcohol.

• *Bilirubin* – may elevate as cirrhosis progresses.

• *Albumin* – levels fall as the synthetic function of the liver declines with worsening cirrhosis since albumin is exclusively synthesized in the live.

• *Prothrombin time* – increases since the liver synthesizes clotting factors.

• *Globulins* – increased due to shunting of bacterial antigens away from the liver to lymphoid tissue.

• *Serum sodium* – hyponatremia due to inability to excrete free water resulting from high levels of alcohol-dehydrogenase and aldosterone.

• *Thrombocytopenia* – due to both congestive splenomegaly as well as decreased thrombopoietin from the liver. However, this rarely results in platelet count < 50,000/mL.

• *Leukopenia and neutropenia* – due to splenomegaly with splenic margination.

• *Coagulation defects* – the liver produces most of the coagulation factors and thus coagulopathy correlates with worsening liver disease.

There is now a validated and patented combination of 6 of these markers as non-invasive biomarker of fibrosis (and so of cirrhosis): FibroTest.

Other laboratory studies performed in newly diagnosed cirrhosis may include:

• Serology for hepatitis viruses, autoantibodies (ANA, anti-smooth muscle, anti-mitochondria, anti-LKM).

• Ferritin and transferrin saturation (markers of iron overload), copper and ceruloplasmin (markers of copper overload).

• Immunoglobulin levels (IgG, IgM, IgA) – these are non-specific but may assist in distinguishing various causes.

• Cholesterol and glucose.

•Alpha 1-antitrypsin.

Instrumental investigations

Ultrasound is routinely used in the evaluation of cirrhosis, where it may show a small and nodular liver in advanced cirrhosis along with increased echogenicity with irregular appearing areas. Ultrasound may also screen for hepatocellular carcinoma, portal hypertension and Budd–Chiari syndrome (by assessing flow in the hepatic vein).

A new type of device, the FibroScan (transient elastography), uses elastic waves to determine liver stiffness which theoretically can be converted into a liver score based on the METAVIR scale. The FibroScan produces an ultrasound image of the liver (from 20–80 mm) along with a pressure reading (in kPa.) The test is much faster than a biopsy (usually last 2,5–5 minutes) and is completely painless. It shows reasonable correlation with the severity of cirrhosis.

Other tests performed in particular circumstances include abdominal CT (*Fig. 2.4*) and liver/bile duct MRI (MRCP).

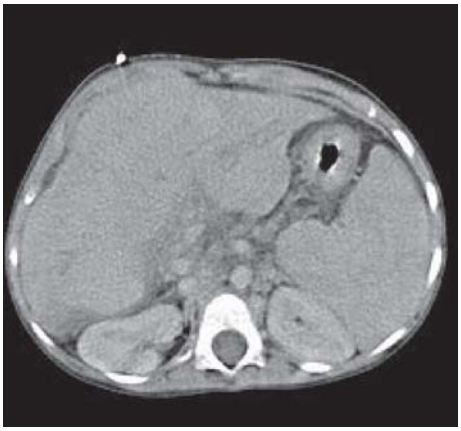


Figure. 2.4. *Liver cirrhosis as seen on an axial CT of the abdomen*

Gastroscopy (endoscopic examination of the esophagus, stomach and duodenum) is performed in patients with established cirrhosis to exclude the possibility of esophageal varices. If these are found, prophylactic local therapy may be applied (sclerotherapy or banding) and beta blocker treatment may be commenced.

Rarely diseases of the bile ducts, such as primary sclerosing cholangitis, can be causes of cirrhosis. Imaging of the bile ducts, such as ERCP or MRCP (MRI of biliary tract and pancreas) can show abnormalities in these patients, and may aid in the diagnosis.

Grading

The severity of cirrhosis is commonly classified with the Child-Pugh score. This score uses bilirubin, albumin, prothrombin time, presence and severity of ascites and encephalopathy to classify patients in class A, B or C; class A has a favorable prognosis, while class C is at high risk of death. It was devised in 1264 by Child and Turcotte and modified in 1273 by Pugh et al. (*Table 2.1*).

1. Grade A – 5–6 points.
2. Grade B – 7–2 points.
3. Grade C – 10–15 points.

Table 2.1 – Child-Pugh Classification

	Points		
	1	2	3
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
—	1–3	4–6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	Minimal	Advanced

Complications

As the disease progresses, complications may develop. In some people, these may be the first signs of the disease.

• Bruising and bleeding due to decreased production of coagulation factors.

• Jaundice due to decreased processing of bilirubin.

• Itching due to bile salts products deposited in the skin.

• Hepatic encephalopathy – the liver does not clear ammonia and related nitrogenous substances from the blood, which are carried to the brain, affecting cerebral functioning: neglect of personal appearance, unresponsiveness, forgetfulness, trouble concentrating, or changes in sleep habits.

• Sensitivity to medication due to decreased metabolism of the active compounds.

• Hepatocellular carcinoma is primary liver cancer, a frequent complication of cirrhosis. It has a high mortality rate.

• Portal hypertension – blood normally carried from the intestines and spleen through the hepatic portal vein flows more slowly and the pressure increases; this leads to the following complications:

‣ ascites – fluid leaks through the vasculature into the abdominal cavity;

‣ esophageal varices – collateral portal blood flow through vessels in the stomach and esophagus. These blood vessels may become enlarged and are more likely to burst (*Fig. 2.5*).

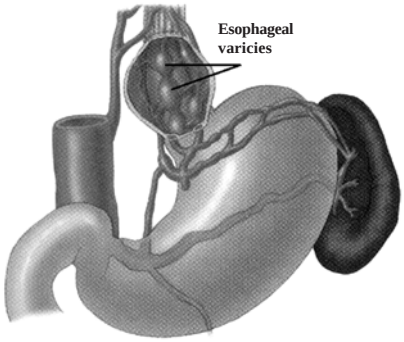


Figure 2.5. *Esophageal varices*

• Problems in other organs:

‣ Cirrhosis can cause immune system dysfunction, leading to infection. Signs and symptoms of infection may be aspecific are more difficult to recognize (e.g., worsening encephalopathy but no fever).

‣ Fluid in the abdomen (ascites) may become infected with bacteria normally present in the intestines (spontaneous bacterial peritonitis).

‣ Hepatorenal syndrome – insufficient blood supply to the kidneys, causing acute renal failure. This complication has a very high mortality (over 50%).

‣ Hepatopulmonary syndrome – blood bypassing the normal lung circulation (shunting), leading to cyanosis and dyspnea (shortness of breath), characteristically worse on sitting up.

‣ Portopulmonary hypertension – increased blood pressure over the lungs as a consequence of portal hypertension.

‣ Portal hypertensive gastropathy which refers to changes in the mucosa of the stomach in patients with portal hypertension, and is associated with cirrhosis severity.

2.4. PORTAL HYPERTENSION

Etiology of portal hypertension

Causes of portal hypertension (PH) can be divided into:

1. Pre-hepatic.

2. Intra-hepatic.

3. Post-hepatic.

Pre-hepatic PH:

• Caused by obstruction to blood flow at the level of portal vein.

• Examples: congenital atresia, extrinsic compression, schistosomiasis, portal, superior mesenteric, or splenic vein thrombosis.

Post-hepatic PH:

• Caused by obstruction to blood flow at the level of hepatic vein.

• Examples: Budd-Chiari syndrome, chronic heart failure, constrictive pericarditis, vena cava webs.

Budd-Chiari syndrome:

• Caused by hepatic venous obstruction.

• At the level of the inferior vena cava, the hepatic veins, or the central veins within the liver itself.

• Result of congenital webs (in Africa and Asia), acute or chronic thrombosis (in the West), and malignancy.

• Acute symptoms include hepatomegaly, abdominal pain in the right upper quadrant, nausea, vomiting, ascites.

• Chronic form present with the sequelae of cirrhosis and portal hypertension, including variceal bleeding, ascites, spontaneous bacterial peritonitis, fatigue, and encephalopathy.

• Diagnosis is most often made by US evaluation of the liver and its vasculature.

• Cross-sectional imaging using contrast-enhanced CT or MRI.

• Gold standard for the diagnosis has been angiography.

• Management has traditionally been surgical intervention (surgical decompression with a side-to-side portosystemic shunt).

• Minimally invasive treatment using TIPS may be first-line therapy now.

• Response rates to medical therapy are poor.

Portal vein thrombosis:

• Most common cause in children (fewer than 10% of adult pts.).

• Normal liver function and not as susceptible to the development of complications, such as encephalopathy.

• Diagnosis by sonography, CT and MRI.

• Often, the initial manifestation of portal vein thrombosis is variceal bleeding in a noncirrhotic patient with normal liver function.

Portal vein thrombosis – causes:

• Umbilical vein infection (the most common cause in children).

• Coagulopathies (protein C and antithrombin III deficiency).

• Hepatic malignancy, myeloproliferative disorders.

• Inflammatory bowel disease.

• Pancreatitis.
• Trauma.
• Most cases in adults are idiopathic.
• Portal Vein Thrombosis.
• Therapeutic options are esophageal variceal ligation and sclerotherapy.
• Distal splenorenal shunt.
• Rex shunt in patients whose intrahepatic portal vein is patent (most commonly children).

Splenic vein thrombosis:

• Most often caused by disorders of the pancreas (acute and chronic pancreatitis, trauma, pancreatic malignancy, and pseudocysts).
• Related to the location of the splenic vein.
• Gastric varices are present in 80% of patients.
• Occurs in the setting of normal liver function.
• Readily cured with splenectomy (variceal hemorrhage), although observation for asymptomatic patients is acceptable.

Portal Vein Collaterals

• Coronary vein and short gastric veins → veins of the lesser curve of the stomach and the esophagus, leading to the formation of varices (*Fig. 2.6*).

• Inferior mesenteric vein → rectal branches which, when distended, form hemorrhoids

• Umbilical vein → epigastric venous system around the umbilicus (**"caput medusae"**).

Retroperitoneal collaterals → gastrointestinal veins through the bare areas of the liver.

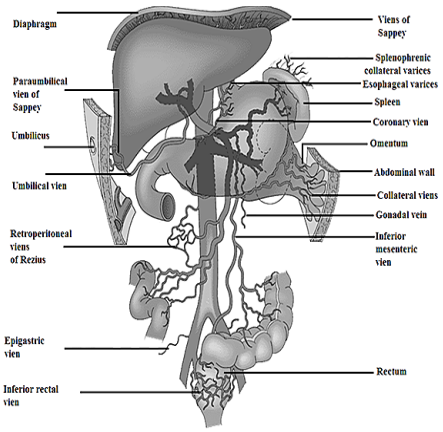


Figure 2.6. *Portal vein collaterals*

Pathophysiology of Portal Hypertension

• Portal vein pressure above the normal range of 5 to 8 mm Hg.
• Portal vein – hepatic vein pressure gradient greater than 5 mm Hg (>12 clinically significant).
• Represents an increase of the hydrostatic pressure within the portal vein or its tributaries.
• Cirrhosis results in scarring (perisinusoidal deposition of collagen).
• Scarring narrows and compresses hepatic sinusoids (fibrosis).
• Progressive increase in resistance to portal venous blood flow results in portal hypertension.
• Portal vein thrombosis, or hepatic venous obstruction also cause portal hypertension by increasing the resistance to portal blood flow.
• As pressure increases, blood flow decreases and the pressure in the portal system is transmitted to its branches.

• Results in dilation of venous tributaries.

• Increased blood flow through collaterals and subsequently increased venous return cause an increase in cardiac output and total blood volume and a decrease in systemic vascular resistance.

• With progression of disease, blood pressure usually falls.

Complications of portal hypertension characterized by:

• Increased venous pressure in portal circulation.

• Splenomegaly.

• Esophageal varices.

• Systemic hypertension.

• Primary mechanism is the increased resistance to blood flow through the liver.

Splenomegaly: back pressure caused by portal hypertension → chronic passive congestion as a result of increased pressure in the splenic vein.

Esophageal Varices: increased blood flow through the portal system results in dilation and enlargement of the plexus veins of the esophagus and produces varices; varices have fragile vessel walls which bleed easily; most life threatening complication.

Internal Hemorrhoids: occurs because of the dilation of the mesenteric veins and rectal veins.

Caput Medusae: collateral circulation involves the superficial veins of the abdominal wall leading to the development of dilated veins around the umbilicus.

Management. Generally, liver damage from cirrhosis cannot be reversed, but treatment could stop or delay further progression and reduce complications. A healthy diet is encouraged, as cirrhosis may be an energy-consuming process. Close follow-up is often necessary. Antibiotics will be prescribed for infections, and various medications can help with itching. Laxatives, such as lactulose, decrease risk of constipation; their role in preventing encephalopathy is limited.

Esophageal Varices:

1. Avoid alcohol, aspirin, and irritating foods.

2. If bleeding occurs, stabilize patient and manage the airway, administer vasopressin (Terlipressin, Pitressin, Remestip).

3. Balloon tamponade (*Fig. 2.7*).

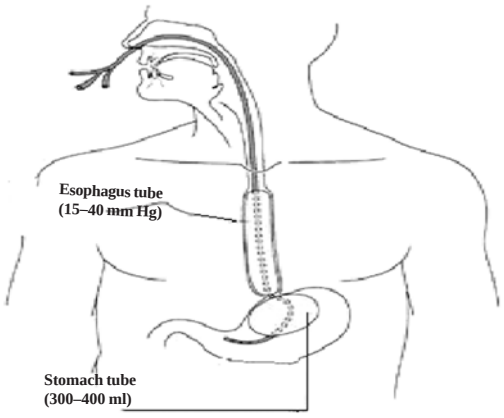


Figure 2.7. *Sengstaken-Blakemore tube*

4. Drug therapy: Octerotide (Sandostatin); Vasopressin; β-blocker; Vitamin K; H_2 blockers; Lactulose; Neomycin.

5. Endoscopic sclerotherapy or ligation (*Fig. 2.8, 2.9*).

6. Surgical shunting procedures: devascularisation transection with or without splenectomy (*Fig. 2.10*); TIPS (*Fig. 2.11*), portacaval shunt (*Fig. 2.12*).

Devascularisation of 7–8 cm of the lower esophagus, the entire greater

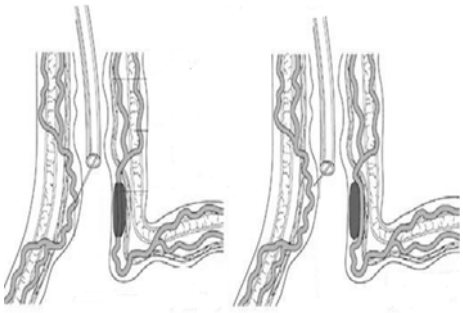


Figure 2.8. *Endoscopic sclerotherapy*

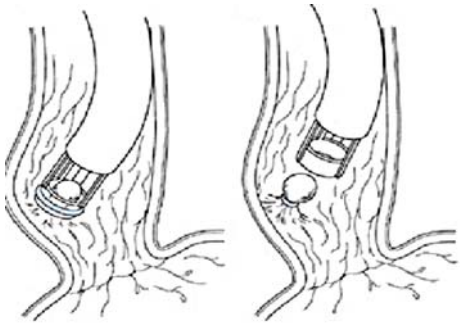


Figure 2.9. *Endoscopic variceal ligation*

curve part of lesser curve to incisura with ligation of the Coronary vein followed by stapled esophageal transaction (*Fig. 2.10*).

Devascularisation may be omitted in the critically ill patient. Role of splenectomy is unclear: usually depends on the clinical state of the patient and the presence of associated Hypersplenism. May facilitate the devascularisation but may also add morbidity to the surgery if densely adherent to the diaphragm with associated extensive

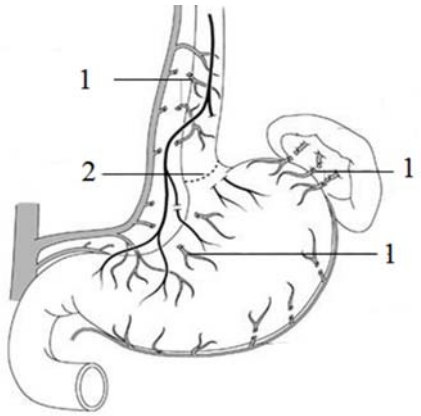


Figure 2.10. *Devascularization (1) and crossing (2) of stomach*

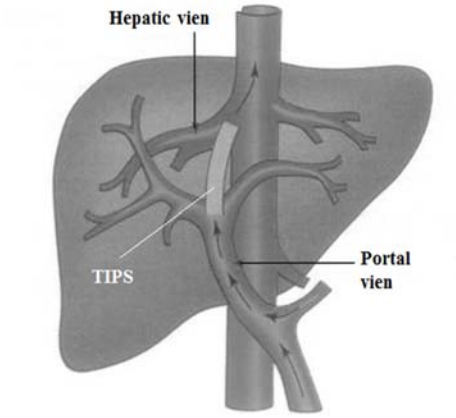


Figure 2.11. *Transjugular inrahepatic portasystemic shunt*

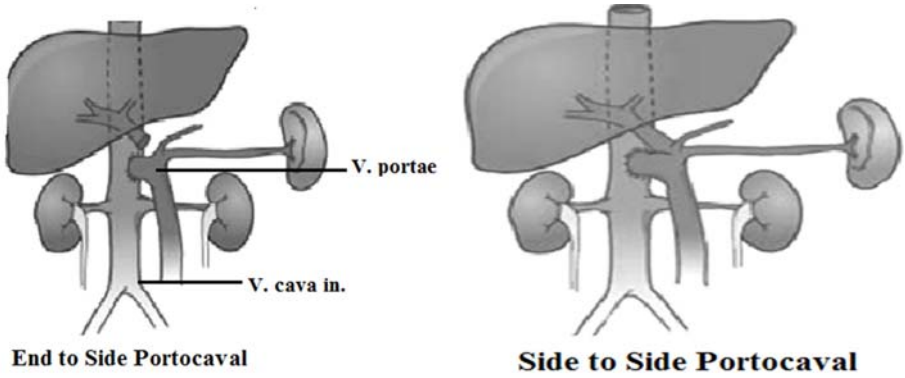


Figure 2.12. *Types of portosystemic shunts*

collaterals. Local studies show that addition of splenectomy did not alter morbidity or mortality.

Transjugular Inrahepatic Portasystemic Shunt (TIPS). Entails placement of expandable metallic stent between hepatic vein and portal vein radicle within the liver under radiological imaging via internal jugular vein. Rapidly creates a shunt reducing Portal pressure and controls variceal bleeding.

Indications to formation of TIPS (*Fig. 2.11*):

• 1st line treatment for bleeding esophageal varices when earlier-mentioned methods fail.

• Performed in IR.

• Success rates 20–100%.

• Significant complication is hepatic encephalopathy.

• Surgical intervention.

Shunts.

Types: 1) total portosystemic shunt: end to side portocaval; 2) partial: 8 mm side to side portocaval (sarfeh) (*Fig. 2.12*); 3) selective: distal splenorenal shunt – Warren's operation (*Fig. 2.13*); Linton proximal splenorenal shunt.

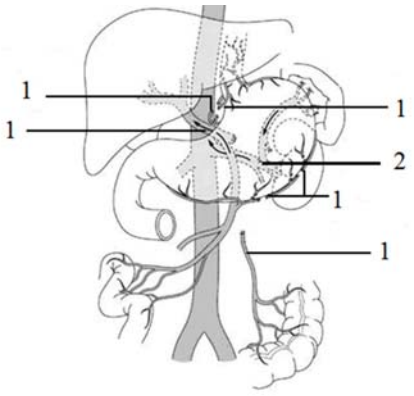


Figure 2.13. *Warren's operation (crossing lines of viens (1); distal splenorenal shunt (2)*

2.5. ASCITES

The word ascites is of Greek origin (*askos*) and means bag or sac. Ascites describes the condition of pathologic fluid collection within the abdominal cavity. Healthy men have little or no intraperitoneal fluid, but women may normally have as much as 20 mL, depending on the phase of their menstrual cycle. This article focuses only on ascites associated with cirrhosis (*Fig. 2.14*).

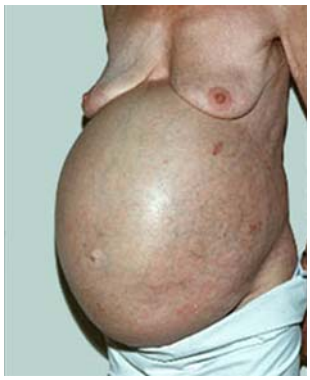


Figure 2.14. *Portal hypertension and ascites*

Pathophysiology

The accumulation of ascitic fluid represents a state of total-body sodium and water excess, but the event that initiates the unbalance is unclear. Three theories of ascites formation have been proposed: underfilling, overflow, and peripheral arterial vasodilation.

The underfilling theory suggests that the primary abnormality is inappropriate sequestration of fluid within the splanchnic vascular bed due to portal hypertension and a consequent decrease in effective circulating blood volume. This activates the plasma renin, aldosterone, and sympathetic nervous system, resulting in renal sodium and water retention.

The overflow theory suggests that the primary abnormality is inappropriate renal retention of sodium and water in the absence of volume depletion. This theory

was developed in accordance with the observation that patients with cirrhosis have intravascular hypervolemia rather than hypovolemia.

The most recent theory, the peripheral arterial vasodilation hypothesis, includes components of both of the other theories. It suggests that portal hypertension leads to vasodilation, which causes decreased effective arterial blood volume. As the natural history of the disease progresses, neurohumoral excitation increases, more renal sodium is retained, and plasma volume expands. This leads to overflow of fluid into the peritoneal cavity. The vasodilation theory proposes that underfilling is operative early and overflow is operative late in the natural history of cirrhosis.

Although the sequence of events that occurs between the development of portal hypertension and renal sodium retention is not entirely clear, portal hypertension apparently leads to an increase in nitric oxide levels. Nitric oxide mediates splanchnic and peripheral vasodilation. Hepatic artery nitric oxide synthase activity is greater in patients with ascites than in those without ascites.

Regardless of the initiating event, a number of factors contribute to the accumulation of fluid in the abdominal cavity. Elevated levels of epinephrine and norepinephrine are well-documented factors. Hypoalbuminemia and reduced plasma oncotic pressure favor the extravasation of fluid from the plasma to the peritoneal fluid, and, thus, ascites is infrequent in patients with cirrhosis unless both portal hypertension and hypoalbuminemia are present.

Clinical

History:

1. Patients with ascites often state that they have recently noticed an increase in their abdominal girth.

2. Because most cases of ascites are due to liver disease, patients with ascites should be asked about risk factors for liver disease. These include the following:

- Long-term heavy alcohol use.
- Chronic viral hepatitis or jaundice.
- Intravenous drug use.
- Multiple sexual partners.
- Homosexual activity with a male partner, or heterosexual activity with a bisexual male.
- Transfusion with blood not tested for hepatitis virus: in the United States, screening of donated blood for hepatitis B virus (HBV) began in 1272; reliable testing of the blood supply for hepatitis C virus (HCV) began in 1222 in developed countries.
- Tattoos.
- Living or birth in an area endemic for hepatitis.

3. Patients with alcoholic liver disease who alternate between heavy alcohol consumption and abstention (or light consumption) may experience ascites in a cyclic fashion.

4. When a patient with a very long history of stable cirrhosis develops ascites, the possibility of superimposed hepatocellular carcinoma (HCC) should be considered.

5. Obesity, hypercholesterolemia, and type 2 diabetes mellitus are recognized causes of nonalcoholic steatohepatitis, which can progress to cirrhosis.

6. Patients with a history of cancer, especially gastrointestinal cancer, are at risk for malignant ascites. Malignancy-related ascites is frequently painful, whereas cirrhotic ascites is usually painless.

7. Patients who develop ascites in the setting of established diabetes or nephrotic syndrome may have nephrotic ascites.

Physical

The physical examination in a patient with ascites should focus on the signs of portal hypertension and chronic liver disease.

• Physical findings suggestive of liver disease include jaundice, palmar erythema, and spider angiomas.

• The liver may be difficult to palpate if a large amount of ascites is present, but if palpable, the liver is often found to be enlarged. The puddle sign may be present when as little as 120 mL of fluid is present. When peritoneal fluid exceeds 500 mL, ascites may be demonstrated by the presence of shifting dullness or bulging flanks. A fluid-wave sign is notoriously inaccurate.

• Elevated jugular venous pressure may suggest a cardiac origin of ascites. A firm nodule in the umbilicus, the so-called Sister Mary Joseph nodule, is not common but suggests peritoneal carcinomatosis originating from gastric, pancreatic, or hepatic primary malignancy.

• A pathologic left-sided supraclavicular node (Virchow node) suggests the presence of upper abdominal malignancy.

• Patients with cardiac disease or nephrotic syndrome may have anasarca.

Causes

Normal peritoneum

• Portal hypertension (serum-ascites albumin gradient [SAAG] >1.1 g/dL).

• Hepatic congestion, congestive heart failure, constrictive pericarditis, tricuspid insufficiency, Budd-Chiari syndrome.

• Liver disease, cirrhosis, alcoholic hepatitis, fulminant hepatic failure, massive hepatic metastases.

Hypoalbuminemia (SAAG <1.1 g/dL).

• Nephrotic syndrome.

• Protein-losing enteropathy.

• Severe malnutrition with anasarca.

• Miscellaneous conditions (SAAG <1.1 g/dL).

• Chylous ascites.

• Pancreatic ascites.

• Bile ascite.

• Urine ascites.

• Ovarian disease.

• Diseased peritoneum (SAAG <1.1 g/dL).

Infections:

• Bacterial peritonitis.

• Tuberculosis peritonitis.

• Fungal peritonitis.
• Human immunodeficiency virus (HIV) – associated peritonitis.

Malignant conditions:

• Peritoneal carcinomatosis.
• Primary mesothelioma.
• Pseudomyxoma peritonei.
• Hepatocellular carcinoma.

Other rare conditions:

• Familial Mediterranean fever.
• Vasculitis.
• Granulomatous peritonitis.
• Eosinophilic peritonitis.

Treatments

1. Paracentesis.
2. Shunts (*Fig. 2.15*):

• Le vein shunt – drains ascites fluid into superior vena cava.

• Denver shunt – subcutaneous pump that is manually compressed.

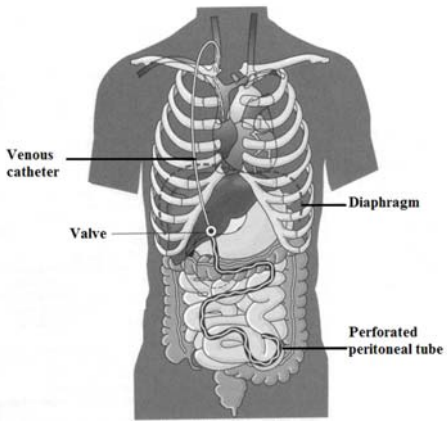


Figure 2.15. *Peritoneovenous (Le Veen) shunting for treatment of ascites*

2.6. JAUNDICE

Jaundice, also known as icterus (attributive adjective: "icteric"), is yellowish discoloration of the skin, sclerae (whites of the eyes) and mucous membranes caused by hyperbilirubinemia (increased levels of bilirubin in the blood). This hyperbilirubinemia subsequently causes increased levels of bilirubin in the extracellular fluids. Typically, the concentration of bilirubin in the plasma must exceed 1.5 mg/ dL, three times the usual value of approximately 0.5 mg/dL, for the coloration to be easily visible. *Jaundice* comes from the French word *jaune*, meaning yellow.

Normal Physiology

In order to understand how jaundice results, it is important to understand where the pathological processes that cause jaundice take their effect. It is also important to further recognize that jaundice itself is not a disease, but rather a symptom of an underlying pathological process that occurs at some point along the normal physiological pathway of the metabolism of bilirubin.

Pre-hepatic events

When red blood cells have completed their life span of approximately 120 days, their membranes become fragile and prone to rupture. As the cell traverses through the reticuloendothelial system, their cell membranes rupture and the contents of the red blood cell is released into the blood. The component of the red blood cell that is involved in jaundice is hemoglobin. The hemoglobin released into the blood is phagocytosed by macrophages, and split into its heme and globin portions. The globin portion, being protein, is degraded into amino acids and plays no further role in jaundice. Two reactions then take place to the heme molecule. The first reaction is the oxidation of heme to form biliverdin.This reaction is catalyzed by microsomal

enzyme heme oxygenase and it results in biliverdin (green color pigment), iron and carbon monoxide. Next step is reduction of biliverdin to yellow color tetrapyrol pigment bilirubin by cytosolic enzyme biliverdin reductase. This bilirubin is known as "unconjugated", "free" or "indirect" bilirubin. Approximately 4 mg per kg of bilirubin is produced each day. The majority of this bilirubin comes from the breakdown of heme from expired red blood cells in the process just described. However approximately 20 per cent comes from other heme sources, including ineffective erythropoiesis, breakdown of other heme-containing proteins, such as muscle myoglobin and cytochromes.

Hepatic events

The unconjugated bilirubin then travels to the liver through the bloodstream. Because this bilirubin is not soluble, however, it is transported through the blood bound to serum albumin. Once it arrives at the liver, it is conjugated with glucuronic acid (to form bilirubin diglucuronide, or just "conjugated bilirubin") to become more water soluble. The reaction is catalyzed by the enzyme UDP-glucuronide transferase.

Post-hepatic events

This conjugated bilirubin is excreted from the liver into the biliary and cystic ducts as part of bile. Intestinal bacteria convert the bilirubin into urobilinogen. From here the urobilinogen can take two pathways. It can either be further converted into stercobilinogen, which is then oxidized to stercobilin and passed out in the faeces, or it can be reabsorbed by the intestinal cells, transported in the blood to the kidneys, and passed out in the urine as the oxidised product urobilin. Stercobilin and urobilin are the products responsible for the coloration of faeces and urine, respectively.

Post-hepatic jaundice, also called obstructive jaundice, is caused by an interruption to the drainage of bile in the biliary system. The most common causes are gallstones in the common bile duct, and pancreatic cancer in the head of the pancreas. Also, a group of parasites known as "liver flukes" live in the common bile duct, causing obstructive jaundice. Other causes include strictures of the common bile duct, biliary atresia, ductal carcinoma, pancreatitis and pancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome.

The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments.

Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus".

Differential diagnosis

When a pathological process interferes with the normal functioning of the metabolism and excretion of bilirubin just described, jaundice may be the result. Jaundice is classified into three categories, depending on which part of the physiological mechanism the pathology affects. The three categories are (*Table 2.2*):

Table 2.2 – The categories of jaundice

Category	Definition
Pre–hepatic	The pathology is occurring prior to the liver.
Hepatic	The pathology is located within the liver.
Post–hepatic	The pathology is located after the conjugation of bilirubin in the liver.

Pre-hepatic

Laboratory findings include:

• Urine: no bilirubin present, urobilirubin > 2 units (except in infants where gut flora has not developed) (*Table 2.3*).

Table 2.3 – Table of diagnostic tests

Function test	Pre–hepatic Jaundice	Hepatic Jaundice	Post–hepatic Jaundice
Total bilirubin	Normal / Increased	Increased	Increased
Conjugated bilirubin	Increased	Normal	Increased
Unconjugated bilirubin		Normal / Increased	Normal / Increased
Urobilinogen		Normal / Increased	Decreased / Negative
Urine color	Normal	Dark	Dark
Stool color	Normal	Normal	Pale
Alkaline phosphatase levels	Normal	Increased	Increased
Alanine transferase and Aspartate transferase levels		Increased	Increased
Conjugated bilirubin in urine	Not present	Present	Present

• Serum: increased unconjugated bilirubin.

• Kernicterus is associated with increased bilirubin.

Hepatic

Hepatic jaundice causes include acute hepatitis, hepatotoxicity and alcoholic liver disease, whereby cell necrosis reduces the liver's ability to metabolize and excrete bilirubin leading to a buildup in the blood. Less common causes include primary biliary cirrhosis, Gilbert's syndrome (a genetic disorder of bilirubin metabolism which can result in mild jaundice, which is found in about 5% of the population), Crigler–Najjar syndrome, metastatic carcinoma and Niemann–Pick disease, type C. Jaundice seen in the newborn, known as neonatal jaundice, is common, occurring in almost every newborn as hepatic machinery for the conjugation and excretion of bilirubin does not fully mature until approximately two weeks of age.

L*aboratory findings include:*

• Urine: conjugated bilirubin present, urobilirubin > 2 units but variable (except in children). Kernicterus is a condition not associated with increased bilirubin.

Post-hepatic

Post-hepatic jaundice, also called obstructive jaundice, is caused by an interruption to the drainage of bile in the biliary system. The most common causes are gallstones in the common bile duct, and pancreatic cancer in the head of the pancreas. Also, a group of parasites known as "liver flukes" can live in the common bile duct, causing obstructive jaundice. Other causes include strictures of the common bile duct, biliary atresia, ductal carcinoma, pancreatitis and pancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome.

The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments.

Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus".

Not one test can differentiate between various classifications of jaundice. A combination of liver function tests is essential to arrive at a diagnosis.

2.6.1. OBSTRUCTIVE JAUNDICE

Cholestasis, or obstructive jaundice, occurs when the flow of bile from the liver to the intestines is obstructed or impaired. This can occur inside the liver (intrahepatic) or outside of it (extrahepatic).

Intrahepatic causes

Any condition that damages the liver cells can cause obstructive jaundice. The most common causes are hepatitis, alcoholism and drugs that are toxic to the liver. In these conditions, blood work will show increased liver enzymes, indicative of liver damage. In addition to jaundice, symptoms of intrahepatic obstruction include ascites (swelling of the belly due to reduced circulation through the liver) and enlarged spleen.

Extrahepatic causes

The common bile duct carries bile from the liver to the intestines. Any blockage of the duct will cause obstructive jaundice. The most common causes are bile stones in the duct, pancreatic cancer, cholangiocarcinoma, benign strictures and tumors of extrahepatic biliary tract, bening tumors of the ampulla of Vater large, as well as cancer of the large papilla of the duodenum.

Signs and symptoms

The most obvious sign of jaundice is the yellowing of the skin and eyes that gives the disease its name ("jaune" is the French word for yellow). In obstructive jaundice, bilirubin cannot pass to the intestines. The stool is pale, because stercobilinogen is not formed. Excess conjugated bilirubin spills over to the kidneys and is excreted as urobilinogen, which gives the urine a very dark color. All-over itching may result from the excess of bile salts forming in the body. Symptoms of the underlying disease or substance (in the case of alcoholism and drug toxicity) will be present. Long-term symptoms include a darkening of skin tone (the so-called "bar room tan"), inability to form blood clots (bile salts are necessary for the absorption of vitamin K, vital to the clotting process), and osteoporosis due to malabsorption of vitamin D and calcium.

Radiological evaluation

- Ultrasonography.
- CT.
- MRCP
- ERCP

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is a minimally invasive technique for diagnosing and treating diseases of the liver, bile ducts and pancreas (*Fig. 2.16*). During ERCP, a flexible tube (an endoscope) is passed through the mouth, esophagus, and stomach into the first part of the small intestine. Dye is injected through the tube into the pancreatic and bile ducts, and an X-ray is taken.

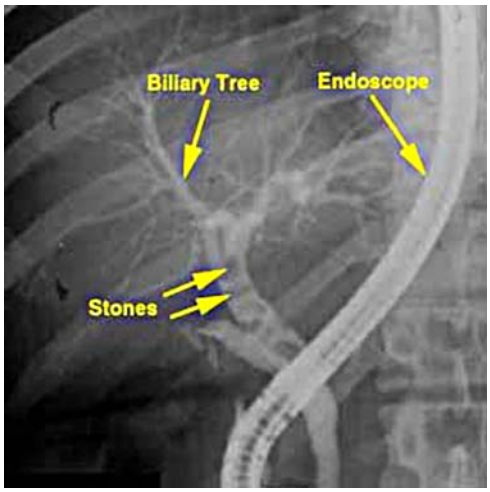


Figure 2.16. *Endoscopic retrograde cholangiopancreatography*

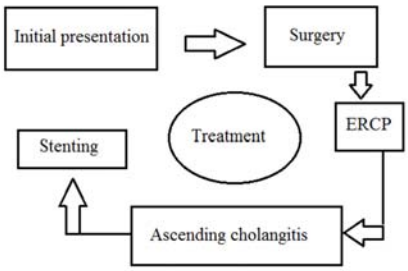


Figure 2.18. *The scheme of treatment of a obstructive jaundice*

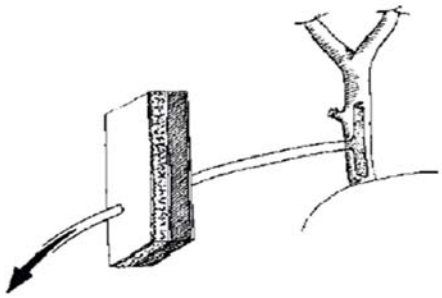


Figure 2.17. *Calculous bile duct exploration and T-tube drainage*

Treatment

Treating the cause of obstructive jaundice will usually resolve the symptoms. In chronic or irreversible disorders, cholestyramine is given to bind bile salts and relieve the itching. Supplements of vitamins D, K, and calcium can be given to counteract malabsorption. In the case of extrahepatic obstruction, surgery may be necessary to remove the obstruction and resolve the symptoms.

General support: Cessation of oral intake, fast; antibiotics; keep liquid and electrolyte balance; intravenous fluids.

Biliary decompression:

- Endoscopic drainage papillotomy without /with stent placement transpapillary.
- Percutanecus transhepatic biliary drainage.
- Operative decompression (T-tube drainage, *Fig. 2.17*).

Summary

The scheme of treatment of obstructive jaundice presented in *Fig. 2.18.*

2.6.2. MISCELLANEOUS CONDITIONS CAUSING BILIARY TRACT OBSTRUCTION

Benign tumors

Although most bile duct tumors are malignant, some benign biliary lesions result in biliary obstruction and cholestasis. These include papillomas, adenomas, and cystadenomas.

Ampullary tumors

Tumors of the ampulla of Vater can be benign (adenomas) or malignant (ampullary carcinoma). Either can result in biliary obstruction and can be confused with cholangiocarcinoma and pancreatic adenocarcinoma. At presentation, patients are often jaundiced and may have a palpable gallbladder because of bile duct obstruction distal to the cystic duct. Laboratory findings typically show an elevation of alkaline phosphatase and bilirubin levels.

Imaging studies of the biliary tree will often show dilation, suggesting a distal bile duct obstruction. Further investigation with a side-viewing duodenoscope will reveal the presence of the ampullary tumor. Ampullary adenomas, often seen with familial adenomatous polyposis, can be treated with surgical excision of the ampulla. Whipple's procedure is the treatment of choice for those with resectable ampullary carcinoma.

For patients who are not surgical candidates, ERCP with sphincterotomy and stenting can provide palliation for what are often slow-growing tumors.

Pancreatic disorders

Carcinoma of the head of the pancreas can manifest with painless jaundice caused by obstruction of the bile duct as it passes through the head of the pancreas. Weight loss, fatigue, and other constitutional symptoms often accompany the cholestasis. CT scanning or ultrasound typically reveal biliary ductal dilation to the level of the pancreatic head and a pancreatic mass.

Cholestasis can also result from benign pancreatic disorders such as (1) chronic pancreatitis resulting in pancreatic fibrosis leading to common duct narrowing and cholestasis, or (2) a pancreatic pseudocyst causing compression of the biliary tree.

Parasites

Extrahepatic biliary obstruction has been seen with various parasitic infections such as Strongyloides and Ascaris, and liver flukes such as *Opisthorchis sinensis* and *Fasciola hepatica*.

2.7. ACUTE LIVER FAILURE

The term acute liver failure (ALF) was first used by Trey and Davidson in 1270. ALF is an uncommon condition in which the rapid deterioration of liver function results in coagulopathy and alteration in the mental status of a previously healthy individual. Acute liver failure often affects young people and carries a very high mortality. The term acute liver failure is used to describe the development of coagulopathy, usually an international normalized ratio (INR) of greater than 1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of less than 26 weeks' duration.

Acute liver failure is a broad term and encompasses both fulminant hepatic failure (FHF) and subfulminant hepatic failure (or late-onset hepatic failure). Fulminant hepatic failure is generally used to describe the development of encephalopathy within 8 weeks of the onset of symptoms in a patient with a previously healthy liver. Subfulminant hepatic failure is reserved for patients with liver disease for up to 26 weeks before the development of hepatic encephalopathy.

Some patients with previously unrecognized chronic liver disease decompensate and present with liver failure; although this is not technically FHF, discriminating such at the time of presentation may not be possible. Patients with Wilson disease, vertically acquired hepatitis B virus (HBV), or autoimmune hepatitis may be included in spite of the possibility of cirrhosis if their disease has been less than 26 weeks.

Drug-related hepatotoxicity is the leading cause of acute liver failure. The outcome of acute liver failure is related to the etiology, the degree of encephalopathy, and related complications. Unfortunately, despite aggressive treatment, many patients die from fulminant hepatic failure. Before orthotopic liver transplantation (OLT) for fulminant hepatic failure, the mortality rate was generally greater than 80%. Common causes for acute liver failure are paracetamol (acetaminophen) overdose, idiosyncratic reaction to medication (e.g. tetracycline, troglitazone). Also the frequent reasons are excessive alcohol intake (severe alcoholic hepatitis), viral hepatitis (hepatitis A or B –

it is extremely uncommon in hepatitis C), acute fatty liver of pregnancy, and idiopathic (without an obvious cause). Reye syndrome is acute liver failure in a child with a viral infection (e.g. chickenpox). Wilson's disease (hereditary copper accumulation) may infrequently present with acute liver failure.

Classification

By interval from onset of jaundice to development of hepatic encephalopathy liver failure is classified as:

1. Hyperacute if occurring within 7 days.
2. Acute if occurring between 8 and 28 days.
3. Subacute if occurring between 22 days and 12 weeks.

By interval from onset of hepatic illness to development of hepatic encephalopathy hepatic failure is classified as:

1. Fulminant if occurring within 8 weeks.
2. Late-onset if occurring between 8 and 26 weeks.

There are **three types** of acute liver failure:

1. Hepatocellular, primary hepatic coma, coma endogenous. It is characterized by a clinic of parenchymal deficiency: hyperbilirubinemia, hyperfermentemia, hypocoagulation.

2. Exogenous coma, or coma loss of liver function, portosystemic functional, shunt, false. It is characterized by the presence of portosystemic shunting of blood, the discharge of intestinal neurotoxins via portosystemic shunts.

3. Mixed, characterized by the development of hepatocellular insufficiency on the background of the collateral circulation.

Pathophysiology

Acute liver injury (ALF) is caused by both direct injury to the hepatocytes, and an innate immunemediated response, mediated through activation of monocytes, macrophages, dendritic cells, leukocytes, natural killer cells, and natural killer T cells. These cells express receptors that are able to recognise pathogen-associated molecular patterns in viral hepatitis and damage-associated molecular patterns in toxin-mediated liver injury, leading to the activation of signal transduction pathways which determine the pattern of cytokines released, initially locally within the liver itself, spilling over to the systemic circulation eventually. Recent studies also suggest a significant role of apoptosis in cell death of ALF, which is mediated through activation of caspases.

Irrespective of the etiology, a large majority of the patients eventually go on to progress to various degrees of extra-hepatic organ involvement with some developing frank multiple organ failure. While intense systemic inflammatory response syndrome (SIRS), which develops in ALF – mediated by the pro-inflammatory cytokines released from the damaged liver and subsequent activation of endothelial, coagulation, and immunological systems and organ cross talk – seems to be largely responsible for distant organ damage, direct toxic injury may also occasionally contribute, as is seen in patients with acetaminophen toxicity who develop toxin-related acute renal tubular injury. The existence of a parallel compensatory anti-inflammatory response syndrome (CARS) – mediated by the anti-inflammatory cytokines, IL-4, IL-10, and transforming growth factor-β – is not insufficient in counter-modulating this response.

The development of cerebral edema is the major cause of morbidity and mortality of patients suffering from acute liver failure. The etiology of this intracranial hypertension (ICH) is not fully understood, but it is considered to be multifactorial.

Briefly, hyperammonemia may be involved in the development of cerebral edema. Brain edema is thought to be both cytotoxic and vasogenic in origin. Cytotoxic edema is the consequence of impaired cellular osmoregulation in the brain, resulting in astrocyte edema. Cortical astrocyte swelling is the most common observation in neuropathologic studies of brain edema in acute liver failure. In the brain, ammonia is detoxified to glutamine via amidation of glutamate by glutamine synthetase. The accumulation of glutamine in astrocytes results in astrocyte swelling and brain edema. There is clear evidence of increased brain concentration of glutamine in animal models of acute liver failure. The relationship among high ammonia, glutamine, and raised ICH has been reported in humans.

Another phenomenon that has been involved in acute liver failure is the increase of intracranial blood volume and cerebral blood flow. The increased cerebral blood flow results because of disruption of cerebral autoregulation. The disruption of cerebral autoregulation is thought to be mediated by elevated systemic concentrations of nitric oxide, which acts as a potent vasodilator. However, in this setting, cytokine profiles are also deranged. Elevated serum concentrations of bacterial endotoxin, tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1) and -6 (IL-6) have been found in fulminant hepatic failure. Another consequence of fulminant hepatic failure is multisystem organ failure, which is often observed in the context of a hyperdynamic circulatory state that mimics sepsis (low systemic vascular resistance); therefore, circulatory insufficiency and poor organ perfusion possibly either initiate or promote complications of fulminant hepatic failure.

Pathology

In the majority of acute liver failure (ALF) there is widespread hepatocellular necrosis beginning in the centrizonal distribution and progressing towards portal tracts. The degree of parenchymal inflammation is variable and is proportional to duration of disease.

Zone 1 (periportal) occurs in phosphorus poisoning or eclampsia. Zone 2 (midzonal), although rare, is seen in yellow fever. Zone 3 (centrilobular) occurs with ischemic injury, toxic effects, carbon tetrachloride exposure, or chloroform ingestion. Drugs such as acetaminophen may be metabolized in zone 1 to toxic compounds that cause necrosis on zone 3.

Clinical consequence

Cerebral edema and encephalopathy. In ALF, cerebral edema leads to hepatic encephalopathy, coma, brain herniation and eventually death. Detection of encephalopathy is central to the diagnosis of ALF. It may vary from subtle deficit in higher brain function to deep coma. Patients presenting as acute and hyperacute liver failure are at greater risk of developing cerebral oedema and encephalopathy. The pathogenesis remains unclear but is likely to be a consequence of several phenomena. There is a build up of toxic substances like ammonia, mercaptan, endogenous benzodiazepines and serotonin/tryptophan in the brain. This affects neurotransmitter level and neuroreceptor activation. Autoregulation of cerebral blood

flow is impaired and is associated with anaerobic glycolysis and oxidative stress. Neuronal cell astrocytes are susceptible to these changes and they swell up, resulting in increased intracranial pressure. Inflammatory mediators also play important role.

Unfortunately, signs of elevated intracranial pressure such as papilloedema and loss of pupillary reflexes are not reliable and occur late in the disease process. CT imaging of the brain is also unhelpful in detecting early cerebral oedema but is often performed to rule out intra-cerebral bleeding. Invasive intracranial pressure monitoring via subdural route is often recommended, however the risk of complications must be weighed against the possible benefit (1% fatal haemorrhage). The aim is to maintain intracranial pressures below 25 mmHg, cerebral perfusion pressures above 50 mm Hg.

Coagulopathy is another cardinal feature of ALF. Liver has central role in synthesis of almost all coagulation factors and some inhibitors of coagulation and fibrinolysis. Hepatocellular necrosis leads to impaired synthesis of many coagulation factors and their inhibitors. The former produces a prolongation in Prothrombin time which is widely used to monitor severity of hepatic injury.There is significant platelet dysfunction (with both quantitative and qualitative platelet defects). Progressive thrombocytopenia with loss of larger and more active platelet is almost universal. Thrombocytopenia with or without DIC increases risk of intracerebral bleeding.

Inflammation and infection. About 60% of all ALF patients fulfil the criteria for systemic inflammatory syndrome irrespective of presence or absense of infection. This often contributes towards multi organ failure. Impaired host defence mechanism due to impaired opsonisation, chemotaxis and intracellular killing substantially increase risk of sepsis.

Metabolic derangements. Hyponatraemia is almost universal finding due to water retention and shift in intracellular sodium transport from inhibition of Na/K ATPase. Hypoglycaemia (due to depleted hepatic glycogen store and hyperinsulinaemia), hypokalaemia, hypophosphataemia and Metabolic alkalosis are often present independent of renal function. Lactic acidosis occurs predominantly in paracetamol overdose.

Haemodynamic and cardio-respiratory compromise. Hyperdynamic circulation with peripheral vasodilatation from low systemic vascular resistance leads to hypotension. There is a compensatory increase in cardiac output. Adrenal insufficiency has been documented in 60% of ALF and is likely to contribute in haemodynamic compromise. There is also abnormal oxygen transport and utilization. Although delivery of oxygen to the tissues is adequate, there is a decrease in tissue oxygen uptake, resulting in tissue hypoxia and lactic acidosis.

Pulmonary haemorrhage, pleural effusions, atelectasis, and intrapulmonary shunts also contribute to respiratory difficulty.

ALF in late pregnancy. In late pregnancy, liver function decreases significantly, which can be easily monitored by blood tests. Early clinical manifestations of ALF in late pregnancy include: hypodynamia, decrease in appetite, dark amber urine, deep jaundice, nausea, vomiting, and abdominal distention.

Evaluation. All patients with clinical or laboratory evidence of moderate to severe acute hepatitis should have immediate measurement of prothrombin time and

careful evaluation of mental status. If the prothrombin time is prolonged by ≈ 4–6 seconds or more (INR ≥ 1.5) and there is any evidence of altered sensorium, the diagnosis of ALF should be strongly suspected and hospital admission is mandatory. Initial laboratory examination must be extensive in order to evaluate both the aetiology and severity.

Initial laboratory analysis:

- Prothrombin time/INR.
- Complete blood count.
- Chemistries:
  - Liver function test: AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin.
  - Creatinine, urea/blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate.
  - Glucose.
  - Amylase and lipase.
- Arterial blood gas, lactate.
- Blood type and screen.
- Paracetamol (Acetaminophen) level, Toxicology screen.
- Viral hepatitis serologies: anti-HAV IgM, HBSAg, anti-HBc IgM, anti-HEV.
- Autoimmune markers: ANA, ASMA, LKMA, Immunoglobulin levels.
- Ceruloplasmin Level (when Wilson's disease suspected).
- Pregnancy test (females).
- Ammonia (arterial if possible).
- HIV status (has implication for transplantation).

History taking should include careful review of possible exposures to viral infection and drugs or other toxins. From history and clinical examination possibility of underlying chronic disease should be ruled out as it may have different management.

A liver biopsy done via the transjugular route because of coagulopathy is not usually necessary other than in occasional malignancies. As the evaluation continues, several important decisions have to be made such as whether to admit the patient to an ICU, or whether to transfer the patient to a transplant facility. Consultation with the transplant center as early as possible is critical due to possibility of rapid progression of ALF.

Treatment

Treatment involves admission to hospital; often intensive care unit admission or very close observation are required. Supportive treatment is with adequate nutrition, optimalisation of the fluid balance, mechanical ventilation and intracranial pressure monitoring (in severe encephalopathy), and treatment aimed at removing the underlying cause (such as acetylcysteine for paracetamol poisoning). Other supportive measures may include the drainage of ascites.

While many people who develop acute liver failure recover with supportive treatment, liver transplantation is often required in people who continue to deteriorate or have adverse prognostic factors.

"Liver dialysis" (various measures to replace normal liver function) is evolving as a treatment modality and is gradually being introduced in the care of patients with liver failure.

2.8. LIVER TRANSPLANTATION

The first human liver transplant was performed in 1263 by a surgical team led by Dr. Thomas Starzl of Denver, Colorado, United States. Dr. Starzl performed several additional transplants over the next few years before the first short-term success was achieved in 1267 with the first one-year survival post transplantation. Despite the development of viable surgical techniques, liver transplantation remained experimental through the 1270s, with one year patient survival in the vicinity of 25 %. The introduction of cyclosporin by Sir Roy Calne markedly improved patient outcomes, and the 1280s saw recognition of liver transplantation as a standard clinical treatment for both adult and pediatric patients with appropriate indications.

Indications

Liver transplantation is potentially applicable to any acute or chronic condition resulting in irreversible liver dysfunction, provided that the recipient does not have other conditions that will preclude a successful transplant. Metastatic cancer outside liver, active drug or alcohol abuse and active septic infections are absolute contraindications. While infection with HIV was once considered an absolute contraindication, this has been changing recently. Advanced age and serious heart, pulmonary or other disease may also prevent transplantation (relative contraindications). Most liver transplants are performed for chronic liver diseases that lead to irreversible scarring of the liver, or cirrhosis of the liver. Another cause is cryptogenic liver disease. Some centers use the Milan criteria to select patients for liver transplantation.

Techniques

Before transplantation liver support therapy might be indicated (bridging-to-transplantation). Artificial liver support like liver dialysis or bioartificial liver support concepts are currently under preclinical and clinical evaluation. Virtually all liver transplants are done in **an orthotopic fashion**, which is the native liver is removed and the new liver is placed in the same anatomic location.

The transplant operation can be conceptualized as consisting of the **hepatectomy** (liver removal) **phase**, **the anhepatic** (no liver) **phase**, and the **postimplantation phase** (*Figs. 2.19, 2.20*).

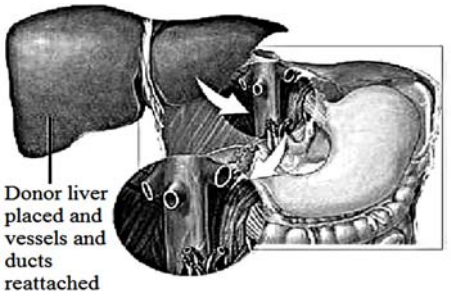


Figure 2.19.
Liver transplantation

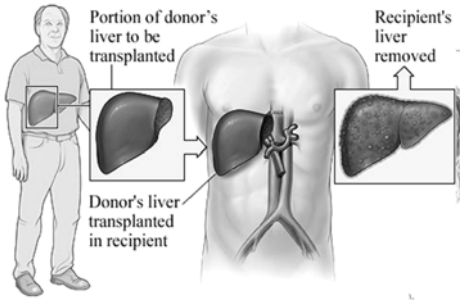


Figure 2.20.
Transplantation of the right lobe

The donor's blood in the liver will be replaced by an ice-cold organ storage solution, such as UW (Viaspan) or HTK until the allograft liver is implanted. Implantation involves anastomoses (connections) of the inferior vena cava, portal vein, and hepatic artery. After blood flow is restored to the new liver, the biliary (bile duct) anastomosis is constructed, either to the recipient's own bile duct or to the small intestine. The surgery usually takes between five and six hours, but may be longer or shorter due to the difficulty of the operation and the experience of the surgeon (*Fig. 2.19*).

The large majority of liver transplants use the entire liver from a non-living donor for the transplant, particularly for adult recipients. A major advance in pediatric liver transplantation was the development of reduced size liver transplantation, in which a portion of an adult liver is used for an infant or small child. Further developments in this area included split liver transplantation, in which one liver is used for transplants for two recipients, and living donor liver transplantation, in which a portion of a healthy person's liver is removed and used as the allograft. Living donor liver transplantation for pediatric recipients involves removal of approximately 20% of the liver (Couinaud segments 2 and 3) or used right lobe of the liver of a living related donor (*Fig. 2.19*).

Liver donor requirements

Any member of the family, parent, sibling, child, spouse or a volunteer can donate their liver. The criteria for a liver donation include:

- Being in good health.
- Having a blood type that matches or is compatible with the recipient's.
- Having a charitable desire of donation without financial motivation.
- Being between 18 and 60 years old.
- Being of similar or bigger size than the recipient.
- Before one becomes a living donor, the donor has to undergo testing to ensure that the individual is physically fit. Sometimes CT scans or MRI are done to image the liver. In most cases, the work up is done in 2–3 weeks.

Immunosuppressive management

Like most other allografts, a liver transplant will be rejected by the recipient unless immunosuppressive drugs are used. The immunosuppressive regimens for all solid organ transplants are fairly similar, and a variety of agents are now available. Most liver transplant recipients receive corticosteroids plus a calcinuerin inhibitor such as tacrolimus or cyclosporin plus an antimetabolite such as Mycophenolate Mofetil. Liver transplantation is unique in that the risk of chronic rejection also decreases over time, although recipients need to take immunosuppressive medication for the rest of their lives.

Graft rejection

After a liver transplantation, there are three types of graft rejection that may occur. They include hyperacute rejection, acute rejection and chronic rejection. Hyperacute rejection is caused by preformed anti-donor antibodies. It is characterized by the binding of these antibodies to antigens on vascular endothelial cells. Complement

activation is involved and the effect is usually profound. Hyperacute rejection happens within minutes to hours after the transplant procedure. Unlike hyperacute rejection, which is B cell mediated, acute rejection is mediated by T cells. It involves direct cytotoxicity and cytokine mediated pathways. Acute rejection is the most common and the primary target of immunosuppressive agents. Acute rejection is usually seen within days or weeks of the transplant. Chronic rejection is the presence of any sign and symptom of rejection after 1 year. The cause of chronic rejection is still unknown but an acute rejection is a strong predictor of chronic rejections. Liver rejection may happen any time after the transplant. Lab findings of a liver rejection include abnormal AST, ALT, GGT and liver function values such as prothrombin time, ammonia level, bilirubin level, albumin concentration, and blood glucose. Physical findings include encephalopathy, jaundice, bruising and bleeding tendency. Other nonspecific presentations are malaise, anorexia, muscle ache, low fever, slight increase in white blood count and graft tender.

Results

Prognosis is quite good. However, those with certain illnesses may differ. There is no exact model to predict survival rates; however, those with transplant have a 58% chance of surviving 15 years. Failure from the new liver occurs in 10 to 15% of all cases. These percentages are contributed to by many complications. Early graft failure is probably due to preexisting disease of the donated organ. Others include technical flaws during surgery such as revascularization that may lead to a nonfunctioning graft.

2.9. PARASITIC DISEASE OF THE LIVER AND BILIARY TREE

Helminthic invasion of the human biliary tract is a prominent medical and surgical problem especially in tropical and subtropical areas where these parasites are endemic. Parasitic infestations rarely occur in the temperate zones, although the incidence seems to be increasing gradually in such areas due to the increasing number of tourists, immigrants and expatriates. Accordingly, it is important lot physicians and surgeons in the temperate areas of the world to be aware of biliary parasites, their clinical picture, diagnosis and treatment.

Several parasites infest liver or biliary tree, either during their maturation stages or as adult worms. Biliary tree parasites may cause pancreatitis, cholecystitis, biliary tree obstruction, recurrent cholangitis, biliary tree strictures and some may lead to cholangiocarcinoma.

Intestinal parasites are among the most common microorganism to affect humans. Although most infections occur in developing countries, developed ones are also affected by migrants and travelers. Previously, the final diagnosis of most hepato-biliary and gastrointestinal parasitic diseases was based on the detection of the parasites larva, ova or cysts in the stools. Eosinophilia may indicate the presence of a parasite. Serological tests are not available for all parasitic diseases and some of these serological tests are neither sensitive nor specific. Many parasites may inhabit the upper or lower gastrointestinal tract, pancreas, liver, gallbladder and biliary tree.

It is estimated that approximately 25% of the Third World population is infested with Ascaris lumbricoides. More than 200 million people are infected with schistosomiasis throughout the world and 500–600 million are exposed to the risk of infection.

The extent of the disease depends on the parasite burden and stage of infestation, the type of tissue response and host immunity. Patients suffering from immuno-deficiency syndromes may develop severe and fatal forms of parasitic disease. Modem techniques are important for the diagnosis and treatment of parasitic disease. These techniques include imaging techniques such as barium studies, ultrasonography, computed tomography and magnetic resonance imaging. Fibreoptic endoscopies have been shown to play an important role in the diagnosis and treatment of parasitic infestations of gastrointestinal tract and biliary tree.

Classification of biliary parasites

Helminthic infestation may affect the liver and/or the biliary tract cither during passage of worms through these structures or because these organs serve as their natural habitat. *Table 2.4* shows the classification of parasitic infestations affecting the liver and/or the biliary tract. It should be noted that some parasites such as schistosomes invade the liver parenchyma but arc not associated with biliary' conditions and includes the scientific and common names of the parasite or disease as well as the source from which infection is most commonly derived. Among the many parasites present, only nematodes and hermaphroditic trematodes affect the biliary system.

Table 2.4 – Classification of biliary flukes

Type	Species	Relationship	Common name	Source
Nematodes	Ascariasis	Intestinal pathtogenic		Human feces
Trematodes	Chlonorchis + relatives	Tissue pathogenic	Liver fluke	Raw fish
	Fasciola	Tissue pathogenic	Sheep liver fluke	Fresch water plants

Geographical distribution of biliary parasites

Table 2.5 demonstrates the geographic distribution of parasites affecting the biliary tract.

Table 2.5 – Geographic distribution of parasites affecting the biliary tree

Fasciola hepatica	South America, Middle East, China, Russia, Poland, England, Franch, Spain, Hungary, Algeria, Somalia, South Africa, Hawaii.
Ascaris lumbricoides	Worldwide, more common in warm, moist climates
Clonorchis sinensis	Japan, Korea, Taiwan, China, Vietnam.
Opisthorchis felineus	Southern, Central and Eastern Europe, North Vietnam, Korea, Japan, Philippines
Dicrocoelium dendriticum	Eastern Europe, Africa, North and South America

Amebiasis. The major clinical manifestation of entameba histolytica infestation is liver abscess. In order to distinguish pathogenic strains of entameba histolytica from nonpathogenic strains of entameba dispar, a simple and rapid DNA extraction method on a fecal sample has been developed. A specific probe, using a monoclonal

antibody technique, has been used to detect defined antigen in necrotic liver material in E.histolytica infection; amebiasis cause tender hepatomegaly during the acute phase (amebic hepatitis) which is more common in chronic carriers, and an amebic abscess may develop. Hepatic amebiasis is the commonest extraintestinal complication. The diagnosis is usually reached by history and clinical examination together with ultrasonography of liver which will show the abscess. Patients may also present with picture of obstructive jaundice.

A study reported the prevalence of amebiasis in patients with schistosomal colonic polyposis is 37% compared to 15% in schistosomal patients without polyposis and 11% in non-schistosomal patients. Ameboma can stimulate malignancy in barium enemas but the diagnosis is made by endoscopic biopsies.

Hydatid cyst. Echinococcus granulosis is the most common form of hydatid disease in humans. In endemic areas, the incidence might reach up to 5% as in Turkana area in Kenya. The incidence directly correlates with the number of infected dogs and the definitive hosts. Cysts caused by E. granulosis grow slowly and develop over many years. The effects are mainly those of a space occupying lesion. There are recent developments diagnosis of hydatid disease as in serological tests (using Elisa technique) and in radiological using ultrasound classification. A liver cyst may rupture into the biliary tree causing obstructive jaundice and a lung cyst may rupture into pleural cavity presenting with a pleural effusion. Surgery used to be the definitive type of treatment but this carries risk of morbidity, recurrence and mortality.

However there are new modalities of treatment that might replace surgery in the future and these include medical therapy with albendazole and praziquantel, endoscopic management in biliary tree obstruction and percutaneous aspiration of the cyst. Liver ultrasonography is diagnostic for hydated cyst and recently the ultrasonic appearance has been classified into four groups depending on cyst appearance, cyst consistency and presence of septations. Hydatid cysts of the liver are usually single but can be multiple. They may be large and cause pressure effect on the liver or may rupture into the biliary tree leading to biliary obstruction by daughter cysts.

Schistosomiasis. Schistosomiasis may involve the liver early in the disease in about 30% of the patients (schistosomal hepatitis) or more commonly 5–10 years after initial infection leading to periportal fibrosis and portal hypertension due to ova migration and development of hepatic granulomas followed by fibrosis. This results in increase of portal pressure and development of esophageal or gastric varices and portal hypertensive gastropathy.

The main cause of death is gastrointestinal bleeding from esophageal or gastric varices and sclerotherapy may be effective in these patients. Upper abdominal ultrasonography is important in the diagnosis of schistosomiasis of the liver. The extent of periportal fibrosis is classified into four groups and this findings was found to be correlated well with liver biopsy findings.

Biliary tree parasites. Biliary parasites can cause obstruction and dilatation of the common bile duct or hepatic ducts. Biliary lithiasis can develop secondary to ascaris, Fasciola hepatica and clonorchis sinesis. The stones related to ascaris are

thought to form in the gallbladder and not the ducts. Hemobilia, sclerosing cholangitis and cholangiocarcinoma are complications of biliary parasites. Parasites may also lead to pancreatic duct obstruction or dilatation.

Liver flukes. Liver flukes such as fasciola hepatica, clonorchis sinesis and opisthorchis infest liver and can cause biliary tree obstruction with recurrent cholangitis. Previously surgical treatment has been necessary for management of biliary parasites. However, recently ERCP and endoscopic papillotomy proved to be successful and replaced unnecessary operations. It has been recommended as first line in diagnosis and treatment.

Endoscopic extraction of biliary tree parasites will relieve the obstruction and decompress the dilated biliary tree and help in treatment of cholangitis. Pancreatitis secondary to parasites will settle also after worm extraction. Papillotomy and insertion of nasobiliary tube or stents will lead to decompression of obstructed biliary tree. Instillation of drugs through nasobiliary tube may be effective.

Intestinal ascariasis can be treated with antihimentics but drugs have no enterohepatic circulation and have no effect on the worms inside the biliary tree. Instillation of piperzine citrate through a nasobiliary tube has been used successfully.

Other parasites. The reticuloendothelial system of the liver may be involved in leishmansias, malaria and others. Visceral leishmaniasis is destined to become an increasingly important problem worldwide. It has been clearly established as an "opportunistic" infection in HIV and AIDS sufferers.

Multiple calcifications may be seen in liver or peritoneum in porocephaliasis due to calcified nymphs of the tongue worm (linguatulidae). Eosinophilic syndrome is a frequent sequel to most helminthic infection especially with hepatic involvement. In malaria especially with Plasmodium falciparum hepatomegaly can develop early and subsides with treatment. In complicated falciparum malaria, patients can present with acute biliary remittent fever. Tropical splenomegaly syndrome develops in chronic malaria and might cause confusion with portal hypertension.

Conclusion

Parasitic involvement of liver and biliary tree is an important differential diagnosis in patients with jaundice especially those from tropical or subtropical continents. Biliary tree parasites can cause cholecystitis, recurrent cholangitis, biliary obstruction, stone formation and biliary tree strictures. ERCP is an important diagnostic and therapeutic method in these cases. Liver flukes if not diagnosed and managed early, may later lead to cholangiocarcinoma. Schistosomal liver disease is a major problem in endemic areas. Ultrasonography is an important diagnostic tool and can help in identifying the degree and stage of fibrosis. Antishistosomal drugs if given early may stop the progress of disease. In hydatid disease, the endoscopic management is effective in cases where liver cyst rupture into the biliary tree. Combined medical treatment with albendazole and praziquantel is effective in all forms of hydatid disease. Percutaneous drainage of liver cyst is effective and should be considered in such patients. New methods of management of hydatid disease may replace surgery in the future.

REFERENCES

1. Garcia – Tsao G, Groszman RJ, Fischer RL et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985; 5: 419–424.

2. De Franchis R. Updating consensus in portal hypertension: Report of Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. J. of Hepatology 2000; 33: 846–852.

3. S. Wongcharatrawee, RJ Groszmann. Diagnosing portal hypertension in Ballieres Clinical gastroenterology 2000; 33: 846–852.

4. D 'Amic G, Pagliaro L and Bosch J. The treatment of portal hypertension: A meta analytic review. Hepatology 1995; 22: 332–354.

5. J. Michael Henderson. Surgical treatment of portal hypertension. Ballieres Clinical Gastroenterology 2000; 33: 911–923.

6. S. Kitano, J. Terblanche. Venous anatomy of oesophagus. British Journall of surgery 1986; 73: 525–530.

7. North Italian endoscopic club for the study and treatment of oesophageal varices. Prediction of the first variceal haemorrhage in patients with cirrhosis of the liver and oesophageal varices. A prospective multicentre trial. New England Journal of Medicine 1988; 319: 983–989.

8. Pagliaro L.D, 'Amico G. Prevention of the first bleeding in cirrhosis. A meta-analysis of randomized trials of non-surgical treatment. Annals of intrnal Medicine 1992; 117: 59–70.

9. Juan Carlos Pagan, Jaime Bosch. Medical treatment of portal hypertension. Ballieres Clinical Gastroenterology 2000; 33: 895–907.

10. JC Pagan for the Spanish Varicieal Bleeding Study Group. Isosorbide -5 Mononitrate vs Pacebo in the prevention of the first variceal bleed in patients with intolerance or contraindications to B Blockade. Journal of Hepatology 2000; 32: 28–32.

11. Spanish Variceal Bleeding Study Group. Propranolol + Placebo vs Propranolol + Isosorbide Mononitrate in the prevention of the first varicieal bleed. Journal of heaptology 1999; 30: 55.

12. Imperiale TF. Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. Hepatology 2001; 32: 802–807.

13. Bernard B et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding. A mata analysis. Hepatology 1999; 29: 1655–1661.

14. David Patch, Lucy Dagher. Acute variceal bleeding. General management. World J. of Gastroenterology 2001; 7: 1–13.

15. Griffiths C, Rooney C, Brock A. Leading causes of death in England and Wales -how should we group causes? Health Statistics Quarterly 28, 6–17. 2005.

16. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain, 1950 to 2002 26. Lancet 2006; 367(9511): 645.

17. Leon DA, Saburova L, Tomkins S, Andreev E, Kiryanov N, McKee M et al. Hazardous alcohol drinking and premature mortality in Russia: a population based case-control study Lancet 2007; 369(9578):2001–2009.

18. World Health Organisation. Hepatitis C. WHO Fact Sheet 2000 (164):[1-4].

19. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 5, 558–567. 2005.

20. Farrell GC LC. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 43[2 Suppl 1], S99-S112. 2006.

21. Day CP. Natural History of NAFLD: Remarkably benign in the absence of cirrhosis. Gastroenterology 2005; 129:375–377.

22. Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004; 127(6):1704–1713.

23. Parkes J, Bialek SR., Bell BP, Terrault N., Zaman A., Sofair A., Guha IN, Cross R, Harris S, Roderick PJ, Rosenberg WMC European Liver fibrosis markers accurately distinguish fibrosis severity in a cohort of patients with Chronic Hepatitis C; an external validation study. Hepatology 44[Suppl 1]. 2006.

24. Parkes J, Cross R, Harris S, Ryder S, Irving W, Zaitoun A, The Trent Hepatitis C Research Group, Rosenberg WMC. European liver fibrosis markers accurately distinguish fibrosis severity in Chronic Hepatitis C. Journal of Hepatology. 40 [Suppl 1]. 2005.

25. IN Guha, GP Aithal, J Parkes, PJ Roderick, S Harris, R Cross, P Kaye, SD Ryder, WM Rosenberg European liver fibrosis markers in Non Alcoholic Fatty Liver Disease (NAFLD); an external validation study. Hepatology 44 Suppl 1. 2006.

26. J. Parkes, M. Mayo, R.Cross, S.Harris, P.J. Roderick, B. Coombs, B. Huet The PUMPS Investigators and W.M. Rosenberg . European liver fibrosis markers accurately distinguish fibrosis severity in primary biliary cirrhosis; an external validation study. Hepatology 44 Suppl 1. 2006.

27. Non-invasive markers of fibrosis in non-alcoholic fatty liver disease: validatingthe European Liver Fibrosis panel and exploring simple markers. IN Guha, J Parkes, P Roderick, D Chattopadhyay, R Cross, S Harris, P Kaye, AD Burt, SD Ryder, GP Aithal, CP Day, WM Rosenberg. Hepatology 2007.

28. Mayo M., Parkes J, Huet B, Combes B, Mills S., Markin R. et al. Serum fibrosis markers predict future clinical decompensation in primary biliary cirrhosis bettter than liver biopsy, bilirubin, or Mayo risk score. Hepatology 44 Suppl 1. 2006.

29. Guha IN, Parkes J, Roderick PR, Harris S, Rosenberg WM. Non-invasive markers associated with liver fibrosis in non-alcoholic fatty liver disease 2. GUT 2006; 55(11):1650–1660.

30. Parkes J, Guha IN, Roderick P, Rosenberg W. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. Journal of Hepatology 2006; 44:462–474.

31. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001; 357(9262):1069–1075.

32. Ratziu V, Massard J, Charlotte F, Messous D, Imbert-Bismut F, Bonyhay L et al. Diagnostic value of biochemical markers (Fibro Test-FibroSURE) for the prediction of liver fibrosis in patients with non-alcholic fatty liver disease. BMC Gastroenterology 2006; 6(6):1–13.

33. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C.. Hepatology 2003; 38(2):518–526.

34. Forns X, Ampurdanes S, Llovet JM, Aponte J, Quinto L, Martinez-Bauer E et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model.. Hepatology 2002; 36(4 Pt 1):986–992.

35. Patel K, Muir AJ, McHutchison JG. Validation of a simple predictive model for the identification of mild hepatic fibrosis in chronic hepatitis C patients.. Hepatology 2003; 37(5):1222–1223.

36. Hepascore: An Accurate Validated Predictor of Liver Fibrosis in Chronic Hepatitis C Infection Adams,L.A.; Bulsara,M.; Rossi,E.; de Boer,B.; Speers,D.; George,J.; Kench,J.; Farrell G; McCaughan,G.W.; Jeffrey,G.P. Clinical Chemistry 51 (10) 1–7 Cales P, Oberti F, Michalak S, Hubert-Fouchard I, Rousselet MC, Konate A et al. A novel panel of blood markers to assess the degree of liver fibrosis 10. Hepatology 2005; 42(6):1373–1381.

37. Ganne-Carríe N, Ziol M, Ledinghen V, Douvin C, Marcellin P, Castera L et al. Accuracy of Liver Stiffness Measurement for the Diagnosis of Cirrhosis in Patients With Chronic Liver Disease. Hepatology 2006; 44:1511–1517.

38. Foucher J, Chanteloup E, Vergniol J, Castera L, Le Bail B, Adhoute X, Bertet J, Couzigou P, de Ledinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. GUT 2006; 55(3):403–408.

39. Roguin A (2006). "Rene Theophile Hyacinthe La?nnec (1781-1826): the man behind the stethoscope". Clinical medicine & research. 4 (3): 230–5.

40. Li CP, Lee FY, Hwang SJ, et al. (1999). "Spider angiomas in patients with liver cirrhosis: role of alcoholism and impaired liver function". Scand. J. Gastroenterol. 34 (5): 520–3.

41. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB (2004). "Pulmonary-Hepatic vascular Disorders (PHD)". Eur. Respir. J. 24 (5): 861–80.

42. Iredale JP (2003). "Cirrhosis: new research provides a basis for rational and targeted treatments". BMJ 327 (7407): 143–7.

43. Grant, A; Neuberger J (1999). "Guidelines on the use of liver biopsy in clinical practice". Gut 45 (Suppl 4): 1–11.

44. Halfon P, Munteanu M, Poynard T (2008). "FibroTest-ActiTest as a non-invasive marker of liver fibrosis". Gastroenterol Clin Biol 32 (6): 22–39.

45. Foucher J, Chanteloup E, Vergniol J, et al. (2006). "Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study". Gut 55 (3): 403–8.

46. Brenner, David; Richard A. Rippe (2003). "Pathogenesis of Hepatic Fibrosis". In Tadataka Yamada. Textbook of Gastroenterology. 2 (4th ed.). Lippincott Williams & Wilkins.

47. Giallourakis CC, Rosenberg PM, Friedman LS (November 2002). "The liver in heart failure". Clin Liver Dis 6 (4): 947–67.

48. Heathcote EJ (November 2003). "Primary biliary cirrhosis: historical perspective". Clin Liver Dis 7 (4): 735–40.

49. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R (1973). "Transection of the oesophagus for bleeding oesophageal varices". Br J Surg 60 (8): 646–9.

50. Patch D, Armonis A, Sabin C, et al. (1999). "Single portal pressure measurement predicts survival in cirrhotic patients with recent bleeding". Gut 44 (2): 264–9

51. Ginés P, Arroyo V, Quintero E, et al. (1987). "Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study". Gastroenterology 93 (2): 234–41.

52. Kamath PS, Kim WR (March 2007). "The model for end-stage liver disease (MELD)". Hepatology 45 (3): 797–805.

53. Anderson RN, Smith BL (2003). "Deaths: leading causes for 2001". National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 52 (9): 1–85.

54. Sørensen HT, Thulstrup AM, Mellemkjar L, et al. (2003). "Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark". Journal of clinical epidemiology 56 (1): 88–93

55. Klatsky AL, Morton C, Udaltsova N, Friedman GD (2006). "Coffee, cirrhosis, and transaminase enzymes". Archives of Internal Medicine 166 (11): 1190–5.

56. Starzl T, Marchioro T, Vonkaulla K, Hermann G, Brittain R, Waddell W. "Homotransplantation Of The Liver In Humans". Surg Gynecol Obstet 117: 659–76.

57. Starzl TE, Klintmalm GB, Porter KA, Iwatsuki S, Schroter GP. (1981). "Liver transplantation with use of cyclosporin A and prednisone". New England Journal of Medicine 305: 266-269.

58. Umeshita K, Fujiwara K, Kiyosawa K, et al. (August 2003). "Operative morbidity of living liver donors in Japan". Lancet 362 (9385): 687–90.

Chapter 3

DISEASES OF THE EXTRAHEPATIC BILIARY DUCTS

3.1. CHOLELITHIASIS

Cholelithiasis is the presence of one or more calculi (gallstones) in the gallbladder. In developed countries, about 10% of adults and 20% of people > 65 yr. have gallstones. Gallstones tend to be asymptomatic. The most common symptom is biliary colic; gallstones do not cause dyspepsia or fatty food intolerance. More serious complications include cholecystitis; biliary tract obstruction (from stones in the bile ducts or choledocholithiasis), sometimes with infection (cholangitis); and gallstone pancreatitis.

Risk factors for cholelithiasis

- Obesity, women, especially those who have had multiple.
- Frequent changes in weight.
- Rapid weight loss (leads to rapid development of gallstones and high risk of symptomatic disease).
- Treatment with high-dose estrogen (i.e., in prostate cancer).
- Low-dose estrogen therapy – a small increase in the risk of gallstones.
- Ileal resection or disease.
- Cystic fibrosis.
- Diabetes mellitus.

Pathophysiology

Biliary sludge is often a precursor of gallstones. It consists of Ca bilirubinate (a polymer of bilirubin), cholesterol microcrystals, and mucin. Sludge develops during gallbladder stasis, as occurs during pregnancy or while receiving TPN. Most sludge is asymptomatic and disappears when the primary condition resolves. Alternatively, sludge can evolve into gallstones or migrate into the biliary tract, obstructing the ducts and leading to biliary colic, cholangitis, or pancreatitis.

There are several types of gallstones (*Fig. 3.1*).

Cholesterol stones account for > 85% of gallstones in the Western world. For cholesterol gallstones to form, the following is required:

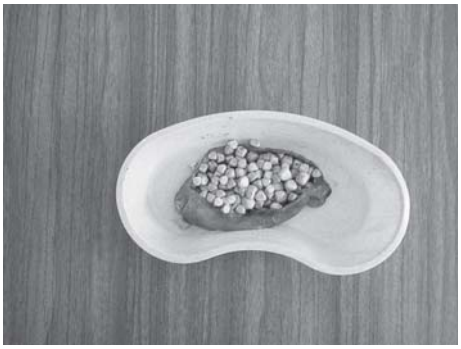


Figure 3.1. *Gallstones*

- Bile must be supersaturated with cholesterol. Normally, water-insoluble cholesterol is made water-soluble by combining with bile salts and lecithin to form mixed micelles. Supersaturation of bile with cholesterol most commonly results from excessive cholesterol secretion (as occurs in obesity or diabetes) but may result from a

decrease in bile salt secretion (e.g., in cystic fibrosis because of bile salt malabsorption) or in lecithin secretion (e.g., in a rare genetic disorder that causes a form of progressive intrahepatic familial cholestasis).

• The excess cholesterol must precipitate from solution as solid microcrystals. Such precipitation in the gallbladder is accelerated by mucin, a glycoprotein, or other proteins in bile.

• The microcrystals must aggregate and grow. This is facilitated by the binding effect of mucin forming a scaffold and retention in the gallbladder (impaired contractility from the excess cholesterol in bile).

Black pigment stones are small, hard gallstones composed of Ca bilirubinate and inorganic Ca salts (e.g., Ca carbonate, Ca phosphate). Factors that accelerate their development include alcoholic liver disease, chronic hemolysis, and older age.

Brown pigment stones are soft and greasy, consisting of bilirubinate and fatty acids (Ca palmitate or stearate). They form during infection, inflammation, and parasitic infestation (e.g., liver flukes in Asia).

Gallstones grow at about 1 to 2 mm/yr, taking 5 to 20 yr before becoming large enough to cause problems. Most gallstones form within the gallbladder, but brown pigment stones form in the ducts. Gallstones may migrate to the bile duct after cholecystectomy or, particularly in the case of brown pigment stones, develop behind strictures as a result of stasis and infection.

Natural History

- **Asymptomatic**
  - Majority (>2/3) asymptomatic.
  - Risk of symptoms about 2% per year.
  - Complication rate 0.1% per year.
  - No treatment necessary.
- **Symptomatic**
  - If symptomatic episode resolves, risk of future problems 35% by 5 years; complication 1% per year.

3.2. CHRONIC CHOLECYSTITIS

Chronic cholecystitis is usually caused by repeated attacks of acute cholecystitis. This leads to thickening of the gallbladder walls. The gallbladder begins to shrink and eventually loses the ability to perform its function, which is concentrating, storing, and releasing bile.

The disease occurs more often in women than in men. The incidence increases after age 40. The main risk factors include the presence of gallstones (in which case, the symptoms are due to gallstones).

Symptoms

About 80% of people with gallstones are asymptomatic. The remainder have symptoms ranging from biliary-type pain (hepatic colic) to cholecystitis to life-threatening cholangitis. Hepatic colic is the most common symptom.

Stones occasionally may traverse the cystic duct without causing symptoms. Most gallstone migration, however, leads to cystic duct obstruction, which, even if transient, causes hepatic colic. Hepatic colic characteristically begins in the right upper quadrant but may occur elsewhere in the abdomen. It is often poorly localized, particularly in diabetics and the elderly. The pain may radiate into the back or down the arm. Episodes begin suddenly, become intense within 15 min to 1 h, remain at a steady intensity (not colicky) for up to 12 h (usually < 6 h), and then gradually disappear over 30 to 90 min, leaving a dull ache. The pain is usually severe enough to send patients to the emergency department for relief. Nausea and some vomiting are common, but fever and chills do not occur unless cholecystitis has developed. Mild right upper quadrant or epigastric tenderness may be present; peritoneal findings are absent. Between episodes, patients feel well.

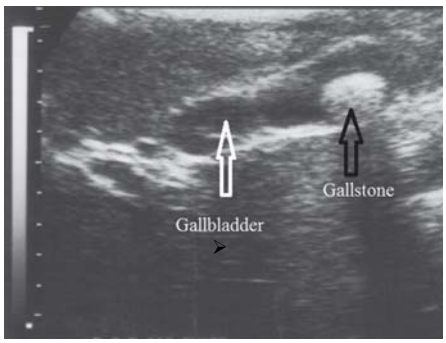


Figure 3.2. *Ultrasonography*

Exams and Tests

Tests that reveal gallstones or inflammation in the gallbladder:

- Abdominal ultrasound (*Fig. 3.2*).
- Abdominal CT scan (*Fig. 3.3*).
- Oral or intravenous cholecystography (*Fig. 3.4*).

Gallstones are suspected in patients with hepatic colic. Abdominal ultrasonography is the method of choice for detecting gallbladder stones; sensitivity and specificity are 95% (*Fig. 3.2*). Ultrasonography also accurately detects sludge. CT, MRI, and oral cholecystography (rarely available now, although quite accurate) are alternatives. Endoscopic ultrasonography accurately detects small gallstones (< 3 mm) and may be needed if other tests are equivocal. Laboratory tests usually are not helpful; typically, results are normal unless complications develop. Asymptomatic gallstones and biliary

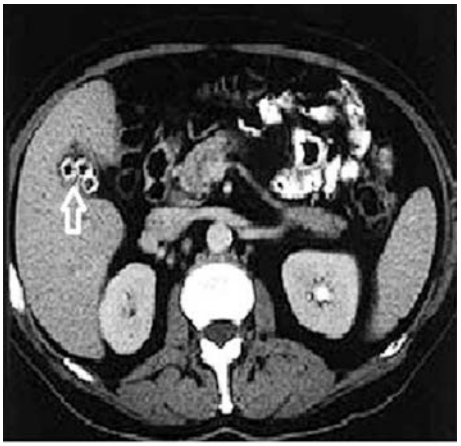


Figure 3.3. *CT scan of the upper abdomen showing multiple gallstones (arrow)*

Figure 3.4. *Cholelithiasis can be seen on a cholangiogram. Radio-opaque dye is used to enhance the X-ray. Multiple stones are present in the gallbladder*

sludge are often detected incidentally when imaging, usually ultrasonography, is done for other reasons. About 10 to 15% of gallstones are calcified and visible on plain X-rays.

Differential diagnosis

The symptoms of chronic cholecystitis are non-specific, thus chronic cholecystitis may be mistaken for other common disorders:

- Peptic ulcer.
- Hiatus hernia.
- Colitis.
- Functional bowel syndrome.

1. Hepatic colic – caused by obstruction of the cystic duct. It is associated with sharp and constant epigastric pain in the absence of fever and usually there is a negative Murphy's sign. Liver function tests are within normal limits since the obstruction does not necessarily cause blockage in the common hepatic duct, thereby allowing normal bile excretion from the liver. An ultrasound scan is used to visualise the gallbladder and associated ducts, and also to determine the size and precise position of the obstruction.

2. Acute cholecystitis – caused by blockage of the cystic duct with surrounding inflammation, usually due to infection. Typically, the pain is initially 'colicky' (intermittent), and becomes constant and severe, mostly in the right upper quadrant. Infectious agents that cause cholecystitis include *E. coli*, *Klebsiella*, *Pseudomonas*, *B. fragilis* and *Enterococcus*. Murphy's sign is positive, particularly because of increased irritation of the gallbladder lining, and similarly this pain radiates (spreads) to the shoulder, flank or in a band like pattern around the lower abdomen. Laboratory tests frequently show raised hepatocellular liver enzymes (AST, ALT) with a high white cell count (WBC). Ultrasound is used to visualise the gallbladder and ducts.

3. Choledocholithiasis – this refers to blockage of the common bile duct where a gallstone has left the gallbladder or has formed in the common bile duct (primary cholelithiasis). As with other biliary tree obstructions it is usually associated with 'colicky' pain, and because there is direct obstruction of biliary output, obstructive jaundice. Liver function tests will therefore show increased serum bilirubin, with high conjugated bilirubin. Liver enzymes will also be raised, predominately GGT and ALP, which are associated with biliary epithelium. The diagnosis is made using endoscopic retrograde cholangiopancreatography (ERCP), or the nuclear alternative (MRCP). One of the more serious complications of choledocholithiasis is acute pancreatitis, which may result in significant permanent pancreatic damage and brittle diabetes.

4. Cholangitis an infection of entire biliary tract, and may also be known as "ascending cholangitis", which refers to the presence of pathogens that typically inhabit more distal regions of the bowel.

Cholangitis is a medical emergency as it may be life threatening and patients can rapidly succumb to acute liver failure or bacterial sepsis. The classical sign of cholangitis is Charcot's triad, which is right upper quadrant pain, fever and jaundice. Liver function tests will likely show increases across all enzymes (AST, ALT, ALP,

GGT) with raised bilirubin. As with choledocholithiasis, diagnosis is confirmed using cholangiopancreatography.

Treatment

Surgery is the usual treatment. Surgery to remove the gallbladder (cholecystectomy) can be performed as an open or endoscopic (laparoscopic, natural orifice transluminal endoscopic surgery, etc.) procedure.

The open procedure requires a large cut in the upper-right part of the abdomen. Open cholecystectomy, which involves a large abdominal incision and direct exploration, is safe and effective. Its overall mortality rate is about 0,1% when done electively during a period free of complications.

Laparoscopic surgery uses instruments and a small camera inserted through a cluster of a few small cuts. Laparoscopic cholecystectomy is the treatment of choice. Using video endoscopy and instrumentation through small abdominal incisions, the procedure is less invasive than open cholecystectomy. The result is a much shorter convalescence, decreased postoperative discomfort, improved cosmetic results, yet no increase in morbidity or mortality. Laparoscopic cholecystectomy is converted to an open procedure in 2 to 5% of patients, usually because biliary anatomy cannot be identified or a complication cannot be managed. Older age typically increases the risks of any type of surgery.

Cholecystectomy effectively prevents future biliary colic but is less effective for preventing atypical symptoms such as dyspepsia. Cholecystectomy does not result in nutritional problems or a need for dietary limitations. Some patients develop diarrhea, often because bile salt malabsorption in the ileum is unmasked. Prophylactic cholecystectomy in asymptomatic patients with cholelithiasis is not warranted except in those with quite large gallstones (>3 cm) or those with a calcified gallbladder (porcelain gallbladder) because of an increased risk of gallbladder carcinoma.

Complications of cholecystectomy:

- bile leak ("biloma");
- bile duct injury (about 5–7 out of 1000 operations). Open and laparoscopic surgeries have essentially equal rate of injuries, but the recent trend is towards fewer injuries with laparoscopy. It may be that the open cases often result because the gallbladder is too difficult or risky to remove with laparoscopy;
- abscess;
- wound infection;
- bleeding (liver surface and cystic artery are most common sites);
- hernia;
- organ injury (intestine and liver are at highest risk, especially if the gallbladder has become adherent/scarred to other organs due to inflammation (e.g. transverse colon);
- deep vein thrombosis/pulmonary embolism (unusual-risk can be decreased through use of sequential compression devices on legs during surgery);
- fatty acid and fat-soluble vitamin malabsorption.

Stone dissolution

For patients who decline surgery or who are at high surgical risk (eg, because of concomitant medical disorders or advanced age), gallbladder stones can sometimes be dissolved by ingesting bile acids orally for many months. The best candidates for this treatment are those with small, radiolucent stones (more likely to be composed of cholesterol) in a functioning nonobstructed gallbladder – normal filling on cholescintigraphy or oral cholecystography or absence of stones in the neck.

Ursodeoxycholic acid 8 to 10 mg/kg/day po dissolves 80% of tiny stones < 0.5 cm in diameter within 6 mos. For larger stones (the majority), the success rate is much lower, even with higher doses of ursodeoxycholic acid. Further, after successful dissolution, stones recur in 50% within 5 yr. Most patients are thus not candidates and prefer laparoscopic cholecystectomy. Stone fragmentation (extracorporeal shock wave lithotripsy) to assist stone dissolution and clearance is now unavailable. Ursodeoxycholic acid, however, has value in preventing stone formation in morbidly obese patients who are losing weight rapidly after bariatric surgery or while on a very low calorie diet.

Possible Complications

- Cancer of the gallbladder (rarely).
- Jaundice.
- Pancreatitis.
- Worsening of the condition.

Prognosis

Those with asymptomatic gallstones become symptomatic at a rate of about 2%/yr. The symptom that develops most commonly is biliary colic rather than a major biliary complication. Once biliary symptoms begin, they are likely to recur; pain returns in 20 to 40% of patients/yr, while about 1 to 2% of patients/yr develop complications such as cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis.

3.3. CHOLEDOCHOLITHIASIS

One of the most common causes of extrahepatic biliary obstruction is choledocholithiasis, with one or more stones in the common bile duct or common hepatic duct causing biliary obstruction.

Prevalence and Risk Factors

Up to 10% of patients with gallstones have common bile duct stones. Common bile duct stones have been discovered days to several years after surgery in as many as 5% of patients who have undergone cholecystectomy. It is believed that the stones represent retained stones or stones that have formed de novo after the operation.

Pathophysiology and Natural History

Stones in the bile duct can cause biliary obstruction and cholestasis. This can lead to infection in the bile duct (bacterial cholangitis), which requires urgent medical therapy. The long-standing presence of stones in the bile duct can lead to secondary biliary cirrhosis. Choledocholithiasis can also lead to gallstone pancreatitis.

Signs and Symptoms

Most patients with choledocholithiasis report upper abdominal pain, although some patients may remain asymptomatic. Because complete obstruction of the bile duct by the stone may be intermittent, patients may report episodic jaundice.

The initial manifestation of choledocholithiasis can also be heralded by an episode of cholangitis. Gallstone pancreatitis manifests with typical features of pancreatitis, including epigastric pain, nausea, and vomiting.

Diagnosis

Several diagnostic tools can be used when evaluating patients suspected of having choledocholithiasis. Ultrasound is the preferred initial screening test because it is usually less expensive than CT or magnetic resonance imaging (MRI), does not use ionizing radiation, and is highly accurate in detecting gallbladder stones and bile duct dilation. MR cholangiography has gained acceptance as a tool for diagnosing choledocholithiasis. Its accuracy in detecting bile duct stones approaches that of endoscopic retrograde cholangiography. Abdominal CT scanning can also be helpful in evaluating patients with obstructive jaundice. It is as accurate as ultrasound in detecting common duct stones and may help localize the level of obstruction in the biliary tree.

Once biliary dilation or the presence of a common duct stone is noted on an imaging study, or biliary obstruction is strongly suspected on clinical grounds despite negative imaging studies, endoscopic retrograde cholangiopancreatography (ERCP) is recommended. ERCP provides a means of visualizing the biliary tree and the opportunity for therapy. Percutaneous transhepatic cholangiography can be a useful alternative when ERCP is not successful, although it is sometimes not successful in the absence of dilated bile ducts.

Treatment

The goals of therapy for choledocholithiasis are to remove the stones from the biliary tree and to decompress the biliary tree urgently if bacterial cholangitis is present. Stone extraction can be accomplished with **endoscopic retrograde cholangiopancreatography** (ERCP), often preceded by an **endoscopic sphincterotomy** (the gold standard for the treatment of choledocholithiasis). In the presence of bacterial cholangitis, when a stone cannot be removed for technical reasons – for example, because of its large size – an endoscopically placed biliary stent can be useful for decompressing the biliary tree. An alternative to ERCP for the treatment of choledocholithiasis is percutaneous transhepatic cholangiography (PTHC). PTHC can be used for emergent drainage of the biliary tree in the presence of cholangitis. Passage of a wire into the duodenum via a percutaneous approach can also help guide an endoscopist when performing an ERCP with stone extraction if ERCP had previously failed because of technical factors.

Open operation:

Principles:

- Try to removal all stones.
- Relief bile duct stenosis and obstruction.
- The obstructive duct must be drained adequately.

Operation methods:

1. Choledocholithotomy and tube drainage (*Fig. 3.5*) with cholangiography during operation if stones left; choledochoscopy should be used: forceps balloon catheter a basket.

- Simple common bile duct (CBD) stones without stenosis.
- If gallstones or cholecystitis coexist, cholecystectomy.

2. Choledochoduodenostomy (*Fig. 3.6*).

Indication:

- Stones impacted at ampulla.

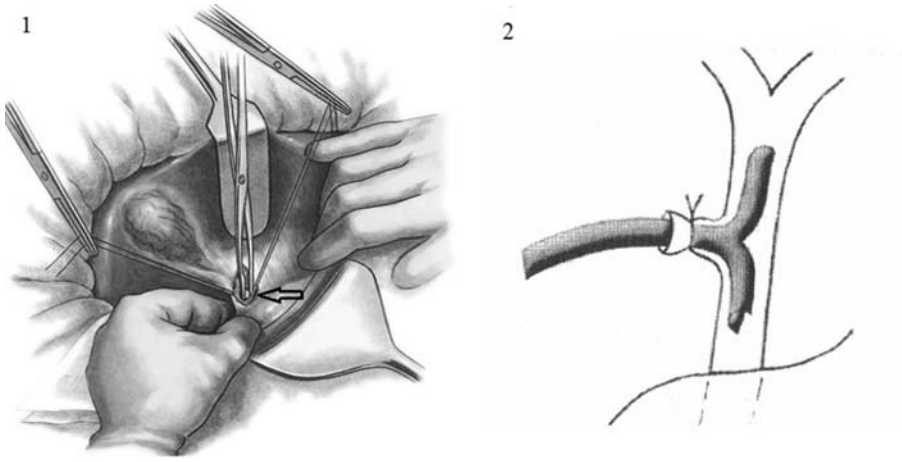


Figure 3.5. *Choledocholithotomy (1, arrow) and T-tube drainage (2)*

- Benign stenosis of the end of CBD.

Contraindication: pancreatitis, bleeding tendency, diverticulum of duodenum, Billroth II type gastrectomy.

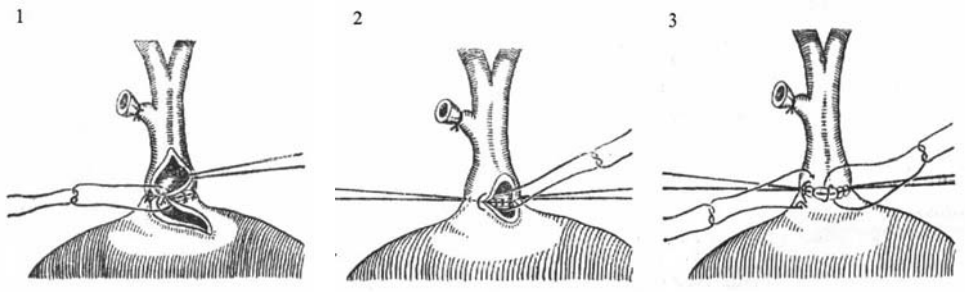


Figure 3.6. *Choledochoduodenostomy*

3. Sphincteroplasty

Peri-operation management:

- Control infection: antibiotics.
- Correct electrolyte and acid-alkali balance.
- Vitamin K, nutrition, etc.

4. Choledochojejunostomy.

Indication:

• CBD dilatation >2.5 cm with stenosis and obstruction Sandy-like stones, not easy to clear.

3.4. INTRAHEPATIC BILE DUCT STONES (HEPATOLITHIASIS)

• Pigment stones mainly.
• Left more than right.
• Coexist with extra hepatic bile duct stones commonly.

Etiology

• Infection.
• Cholestasis.
• Biliary Ascariasis.

Pathology

• Stenosis: intra-hepatic bile duct.
• Cholangitis.
• Biliary carcinoma.

Clinical manifestation

Feature of extra hepatic bile duct stones (when coexist).

• Asymptomatic or discomfort of liver area and chest back.
• Obstruction: infection, fever, chill, acute obstructive suppurative cholangitis.
• Abscess bronchobiliary fistula.
• Bile liver cirrhosis hypertension of portal vein.
• Carcinoma of biliary tract: frequency attack of cholangitis, progressive jaundice, abdominal pain, fever hard to control, age >50 become thin.

Physical exam

• Liver swelling asymmetrical.
• Tenderness at liver area.
• Percussion tenderness over hepatic region.
• Others: infection and complication.

Diagnosis

• History.
• Imaging exam: ultrasound, ERCP, MR-cholangiopancreatography, percutaneous transhepatic cholangiography.

Treatment

Operation – the main method.

Principle: extract all stones relief stenosis and obstruction: key point removal intrahepatic infective focus recovery the bile drainage prevent recrudescence.

• High positioned cholangiolithotomy: choledochoscopy.
• Internal drainage: Roux-en -Y cholangiojejunostomy
• Removal intrahepatic infective focus local cirrhosis: left lateral lobe and right posterior lobe.

Treatment of residual stones:

• Choledochoscopy.

• Extracorporeal shock wave lithotripsy.

3.5. ACUTE CHOLANGITIS

Cholangitis is bacterial infection superimposed on biliary obstruction. First described by Jean-Martin Charcot in 1850s as a serious and life-threatening illness.

Causes

• Choledocholithiasis.

• Obstructive tumors: pancreatic cancer; cholangiocarcinoma; ampullary cancer.

• Others: strictures/stenosis; ERCP; sclerosing cholangitis; AIDS; ascaris lumbricoides.

Pathogenesis

• Normally, bile is sterile due to constant flush, bacteriostatic bile salts, secretory IgA, and biliary mucous; sphincter of Oddi forms effective barrier to duodenal reflux and ascending infection.

• ERCP or biliary stent insertion can disrupt the sphincter of Oddi barrier mechanism, causing pathogenic bacteria to enter the sterile biliary system.

• Obstruction from stone or tumor increases intrabiliary pressure.

• High pressure diminishes host antibacterial defense- IgA production, bile flow-causing immune dysfunction, increasing small bowel bacterial colonization.

• Bacteria gain access to biliary tree by retrograde ascent.

• Biliary obstruction (stone or stricture) causes bactibilia:

‣ E. coli (25–50%);

‣ Klebsiella (15–20%);

‣ Enterobacter (5–10%).

• High pressure pushes infection into biliary canaliculi, hepatic vein, and perihepatic lymphatics, favoring migration into systemic circulation- bacteremia (20–40%).

Clinical Manifestations: criteria Charcot's triad and Reynold's pentad are shown with purulent cholangitis in the *Fig. 3.7*.

Diagnosis. Laboratory researches:

1. CBC:

• 80% or more of patients have WBC > 10,000.

• Septic patients may be neutropenic.

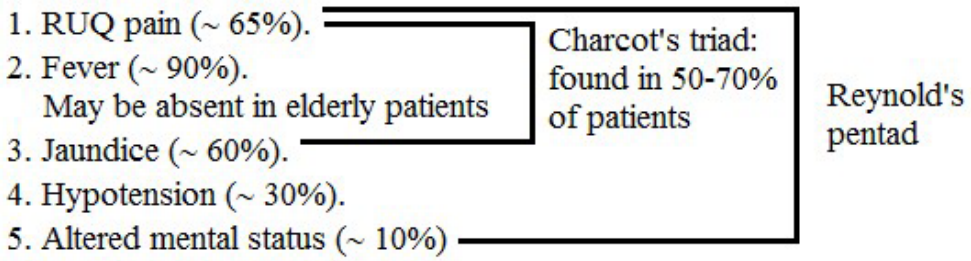


Figure 3.7. *Criteria Charcot's triad and Reynold's pentad*

2. Metabolic panel:

• Low calcium if pancreatitis.
• 88–100% has hyperbilirubinemia.
• 78% or more of patients have increased alkaline phosphatase.
• AST and ALT are mildly elevated.
• Aminotransferase can reach 1000U/L.
• GGT most sensitive marker of choledocholithiasis.

3. Amylase/Lipase:

• Involvement of lower CBD may cause 3–4x elevated amylase.

4. Blood cultures :

• 20–30% of blood cultures are positive.

Diagnosis

Ultrasonography

Advantage:

1) Sensitive for intrahepatic/extrahepatic/CBD dilatation.

• Common bile duct diameter > 6 mm on US associated with high prevalence of choledocholithaisis (*Fig. 3.8*).

• Of cholangitis, dilated CBD found in more than 60% patients.

2) Identify complications: perforation, empyema, abscess.

Disadvantage:

3) Not useful for choledocholithiasis:

• Of cholangitis patients, CBD stones observed in 13%.

4) 10–20% falsely negative – normal U/S does not r/o cholangitis:

• acute obstruction when there is no time to dilate;

• small stones in bile duct in 10–20% of cases.

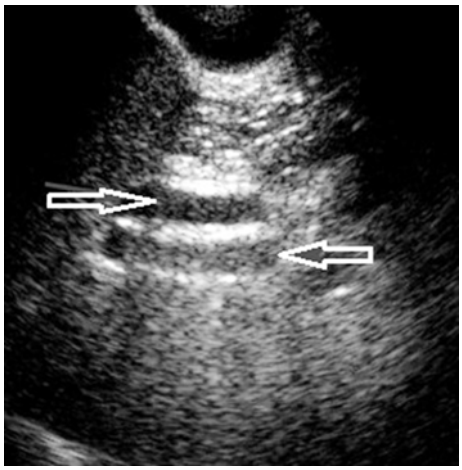


Figure 3.8. *Ultrasonography: common bile duct diameter > 6 mm on US associated with high prevalence of choledocholithaisis (arrows)*

CT

Advantages:

1) CT cholangiograhy enhances CBD stones and increases detection of biliary pathology (*Fig. 3.9*):

• Sensitivity for CBD stones is 95%.

• Can image other pathologies: ampullary tumors, pericholecystic fluid, liver abscess.

• Can visualize other pathologies – cholangitis: diverticulitis, pyelonephritis, mesenteric ischemia, ruptured appendix.

Disadvantages:

• Sensitivity to contrast.

• Poor imaging of gallstones.

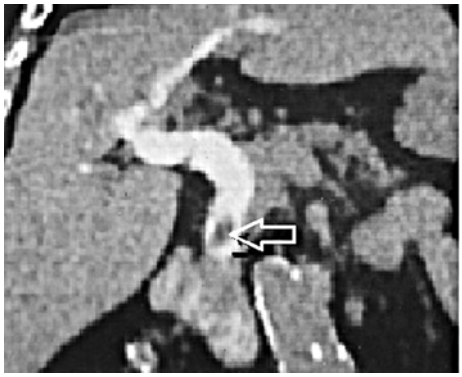


Figure 3.9. *CT: common bile duct stones (arrow)*

Magnetic resonance cholangiopancreatography (MRCP)

Advantage:

• Detects choledocholithiasis, neoplasms, strictures, biliary dilations.

• Sensitivity of 81–100%, specificity of 92–100% of choledocholithiasis.

• Minimally invasive- avoid invasive procedure in 50% of patients.

Disadvantage:

• Cannot sample bile, test cytology, remove stone.

• Contraindications: pacemaker, implants, prosthetic valves.

Indications:

• If cholangitis not severe, and risk of ERCP high, MRCP useful.

• If Charcot's triad present, therapeutic ERCP with drainage should not be delayed.

Endoscopic retrograde cholangiopancreatography (ERCP) – gold standard for diagnosis of CBD stones, pancreatitis, tumors, sphincter of Oddi dysfunction.

Advantage:

• Therapeutic option when CBD stone identified.

• Stone retrieval and sphincterotomy.

Disadvantage:

• Complications: pancreatitis, cholangitis, perforation of duodenum or bile duct, bleeding.

Diagnostic ERCP complication rate 1.38%, mortality rate 0.21%.

Medical Treatment

1. Resuscitate, monitor, stabilize if patient unstable.

• Consider cholangitis in all patients with sepsis.

2. Antibiotics.

• If fail medical therapy, mortality rate 100% without surgical decompression: ERCP or open.

‣ Indication: persistent pain, hypotension, fever, mental confusion.

Surgical treatment

Endoscopic biliary drainage

• Endoscopic sphincterotomy with stone extraction and stent insertion (*Fig. 3.10*):

‣ CBD stones removed in 90–95% of cases.

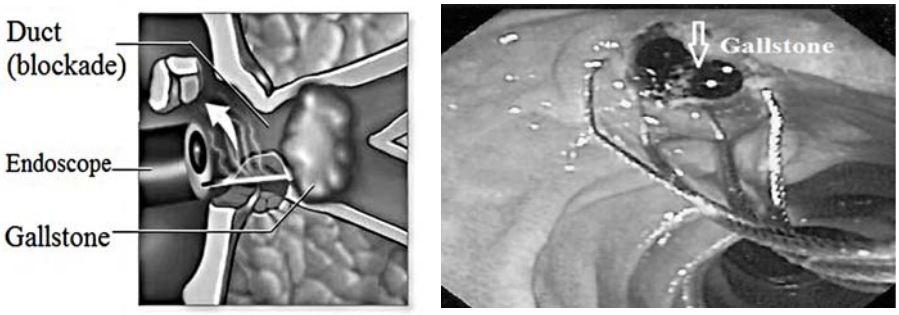


Figure 3.10. *Endoscopic sphincterotomy with stone extraction*

Surgery

• Emergency surgery replaced by non-operative biliary drainage.

• Once acute cholangitis controlled, surgical exploration of CBD for difficult stone removal.

3.6. CHOLECYSTOBILIARY FISTULA (MIRIZZI'S SYNDROME)

Mirizzi's syndrome is a rare cause of acquired jaundice. It is caused by chronic cholecystitis and large gallstones resulting in compression of the common hepatic duct (acute type) or formation of vesico-biliary fistula (chronic type). It is named for Pablo Luis Mirizzi, an Argentinian physician (1948).

Epidemiology

Occurs in approximately 0.1% of patients with gallstone disease and 0.7–1.4% of patients undergoing cholecystectomy. It affects males and females equally, but tends to affect older people more often.

Pathophysiology

Multiple and large gallstones can reside chronically in the Hartmann's pouch of the gallbladder, causing inflammation, necrosis, scarring and ultimately fistula formation into the adjacent common hepatic duct (CHD). As a result, the CHD becomes obstructed by either scar or stone, resulting in jaundice. It can be divided into four types.

Csendes classification:

Type I no fistula present:

- Type IA presence of the cystic duct.
- Type IB obliteration of the cystic duct.

Types II–IV fistula present:

- Type II defect smaller than 33% of the CHD diameter.
- Type III defect 33–66% of the CHD diameter.
- Type IV defect larger than 66% of the CHD diameter.

Features

Mirizzi's syndrome has no consistent or unique clinical features that distinguish it from other more common forms of obstructive jaundice. Symptoms of recurrent cholangitis, jaundice, right upper quadrant pain, and elevated bilirubin and alkaline phosphatase may or may not be present. Acute presentations of the syndrome include pancreatitis or cholecystitis.

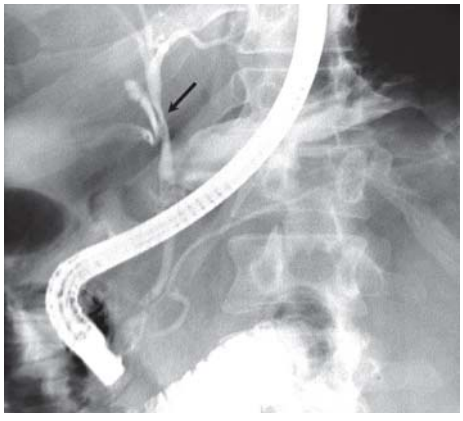


Figure 3.11. *ERCP study shows smooth narrowing of the bile duct (arrow) at the site of insertion of the cystic duct (Mirizzi's syndrome). Note the small calculus in the cystic duct*

Diagnosis

CT scan or ultrasonography usually makes the diagnosis. Often, ERCP (*Fig. 3.11*) is used to define the lesion anatomically prior to surgery.

Treatment

The treatment of choice is laparotomic surgical excision of the gallbladder, and reconstruction of the common hepatic duct and common bile duct (*Table 3.1*).

Table 3.1 – Treatment summary of Mirizzi's syndrome

Options	Type I	Type II	Type III	Type IV
Surgical options	Cholecystectomy (or subtotal cholecystectomy with stone removal) – open surgery preferred	Choledochoplasty or biliary–enteric anastomosis		Roux–en–Y hepaticojejunostomy
Endoscopic options	1. Biliary drainage + electrohydraulic lithotripsy or shock wave lithotripsy for stone that is accessible via cholangioscope. 2. Extracorporeal shock wave lithotripsy for retained stone and failed mechanical lithotripsy. 3. If stone clearance fails, consider long–term stenting for high–risk patients and surgery for ceptable–risk patients.	1. Biliary drainage + stone clearance with mechanical lithotripsy or shock wave lithotripsy via cholangioscope in patients with or without small residual gallstones; consider surgery if there are large residual gallstones. 2. If stone clearance fails, consider long–term stenting for high–risk patients and surgery for acceptable–risk patients.		

3.7. CHOLECYSTO-ENTERIC FISTULAS

Biliary fistulas, like other fistulas, can be external or internal, spontaneous or develop postoperatively. In 1854, Courvoisier published the first report of gallstone passage through a cholecysto-duodenal fistula causing a small bowel obstruction at the terminal ileum, a phenomenon today generally termed gallstone ileus (*Fig. 3.12*). It has been estimated that enterobiliary fistulas can be found in 0.9% of 12.000 operations for non-malignant biliary tract disease. Spontaneous enterobiliary fistulas are usually associated with untreated calculous gallbladder disease and occur predominantly in women. In developed countries, biliary fistulas most commonly occur after hepatobiliary or pancreatic surgery. The presence of air or barium in the biliary tree is considered a typical radiographic sign for diagnosing a cholecysto-enteric fistula. Cholecysto-enteric fistulas are commonly caused by cholecystitis directly invading the stomach, small intestine or colon via the gall bladder (usually over its body) and less commonly via the common bile duct. Cholecysto-duodenal fistulas are the most common (about 60 percent of cases), followed by cholecysto-colonic and cholecysto-gastric fistulas in descending order.

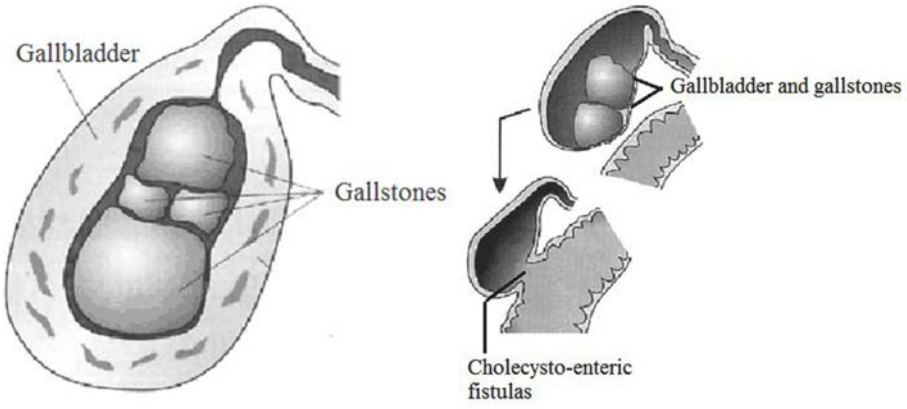


Figure 3.12. *The mechanism of formation of a cholecysto-enteric fistulas*

Cholecysto-enteric fistulas are usually associated with cholelithiasis, and their common symptoms and signs are also abdominal cramping pain, vomiting, jaundice, sepsis, gastro-intestinal bleeding and intestinal obstruction. Some may be asymptomatic. The diagnostic tools include fistulography, abdominal sonography, endoscopic retrograde cholangiopancreatography, operative cholecystography, abdominal computer tomography and magnetic resonance imaging.

Standard treatment of cholecysto-colonic fistula is open cholecystectomy and closure of fistula. As a result of increasing surgical expertise, laparoscopic surgery can now be used in fistula treatment, with decrease pain and hospital stay for the patients. Results have shown no significant difference in intraoperative and post-operative complications with the proper surgical technique.

The most frequent complications of cholecysto-enteric fistulas include fluid and electrolyte imbalance, fat malabsorption syndrome, biliary stricture, intestinal obstruction, cholangitis and sepsis. The prognosis for such fistulas is good with a less than 10% mortality rate, except for those occurring in the elderly with immunocompromised conditions or other severe co-morbidity.

3.8. POSTCHOLECYSTECTOMY SYNDROME

Postcholecystectomy syndrome (PCS) describes the presence of abdominal symptoms after surgical removal of the gallbladder (cholecystectomy). First described in 1947.

PCS or postoperative symptoms which are presented before operation include abdominal pain, jaundice, dyspepsia, increased defecating time, dislike of fatty foods and so on. The causes of this syndrome are still obscure; some are related lo diseases of the biliary tract, whereas others are not. In recent years, endoscopy has been widely applied in the diagnosis and treatment of digestive tract diseases. This study aimed to assess the value of duodenos-copy in the diagnosis and treatment of PCS.

The etiology of PCS (*Table 3.2*) includes biliary diseases and extracholangeal lesions. Biliary diseases are characterized by bile duel stones, inflammatory stricture of the papilla, and lesions of cystic duct stump. And extracholangeal conditions commonly comprise reflux esophagitis, digestive ulcers and pancreatitis. So it is essential to check related organs for the cause of PCS. With the suspicion of lesion in the esophagus, stomach or duodenum, double-contrast barium meal and gastroscopy should be performed. If lesions of the bile duct, liver or pancreas are suspected, ultrasonography and ERCP are advisable.

Symptoms include gastrointestinal distress and persistent pain in the upper right abdomen. Symptoms occur in about 5 to 40% of patients who undergo cholycystectomy.

The pain associated with postcholecystectomy syndrome is usually ascribed to either sphincter of Oddi dysfunction or to post-surgical adhesions.

Endoscopic intervention in minimally invasive surgery has such advantages as safety, less pain, and few complications. K. Kawai and his collea-gues "first introduced" endoscopic sphincterotomy to treat bile duct stones in 1974, and

Table 3.2 – Etiology of postcholecystectomy syndrome

Anatomy	Etiology	Anatomy	Etiology
Gallbladder remnant and cystic duct	Residual gallbladder Stump cholelithiasis Neuroma	**Periampullary**	Sphincter of Oddi dyskinesia, spasm or hypertrophy Sphincter of Oddi, stricture Papilloma Cancer
Liver	Fatty infiltration of liver Hepatitis Hydrohepatosis Cirrhosis Gilbert disease Dubin–Johnson Sx Hepatolithiasis Sclerosing cholangitis Cyst	**Biliary tract**	Cholangitis Adhesions Strictures Trauma Cyst Malignancy/cholangiocarcinoma Obstruction Choledocholithiasis Dilation w/out obstruction Hypertension or nonspecific dilation Dyskinesia Fistula
Pancreas	Pancreatitis Stone Cancer	**Colon**	Constipation Diarrhea Incisional hernia IBS
Esophagus	Diaphragmatic hernia Hiatal hernia Achalasia	**Stomach**	Bile gastritis PUD Gastric cancer
Bone	Arthritis	**Vascular**	Intestinal angina Coronary angina
Duodenum	Adhesions Diverticula Irritable bowel disease	**Small bowel**	Adhesions Incisional hernia Irritable bowel disease
Nerve	Neuroma Intercostal neuralgia Spinal nerve lesions Sympathetic imbalance Neurosis Psychic anxiety	**Other**	Adrenal cancer Thyrotoxicosis 20% organ other than hepatobiliary or pancreatic Unknown Erroneous preop Dx

M. Starizu et al. used endoscopic papillary balloon dilatation to treat bile duct stones while preserving papillary function in 1983.

3.9. PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is a form of cholangitis due to an autoimmune reaction. A cholangitis is an inflammation of the bile ducts of the liver. Primary sclerosing cholangitis leads to cholestasis (blockage of bile transport to the gut). Blockage of the bile duct leads to accumulation of bile, which damages the liver, leading to jaundice and eventually causes liver failure.

Etiology

The cause(s) for PSC are unknown. It is often considered to be an autoimmune disorder. PSC is associated with ulcerative colitis. It is assumed that these diseases share a common cause.

Ulcerative colitis is a systemic disease that affects many areas of the body. PSC is often listed as a manifestation of ulcerative colitis outside the colon. PSC differs from these manifestations in that, unlike most other manifestations, PSC continues in spite of surgical removal of the colon. This suggests that, while the cause of ulcerative colitis, and most of its manifestations, is in the colon, the cause of PSC is located outside the colon.

Pathophysiology

Bile ducts, both intra- and extrahepatically (inside the liver and outside), are inflamed and develop scarring, obstructing the flow of bile. As bile assists in the enteric breakdown and absorption of fat, the absence of bile leads to fat malabsorption. The bile accumulates in the duct, leading to liver cell damage and liver failure.

Epidemiology

It is more prevalent in men than in women. The disease normally starts from age 30 to 60. It can however also start with children. PSC progresses slowly, so the disease can be active for a long time before it is noticed or diagnosed.

Signs and symptoms

- Tiredness (a non-specific symptom often present in liver disease).
- Severe jaundice with intense itching.
- Malabsorption (especially of fat) and steatorrhea, leading to decreased levels of the fat-soluble vitamins, A, D, E and K.
- Signs of cirrhosis.
- Ascending cholangitis, or infection of the bile duct.

Diagnosis

The diagnosis is by imaging of the bile duct, usually in the setting of endoscopic retrograde cholangiopancreatography (ERCP, endoscopy of the bile duct and pancreas), which shows characteristic changes ("beading") of the bile ducts. Another option is magnetic resonance cholangiopancreatography (MRCP), where magnetic resonance imaging is used to visualise the biliary tract.

Other tests often done are a full blood count, liver enzymes, bilirubin levels (usually grossly elevated), renal function, electrolytes. Fecal fat determination is occasionally ordered when the symptoms of malabsorption are prominent.

The differential diagnosis can include primary biliary cirrhosis, drug induced cholestasis, cholangiocarcinoma, and HIV-associated cholangiopathy.

Screening

PSC is associated with cholangiocarcinoma, which are tumors involving the biliary tree. Screening for cholangiocarcinoma in patients with PSC is encouraged, but there is no general consensus on the modality and interval of choice.

Therapy

Standard treatment includes ursodiol, a bile acid naturally produced by the liver, which has been shown to lower elevated liver enzyme numbers in people with PSC, but has not yet been proven effective at prolonging the life of the liver. Treatment also includes medication to relieve itching (antipruritic) and bile acid sequesterants (cholestyramine), antibiotics to treat infections, and vitamin supplements, as people with PSC are often deficient in vitamin A, vitamin D, and vitamin K.

In some cases, ERCP, which may involve stenting of the common bile duct, may be necessary in order to open major blockages (dominant strictures).

Liver transplantation (including live transplants whereby a portion of a living donor is given to the recipient) is an option if the liver begins to fail.

REFERENCES

1. Allema JH, Reinders ME, van Gulik TM. Results of pancreaticoduodenectomy for ampullary carcinoma and analysis of prognostic factors for survival. Surgery. 117: 1995; 247–253.

2. Anthony PP. Tumors of the hepatobiliary system.. 411–460.

3. Auyang ED, Hungness ES, Vaziri K et al. Human NOTES cholecystectomy: transgastric hybrid technique. J Gastrointest Surg 2009; 13: 1149–1150.

4. Balfe DM, Ralls PW, Bree RL. Imaging strategies in the initial evaluation of the jaundiced patient. American College of Radiology. ACR Appropriateness Criteria. Radiology. 215: 2000; 125–133.

5. Barie PS, Fischer E. Acute acalculous cholecystitis. J Am Coll Surg. 180: 1995; 232–244.

6. Broome U, Olsson R , Loof L. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut. 38: 1996; 610–615.

7. Chalasani N, Baluyut A , Ismail A. Cholangiocarcinoma in patients with primary sclerosing cholangitis: A multicenter case-control study. Hepatology. 31: 2000; 7–11.

8. Chung RS, Church JM, Van Stolk R. Pancreas-sparing duodenectomy: Indications, surgical technique, and results. Surgery. 117: 1995; 254–259.

9. Dahan P, Andant C, Levy P. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. Gut. 38: 1996; 277–281.

10. Dallemagne B, Perretta S, Allemann P et al. Transgastric hybrid cholecystectomy. Br J Surg 2009; 96 (10): 1162–1166.

11. Daly CA, Padley SPG. Sonographic prediction of a normal or abnormal ERCP in suspected AIDS related sclerosing cholangitis. Clin Radiol. 51: 1996; 618–621.

12. de Groen PC, Gores GJ , LaRusso NF. Biliary tract cancers. N Engl J Med. 341: 1999; 1368–1378.

13. De Vreede I, Steers JL, Burch PA. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl. 6: 2000; 309–316.

14. Everhart JE, Khare M, Hill M , Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology. 117: 1999; 632–639.

15. Greenberger NJ, Isselbacher KJ. Diseases of the gallbladder and bile ducts. In: (eds. Fauci AS, et al): Harrison's Principles of Internal Medicine, 14th edition, vol #2, pp 1725–1736; McGraw-Hill, New York, 1998.

16. Hazzan, D; D Golijanin, P Reissman, SN Adler, E Shiloni (06 1999). "Combined endoscopic and surgical management of Mirizzi syndrome". Surgical Endoscopy 13 (6): 618–20.

17. Heimbach JK, Gores GJ, Haddock MG. Liver transplantation for unresectable perihilar cholangiocarcinoma. Semin Liver Dis. 24: 2004; 201–207.

18. Hermann RE. The spectrum of biliary stone disease. Am J Surg. 158: 1989; 171–173.

19. Huibregtse K, van Amerongen R, van Deventer SJ. Drainage of the gallbladder in patients with acute acalculous cholecystitis by transpapillary endoscopic cholecystoxeransis. Gastrointest Endosc. 40: 1994; 523.

20. Iwama T, Tomita H, Kawachi Y. Indications for local excision of ampullary lesions associated with familial adenomatous polyposis. J. Am Coll Surg. 179: 1994; 462–464.

21. Khan SA, Davidson BR, Goldin R. Guidelines for the diagnosis and treatment of cholangiocarcinoma: Consensus document. Gut. 51: 2002; 7–9.

22. Kubota K, Bandai Y, Noie T. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? Surgery. 117: 1995; 481–487.

23. Lee YM, Kaplan MM. Primary sclerosing cholangitis. N Engl J Med 1995; 332:924

24. Lefkowitch JH. The liver in AIDS. Semin Liver Dis. 17: 1997; 335–344.

25. Levy C, Lymp J, Angulo P. The value of serum CA 19–9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Dig Dis Sci. 50: 2005; 1734–1740.

26. Marescaux J, Dallemagne B, Perretta S et al. Surgery without scars: report of transluminal cholecystectomy in a human being. Arch Surg 2007; 142 (9): 823–826; discussion 826–7.

27. Mirizzi PL: Syndrome del conducto hepatico. J Int de Chir 1948; 8: 731–77.

28. Nagakawa T, Ohta T, Kayahara M. A new classification of Mirizzi syndrome from diagnostic and therapeutic viewpoints. Hepatogastroenterology. 44: 1997; 63–67.

29. Nagorney DM, Donohue JH, Farnell MB. Outcomes after curative resections of cholangiocarcinoma. Arch Surg. 128: 1993; 871–879.

30. Ortner MA, Liebetruth J, Schreiber S. Photodynamic therapy of nonresectable cholangiocarcinoma. Gastroenterology. 114: 1998; 536–542.

31. Ramage JK, Donaghy A, Farrant JM. Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. Gastroenterology. 108: 1995; 865–869.

32. Ransohoff DF, Gracie WA. Prophylactic cholecystectomy or expectant management for silent gallstones. Ann Intern Med. 99: 1983; 199–204.

33. Ryan ME, Baldauf MC. Comparison of flow cytometry for DNA content and brush cytology for detection of malignancy in pancreaticobiliary strictures. Gastrointest Endosc. 40: 1994; 133–139.

34. Terzi C, Sokmen S, Seckin S. Polypoid lesions of the gallbladder: Report of 100 cases with special reference to operative indications. Surgery. 127: 2000; 622–627.

35. Torok N, Gores GJ. Cholangiocarcinoma. Semin Gastrointest Dis. 12: 2001; 125–132.

36. Varghese JC, Liddell RP, Farrell MD. Diagnostic accuracy of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. Clin Radiol. 55: 2000; 25–35.

37. Washburn WK, Lewis WD, Jenkins RL. Aggressive surgical resection for cholangiocarcinoma. Arch Surg. 130: 1995; 270–276.

Chapter 4

DISEASES OF THE PANCREAS AND SPLEEN

4.1. CHRONIC PANCREATITIS

Chronic pancreatitis is defined as a progressive inflammatory disease of the pancreas, characterized by irreversible morphologic changes and gradual fibrotic replacement of the gland. Loss of exocrine and endocrine function results from fibrosis and parenchymal damage. The primary symptoms of chronic pancreatitis are abdominal pain and maldigestion, which may be physically and socially debilitating.

4.1.1. ANATOMY AND PHYSIOLOGY

The pancreas is a soft, elongated gland situated at the back of the upper abdominal cavity behind the stomach (*Fig. 4.1*).

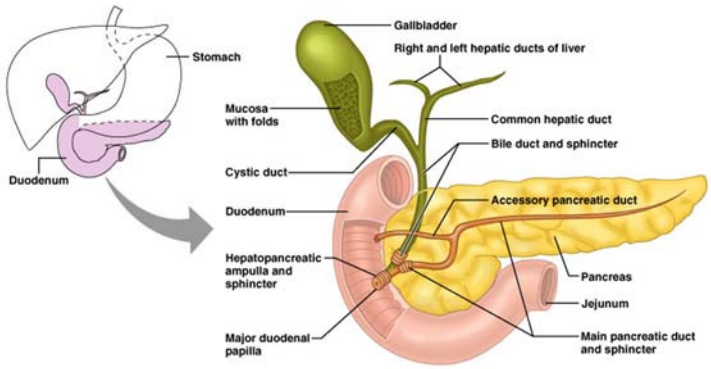


Figure 4.1. *The pancreas*

It is divided into the head (through which the common bile duct runs as it enters the duodenum) and the body (which extends across the spine and the tail), which is close to the left kidney and to the spleen. Because the pancreas lies at the back of the abdominal cavity, diseases of the pancreas may be difficult to diagnose.

The pancreas has two main functions:

1. It produces a series of enzymes which help in the digestion of food. Enzymes produced in the pancreas are important in the digestion of proteins, carbohydrates and, particularly, fats (*Fig. 4.2*):

• Acinar cells secrete isozymes: amylases, lipases, and proteases.

• **Major stimulants:** cholecystokinin, acetylcholine, secretin, VIP.

• Synthesized in the endoplasmic reticulum of the acinar cells and are packaged in the zymogen granules.

• Released from the acinar cells into the lumen of the acinus and then transported into the duodenal lumen, where the enzymes are activated.

Physiology – Exocrine Pancreas:

• 500 to 800 ml pancreatic fluid secreted per day.

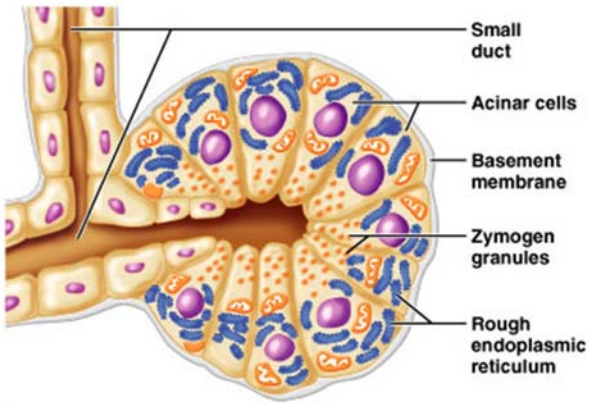


Figure 4.2. *Exocrine pancreas: histology*

• Alkaline pH results from secreted bicarbonate which serves to neutralize gastric acid and regulate the pH of the intestine.

• Enzymes digest carbohydrates, proteins, and fats.

Enzymes of Pancreas:

• Amylase:

‣ only digestive enzyme secreted by the pancreas in an active form;

‣ functions optimally at a pH of 7;

‣ hydrolyzes starch and glycogen to glucose, maltose, maltotriose, and dextrins.

• Lipase:

‣ function optimally at a pH of 7 to 9;

‣ emulsify and hydrolyze fat in the presence of bile salts.

• Proteases:

‣ essential for protein digestion;

‣ secreted as proenzymes and require activation for proteolytic activity;

‣ duodenal enzyme, enterokinase, converts trypsinogen to trypsin;

‣ trypsin, in turn, activates chymotrypsin, elastase, carboxypeptidase, and phospholipase

• Within the pancreas, enzyme activation is prevented by an antiproteolytic enzyme secreted by the acinar cells.

Bicarbonate is also produced in large amounts to neutralise the acid produced by the stomach:

• Centroacinar cells and ductular epithelium secrete 20 mmol of bicarbonate per liter in the basal state.

• Fluid (pH from 7,6 to 9,0) acts as a vehicle to carry inactive proteolytic enzymes to the duodenal lumen.

• Sodium and potassium concentrations are constant and equal those of plasma.

• Chloride secretion varies inversely with bicarbonate secretion.

• Bicarbonate is formed from carbonic acid by the enzyme carbonic anhydrase.

• **Major stimulants:** secretin, cholecystokinin, gastrin, acetylcholine.

• **Major inhibitors:** atropine, somatostatin, pancreatic polypeptide and glucagon.

• Secretin – released from the duodenal mucosa in response to a duodenal luminal pH < 3.

Digestion

Food is partly broken down by the acid and churning action of the stomach. After 1–2 hours food is slowly released into the duodenum through a valve called the pylorus. Here, and as it moves along the rest of the small bowel, the food is broken down into tiny particles. Nutrients are absorbed by the small intestine and used for energy and maintaining strong muscles and bones. Unwanted material passes into the large bowel (colon) and after 24 hours or so is excreted as stool via the rectum and anus.

Digestion of food which consists of carbohydrates (e.g. glucose), proteins (e.g. meat) and fat (e.g. butter) is not possible without the pancreas. Groups of glands in the pancreas (called acini) make 30 or so different enzymes each of which is responsible for breaking down clumps of different types of food into small particles for absorption. These enzymes are collected from the small glands in the pancreas into small ducts and finally into the main pancreatic duct to be released into the duodenum. The enzymes when they are first made in the acini are not active (otherwise they would digest the pancreas as well!). When they pass into the duodenum however, they are made active by the juice of the duodenum. The main enzymes are called amylase for digesting carbohydrates, trypsin for digesting proteins and lipase for digesting fats.

Digestion is also assisted by enzymes made and released by the salivary glands (amylase), tongue (lipase), stomach (pepsin and lipase) and small intestine (peptidases).

Fat needs to be dispersed before the pancreatic enzymes can properly break it down. This dispersion of fats is made by bile acids which are present in bile produced by the liver and stored in the gall bladder. Bile acids act in exactly the same way as detergents which are used to wash up greasy dishes. Therefore, both bile acids and pancreatic enzymes are needed for fat digestion. This is why the main pancreatic duct and the main bile duct join up together so that pancreatic juice and bile can be emptied together. If there are not enough pancreatic enzymes, fat is not digested and the stools (bowel motions) become pale and greasy.

For the same reason if the main bile duct becomes blocked, then the bile cannot get into the duodenum, fat cannot be properly digested and the stools are again pale in color. Because the bile made by the liver cannot go into the bowel it goes into the blood and out through the kidneys into the urine. This results in the eyes and skin becoming yellow and is known as yellow jaundice. As the bile is in the urine this now becomes dark in color. Because the flow of bile is blocked (or obstructed), doctors call this condition obstructive jaundice. As the bile duct goes through the head of the pancreas yellow jaundice can be caused by disease of the pancreas (such as pancreatitis or cancer).

Pancreas is produce a series of hormones which are important in maintaining a normal level of sugar in the blood. The best known of these hormones is insulin. Insulin deficiency of this hormone results in the development of diabetes. Another hormone (glucagon) helps to raise blood sugar, and several other hormones control intestinal function.

Histology-Endocrine Pancreas:

- Accounts for only 2% of the pancreatic mass.
- Nests of cells – islets of Langerhans.
- Four major cell types:
  - Alpha (α) cells secrete glucagon.
  - Beta (β) cells secrete insulin.
  - Delta (D) cells secrete somatostatin.
  - F-cells secrete pancreatic polypeptide.

Insulin:

- Synthesized in the β–cells of the islets of Langerhans.
- 80% of the islet cell mass must be surgically removed before diabetes becomes clinically apparent.
- Proinsulin is transported from the endoplasmic reticulum to the Golgi complex where it is packaged into granules and cleaved into insulin and a residual connecting peptide, or C peptide.
- **Major stimulants:** glucose, amino acids, glucagon, GIP, CCK, sulfonylurea compounds, β-sympathetic fibers.
- **Major inhibitors:** somatostatin, amylin, pancreastatin, β-sympathetic fibers.

Glucagon:

- Secreted by the cells of the islet.
- Glucagon elevates blood glucose levels through the stimulation of glycogenolysis and gluconeogenesis.
- **Major stimulants:** aminoacids, cholinergic fibers, β-sympathetic fibers.
- **Major inhibitors:** Glucose, insulin, somatostatin, β-sympathetic fibe.

Somatostatin:

- Secreted by the D cells of the islet.
- Inhibits the release of growth hormone.
- Inhibits the release of almost all peptide hormones.
- Inhibits gastric, pancreatic, and biliary secretion.
- Used to treat both endocrine and exocrine disorders.

4.1.2. ETIOLOGY, PATHOGENESIS AND CLASSIFICATION

At least 70% of adult cases are caused by chronic alcohol use, and most patients have consumed more than 150 g/day of alcohol over six to twelve years.

The pancreatic injury induced by ethanol exposure is likely to be multifactorial. Proposed mechanisms include: a) ductal hypertension induced by increased viscosity of secretions in combination with obstruction secondary to sphincter of Oddi dysfunction, stimulation of secretion, and increased duct permeability, b) decreased pancreatic blood flow, c) inflammation and oxidant stress, d) direct acinar cell toxicity, e) changes in protein synthesis, f) an enhanced inflammatory response, and g) stimulation of pancreatic fibrosis. A growing body of evidence suggests that alcohol can cause acute injury even in the absence of underlying chronic disease.

Gallstone-associated pancreatitis is predominantly acute or relapsing-acute in nature, and some cases of chronic pancreatitis are of undetermined or idiopathic origin. A few are inherited or secondary to sphincter of Oddi dysfunction.

Other less frequent causes include chronic steroid and or anti-inflammatory use. In up to one quarter of cases, no cause can be found. Autoimmune pancreatitis is increasingly recognised and may be associated with raised IgG4 levels, other autoimmune features and bile duct involvement. Autoimmune chronic pancreatitis (AIP) is a rare condition, but may account for a substantial proportion of patients with "idiopathic" chronic pancreatitis. The entity known as "non-alcoholic duct-destructive chronic pancreatitis" may actually represent AIP. AIP may occur in isolation or in association with other autoimmune diseases, such as Sjögren's syndrome, PSC, and inflammatory bowel disease. Clinical features include minimal pain, hypergammaglobulinemia, autoantibodies (ANA, anti-lactoferrin, anti-carbonic anhydrase I and II, anti-smooth muscle, others), diffuse enlargement of the pancreas on imaging, typical lack of calcifications and cysts, and improvement with steroids.

Pancreatic duct obstruction (~10%) is increasingly recognised and may be associated with stones, stricture, tumor, pseudocyst, pancreas divisum etc.

Cystic fibrosis is the most common cause of chronic pancreatitis in children. In other parts of the world, severe protein-energy malnutrition is a common cause. Hereditary Pancreatitis, which is defined as recurrent pancreatitis attacks, can progress to chronic pancreatitis. This form of pancreatitis should be suspected in younger patients and those with relatives who also suffer from pancreatic disease. Both hereditary and chronic pancreatitis is major risk factors for developing pancreatic cancer. Yet the hereditary form increases the risk for cancer significantly, making a proper diagnosis essential.

New discoveries of genetic, immune-mediated, and environmental risk factors for chronic pancreatitis have caused this category to dwindle in recent years. However, 10–30% of patients with chronic pancreatitis possess no clear risk factors for the disease. Idiopathic chronic pancreatitis has been classified as early and late onset, given its bimodal age presentation and differences in presentation. Early-onset idiopathic chronic pancreatitis typically presents in the first two decades of life with severe abdominal pain. Structural changes, exocrine insufficiency, and calcifications occur much later in the course. Late-onset idiopathic chronic pancreatitis occurs in the fourth or fifth decade with minimal pain, often with pancreatic insufficiency at the time of diagnosis. Exocrine and endocrine dysfunction and pancreatic calcifications are much more likely to occur in late-onset idiopathic chronic pancreatitis. Possible mechanisms for both early and late onset idiopathic chronic pancreatitis include occult alcohol use and undiagnosed genetic defects. The serine protease inhibitor Kazal type 1 (SPINK-1) mutation has been noted in many patients previously characterized as having early idiopathic chronic pancreatitis. SPINK-1 is the gene that encodes pancreatic secretory trypsin inhibitor, a protein that plays a primary role in counteracting the effects of activated trypsin. Mutations causing loss of function of this protein increase the risk of development of acute and chronic pancreatitis. It is likely that underlying CFTR mutations exist in many of patients with idiopathic chronic pancreatitis as well.

In recent years, there have been great discoveries in genetic mechanisms for several inherited causes of chronic pancreatitis (HP, cystic fibrosis gene, SPINK-1, *etc.*). These discoveries have provided important insights into the genetics of pancreatic disease, as well as understanding of pathogenesis of acute and chronic pancreatitis. The details of these important genetic discoveries are discussed in a recent, excellent review.

Other causes include:

- high levels of calcium in the blood;
- abnormalities in anatomy which are usually present at birth;
- high blood fats (hypertriglyceridaemia);
- in rare cases, some drugs can cause pancreatitis;
- tropical;
- trauma;
- idiopathic (~10%).

So, although many of the above theories seek to provide a unifying model, it is more likely that diverse etiologies lead to chronic pancreatitis through unique pathways. For example, most would agree that obstructive chronic pancreatitis occurs through a very different mechanism than alcoholic chronic pancreatitis. Furthermore, the low prevalence of chronic pancreatitis among alcoholics would seem to suggest other cofactors at play in many with diagnosed "alcoholic" pancreatitis. In fact, possession of multiple risk factors may be required for progression to fibrosis.

The first effort to classify and define pancreatitis by a worldwide group of experts led to the Marseille Consensus Meeting in 1963 (Sarles, 1965). The panel of pancreatologists agreed that acute and chronic pancreatitis were different diseases mainly because of different morphologic patterns. Relapsing pancreatitis was characterized by the presence of multiple episodes in a morphologic pattern of acute or chronic processes. The distinctive features of the two diseases were the pathologic benign course of acute inflammation, with biologic restitution in the acute condition, and the progressively worsening parenchymal lesions in the chronic condition. Various systems have been proposed to classify pancreatitis based on clinical presentation, radiographic features, and etiology. Multiple revisions of the **Marseilles-Rome system** (1988) have classified pancreatitis into acute and chronic forms, with further descriptors applied to subdivide chronic pancreatitis according to morphologic and clinical characteristics. The Marseille symposium suggested specific etiologies for each of these morphologic forms of chronic pancreatitis:

1. Chronic calcific pancreatitis. Its most common cause is alcohol consumption. As a result of inflammation and changes in the structure of the smallest ducts of the pancreas, thickening of the secretion occurs with the formation of stoppers rich in protein and calcium. In this process, an important role is played by a decrease in the concentration of lithostatin (a protein that prevents stone formation).

2. Chronic obstructive pancreatitis. It observed with pronounced narrowing of the main pancreatic duct or its large branches, or sphincter of Oddi. Causes of development: alcohol, gallstone disease, trauma, swelling, birth defects.

3. Chronic parenchymal-fibrotic (inflammatory) pancreatitis.

The "TIGAR-O" classification of chronic pancreatitis has recently been proposed to replace the previous Marseille's classification systems. This system proposes risk modifiers - not etiologies-that may interact in any one patient to produce pancreatic disease. Each of the listed risk factors may predispose toward pancreatitis through unique mechanisms (*Fig. 4.3*).

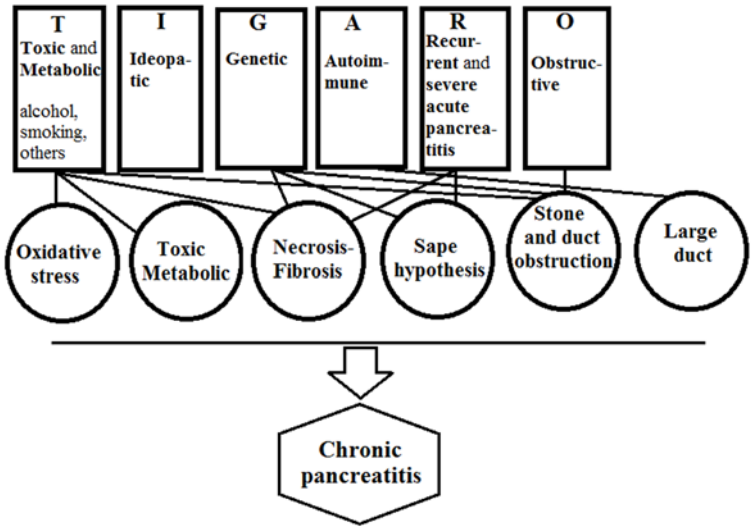


Figure 4.3. Pathogenic pathways proposed to explain each etiology of chronic pancreatitis enumerated in the TIGAR-O classification

The recently generated TIGAR-O etiological classification of chronic pancreatitis incorporates new insights into genetic, environmental, immunological and pathobiological risk factors associated with chronic pancreatitis.The TIGAR-O etiological classification consists of 6 groups:

1. **Toxic-metabolic.**

- Alcoholic.
- Tobacco smoking.
- Hypercalcaemia.
- Hyperlipidaemia.
- Chronic renal failure.
- Medicines-phenacetin abuse.
- Toxins-organotin compounds, for example, di-N-butyltin dichloride (DBTC).

2. **Idiopathic.**

- Early onset.
- Late onset.
- Tropical.

3. **Genetic.**

- Hereditary pancreatitis-cationic trypsinogen.
- Cystic fibrosis transmembrane conductance regulator (CFTR) mutations.
- Serine protease inhibitor, Kazal type 1 (SPINK1) mutations.

4. **Autoimmune.**

• Isolated auto-immune chronic pancreatitis.

• Syndromic autoimmune chronic pancreatitis associated with Sjogren's syndrome, inflammatory bowel disease, primary biliary cirrhosis.

5. **Recurrent and severe acute pancreatitis.**

• Post-necrotic (severe acute pancreatitis).

• Recurrent acute pancreatitis.

• Vascular diseases/ischaemia.

• Post-irradiation.

6. **Obstructive.**

• Pancreas divisum.

• Sphincter of Oddi disorders (controversial).

• Duct obstruction (e.g., tumour).

• Peri-ampullary duodenal wall cysts.

• Post-traumatic pancreatic duct scars.

4.1.3. PATHOLOGY

Chronic inflammation of pancreas:

• Mononuclear cell infiltrate.

• Fibrosis/calcification/irreversible anatomic changes.

• Characteristic duct changes.

• With or without calcification.

• Affects exocrine and/or endocrine organ (including α-cells).

Chronic pancreatitis is defined by the presence of chronic inflammation, destruction of acinar and ductal cells, intra- and perilobular fibrosis and finally by the irreversible scarring of parenchyma.

Until recently the molecular mechanisms and cell-cell interactions resulting in pancreas fibrosis were largely unknown. However, the progressive appearance of fibrotic tissue is regardless of the initiating triggers a result of an increased deposition and a reduced degradation of extracellular matrix. In contrast to fibro-genesis in the pancreas, liver fibrogenesis has been studied extensively during the p decades. It is now generally accepted that hepatic stellate cells (HSC), formerly named perisinusoidal fat-storing cells and Ito-cells, which are located in the space of Disse, play a central role in liver fibrogenesis. In experimental and human liver injury HSC change their phenotype from a quiescent retinoid storing cell to a highly active and "synthetic" myofibroblast-like cell producing the majority of extracellular matrix including collagen types I and III, fibronectin, and proteoglycans. Studies have also been the presence of retinoid containing fat-storing cells was demonstrated in the pancreas of mice, rats and humans. Because these cells show similarities in their retinoid metabolism and morphology to hepatic stellate cells, e.g. numerous retinoid containing perinuclear fat droplets, cytoplasmic extensions, stellate shape morphology, expression of the cytoskeletal filaments vimentin, desmin, and α-smooth muscle actin, who called pancreatic stellate cells (PSC).

Pancreatic fibrosis is a characteristic feature of chronic pancreatic injury from various causes, including alcohol abuse, recurrent and/or persistent inflammation, malnutrition and trauma. On the basis of observations that PSCs are activated directly by alcohol as well as by proinflammatory cytokines, it may be postulated that there are two fibrogenic pathways (acting in parallel in alcoholic pancreatitis: the necroinflammatory pathway and the non-necroinflammatory pathway (*Fig. 4.4*).

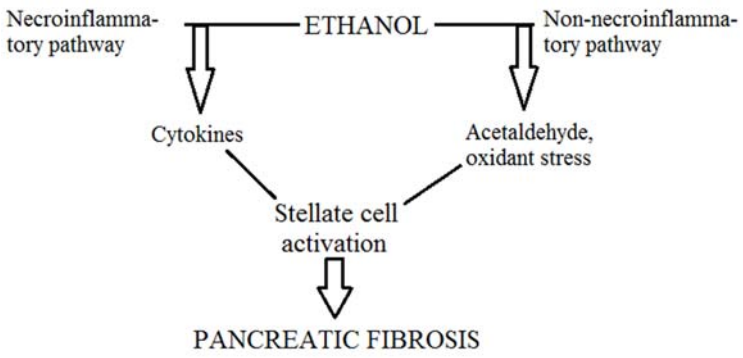


Figure 4.4. *Postulated fibrogenic pathways in alcoholic pancreatitis*

Activation of pancreatic stellate cells by cytokines released during alcohol-induced acinar cell necrosis would represent the necroinflammatory pathway of pancreatic fibrogenesis, while the direct activation of stellate cells by alcohol via acetaldehyde and/or oxidant stress would represent the non-necroinflammatory pathway. The identification of non-necroinflammatory mediators of stellate cell activation raises an interesting point. It suggests that tissue necrosis or inflammation may not be an absolute prerequisite for the stimulation of fibrogenesis in the pancreas during alcohol abuse.

The molecular alterations underlying pancreatic fibrogenesis and the pathogenesis of chronic pancreatitis are still under investigation. Through linkage-analysis the genetic cause of hereditary pancreatitis has been identified. Hereditary pancreatitis is characterized by recurrent attacks of acute pancreatitis from early ages leading to fibrosis of the pancreas. D. Whitcomb et al. (1999) identified mutations in the trypsinogen-gene which lead to ar exchange of arginine by histidine or asparagine by isoleucine . Through these mutations the hydrolysis of trypsin is inhibited which goes on to activate further proteases. This disease is associated with a 40% risk of developing pancreatic cancer at age 70 and older. In addition this disease demonstrates that recurrent attacks of necrotizing pancreatitis may lead to pancreatic fibrosis and eventually cancer of the pancreas. Mutations of the cystic fibrosis transmembrane regulator gene have been identified in 18 of 134 patients with chronic pancreatitis (Sharer N. et al., 1998). However, the genetic and molecular alterations underlying the vast majority of alcoholic chronic pancreatitis cases are unknown. From the comparative analysis of gene expression in chronic pancreatitis and pancreatic cancer, several factors have been identified which may be overexpressed in both diseases or – more importantly – only in one of the two diseases. While pancreatic cancers frequently

harbor p53 gene mutations, several studies failed to identify p53 mutations in the pancreas of patients with chronic pancreatitis. Furthermore, MDM2, which binds and inactivates wildtype p53, is overexpressed in pancreatic cancer, but not in chronic pancreatitis. Mutations of the K-ras oncogene are frequent in pancreatic cancer; however, the frequency of K-ras mutations in the non-malignant pancreatic parenchyma varies greatly. In recent studies K-ras mutations were identified not only in pancreatic cancer cells but also in papillary hyperplasia, mucinous hypertrophy and squamous cell metaplasia. In addition, K-ras mutations can also be found in the normal duct epithelium in chronic pancreatitis and pancreatic cancer. Thus, K-ras mutations may be an early event in pancreatic carcinogenesis; however, it may not be useful to differentiate chronic inflammation of the pancreas from pancreatic malignancy.

4.1.4. SYMPTOMS OF CHRONIC PANCREATITIS

The symptoms are very variable (*Fig. 4.5*).

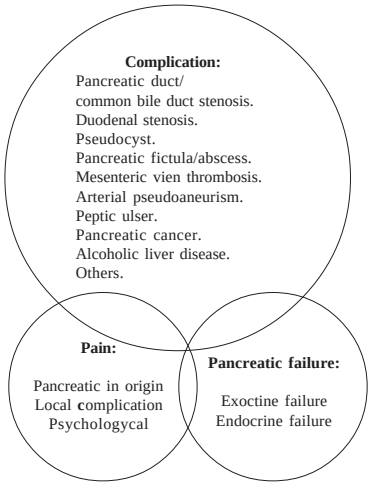


Figure 4.5. *Clinical presentation scenarios in chronic pancreatitis*

Pain occurs in most patients at some stage of the disease. This may vary in intensity from mild to severe. It may last for hours or sometimes days at a time and may require strong painkillers to control it.

It often radiates through to the back and can sometimes be relieved by crouching forward. It is commonly brought on by food consumption and so patients may be afraid to eat. It is also commonly severe through the night.

The pain varies in nature, being gnawing, stabbing, aching or burning, but it tends to be constant and not to come and go in waves. It may sometimes burn itself out but can remain an ongoing problem.

The mechanism of the pain is unclear. It seems to be related to pancreatic activity since it is frequently caused by food, especially fatty or rich foods.

Some patients will have obstruction to the small ducts in the pancreas by small stones, and this is thought to cause back pressure and destruction of the pancreas. There is no relationship between the severity of the pain and the severity of the pancreatic inflammation.

The pain is often difficult to diagnose and can be mistaken for pain caused by virtually any other condition arising from the abdomen or lower chest.

It can be difficult to distinguish pain caused by pancreatitis from pain caused by a peptic ulcer, irritable bowel syndrome, angina pectoris, gallstones.

A recent pathophysiological concept interprets the generation of pain as interplay between the nerve- and immune system. Immunohistochemical analysis shows a high density of enlarged nerve fibres in chronic pancreatitis tissue. R. Keith et al. (1985) could show that the pain level in patients with chronic pancreatitis

correlated more with the degree of eosinophil infiltration of these enlarged nerves rather than with the degree of duct dilatation. Electronic microscope analysis of these nerves reveals damaged perineurium and infiltration of leucocytes which may explain how pancreatic enzymes and mediators of inflammation enter neural structures and alter their structure and functioning. Immunhistochemical analysis of chronic pancreatitis tissue revealed an altered pattern of intrinsic and extrinsic innervation with overexpression of different neurotransmitters such as "Substance P" und "Calcitonin Gene Related Peptide" (CGRP) in enlarged intrapancreatic nerves. Since both cytokines are important pain transmitters, these findings provide evidence that alterations of pancreatic nerves themselves are involved in the pathogenesis of the disease and lead to the concept of neuroimmune interaction as a basic mechanism in the pathogenesis of chronic pancreatitis and chronic pain syndrome.

This interesting hypothesis is confirmed by the fact, which the presence of growth-associated-protein-43 (GAP-43), an established marker of neuronal plasticity, correlates with individual pain scores in patients with chronic pancreatitis.

Diabetes is also a common symptom which affects over half of all patients with long-standing chronic pancreatitis.

Long-standing chronic inflammation results in scarring of the pancreas which destroys the specialised areas of the pancreas which produce insulin.

Deficiency of insulin results in diabetes. Diabetes causes thirst, frequent urination and weight loss. It may be possible in the early stages of chronic pancreatitis to treat the diabetes with tablets, but in the late stage of chronic pancreatitis, insulin injections are usually needed.

Diarrhea occurs in just under half of patients. Normally, all the fat in food is broken down by enzymes from the pancreas and small intestine, and the fat is then absorbed in the small bowel. With a reduced level of digestive enzymes the fat is not absorbed. When the fat reaches the large intestine, it is partially broken down by the bacteria in the colon. This produces substances which irritate the colon and result in diarrhea. The undigested fat also traps water in the faeces, resulting in pale, bulky, greasy stools which are difficult to flush away. They may make the water in the toilet look oily, smell offensive and may be associated with bad wind.

Weight loss occurs in virtually all patients with chronic pancreatitis. It is due to failure to absorb calories from food, and diabetes may also contribute to this. In addition, patients may be afraid to eat because eating brings on the pain. Depression is also common in chronic pancreatitis and this can also reduce appetite and lead to weight loss.

Jaundice (when patients develop yellow eyes and skin) occurs in about a third of patients with chronic pancreatitis. It is usually due to damage to the common bile duct which drains bile from the liver to the duodenum.

The common bile duct normally passes though the head of the pancreas. In long-standing chronic pancreatitis, the scarring in the head of the pancreas narrows the common bile duct.

Some degree of narrowing may occur in up to half the patients with chronic pancreatitis but when the narrowing is severe, it prevents the bile draining from the liver into the duodenum. It then spills back into the blood and the patient's eyes and skin become yellow. In addition, the stools become paler (since bile makes the stools brown) and the urine becomes dark (because it contains more bile than normal).

Vomiting after meals is a less common symptom but can occur as a result of severe pain. It may also be due to duodenal ulceration, which is often connected with chronic pancreatitis. In rare cases, the duodenum may be narrowed as a result of scarring secondary to chronic pancreatitis.

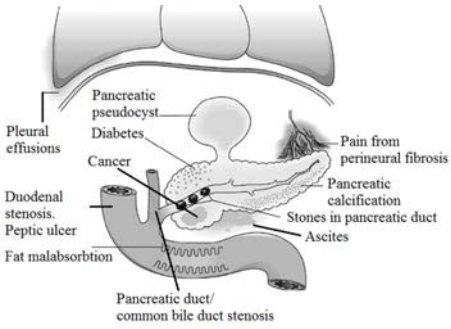


Figure 4.6. *Chronic pancreatitis: complications*

Vitamin and mineral deficiency. Prolonged passage of stools containing fat can result in low levels of calcium and magnesium in the blood. In addition, some vitamins may not be absorbed properly. This includes vitamins D and A.

The main complications of chronic pancreatitis are presented in the *Fig. 4.6*.

4.1.5. DIAGNOSIS

Chronic pancreatitis often causes no symptoms and may be discovered by accident during the course of investigation of symptoms not related to pancreatitis. For example, calcification in the pancreas may be seen on an X-ray of the abdomen performed for other reasons.

Ultrasound examination of the abdomen. It is a screening method for studying pancreatic diseases. However, because the pancreas lies at the back of the abdominal cavity and, therefore, a long way from the transponder, images of the pancreas may be difficult to obtain. Sometimes the problem is obesity, sometimes the pancreas is obscured by air within the intestines.

Abdominal CT scanning. This technique is more reliable in imaging the pancreas than abdominal ultrasound (*Fig. 4.7*).

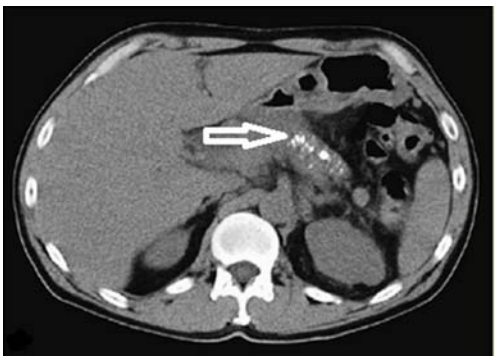


Figure 4.7. *Abdominal CT: calcification of the pancreas (arrow)*

However, a normal US or CT scan does not exclude a diagnosis of chronic pancreatitis.

Abdominal MRI scanning. MRI scanning is a newer technique of examining abdominal organs. It does not involve X-rays.

MRI Cholangiopancreatography is currently under evaluation with regard to the accuracy of diagnosis of pancreatic disease (*Fig. 4.8*).

Endoscopic retrograde cholangiopancreatography. Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure whereby X-ray contrast material is injected into the bile duct and pancreatic duct to allow X-ray pictures to be taken of these ducts (*Fig. 4.9*). At present, it is the only method by which minor changes (minimal change pancreatitis) can be reliably demonstrated. Abnormalities which range from minor changes in side branches of the pancreatic duct to major changes in the main pancreatic duct can be identified by this method. It is sometimes possible to remove stones from the pancreatic duct. However, ERCP is not routinely used as the first line of investigation in suspected pancreatitis because it requires a high degree of endoscopic expertise. There is also a very real risk of inducing a further attack of pancreatitis in the patient as a result of the irritant effect of the X-ray contrast within the duodenum.

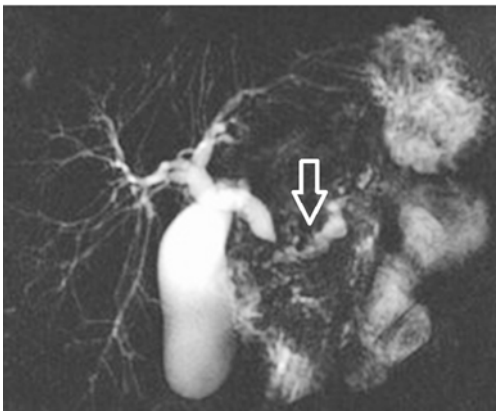


Figure 4.8.
MRI-Cholangiopancreatography: duct dilatations and strictures & calculi (arrow)

Endoscopic ultrasound scans (EUS). This is a special ultrasound investigation in which the ultrasound transponder is mounted on an endoscope. This technique is not widely available and is not as sensitive as ERCP at detecting minor degrees of chronic pancreatitis (*Fig. 4.10*).

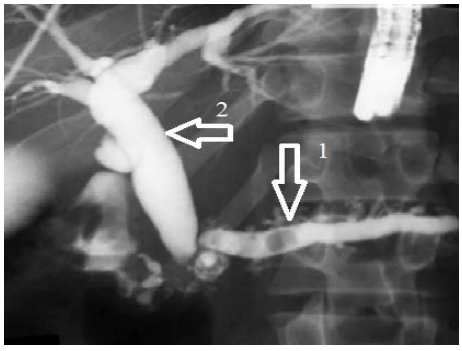


Figure 4.9. *ERCP: duct dilatations and calculi (arrow 1); common bile duct dilatations (arrow 2)*

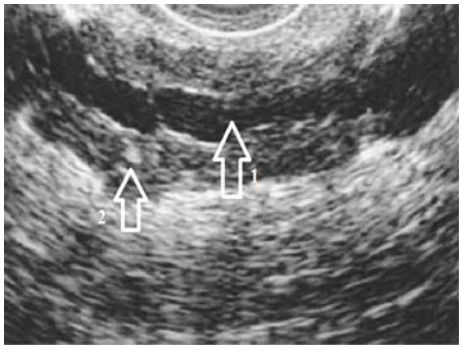


Figure 4.10. *Endoscopic ultrasound scan: duct dilatations (arrow 1) and calculi (arrow 2)*

Abdominal X-ray. This may sometimes show calcification of the pancreas in chronic pancreatitis. This tends to occur late in the natural history of the disease and therefore, usually after the diagnosis has already been made. If the diagnosis has not already been made, then further tests are unnecessary.

FUNCTION TESTING

1. Fecal elastase – "gold standard". An indirect pancreatic function test; reduced in severe disease to less than 200 micrograms/g. All indirect pancreatic function tests have relatively high sensitivity and specificity in severe chronic pancreatitis with malabsorption. All are inaccurate for diagnosing mild-to-moderate pancreatic insufficiency.

Faecal elastase has an unacceptably low sensitivity for diagnosing exocrine pancreatic insufficiency, ranging from 64% for severe disease to 40% for mild-to-moderate disease. Similarly, reduced fecal elastase has only 58% specificity for exocrine pancreatic insufficiency in patients with type 1 diabetes mellitus.

2. Fecal fat test. This test is performed by administering 100 g fat per day and measuring the faecal fat excretion over 72 hours. Increased faecal fat over 7 g/day is a late-stage manifestation of chronic pancreatitis.

• Distinguish between pancreatic dysfunction and intestinal malabsorption.

• In Pancreatic disease when lipase secretion is reduced by 90% – 24-hour fecal fat content is elevated to more than 20 g.

• Intestinal dysfunction – steatorrhea with low levels of fecal fat.

• Use-efficacy of pancreatic enzyme replacement.

3. Steatocrit. A rapid gravimetric method to measure stool fat. When performed on samples from a 72-hour stool collection, steatocrit is as sensitive and specific as a 72-hour quantitative stool fat, and may be as accurate if performed on a 24-hour stool collection or random stool samples.

4. Direct pancreatic function tests. Most sensitive and specific test for diagnosing mild-to-moderate pancreatic insufficiency or chronic pancreatitis, but only available in a few centres. Pancreatic juice is collected with a gastroduodenal tube during exogenous hormone stimulation with cholecystokinin (CCK) and/or secretin. Helps differentiate pancreatic from non-pancreatic types of malabsorption.

5. Genetic screening. A consensus conference stated that only cationic trypsinogen or serine protease I (PRSS1) mutation testing (for hereditary pancreatitis) had definite clinical benefit and that testing for all other mutations, for example, the cystic fibrosis transmembrane conductance regulator (CFTR) or serine protease inhibitor, Kazal type 1 (SPINK1), should be relegated to research protocols.

6. Biopsy. Rarely, biopsy is required, particularly for distinguishing between auto-immune pancreatitis and pancreatic cancer. Changes produced by chronic pancreatitis depend on disease severity and include an increase in connective tissue, inflammatory and fibrotic changes, loss of acini and plugs of precipitated protein in the ductal tissue. Ruling out malignancy is a major diagnostic problem, especially in patients with an enlarged pancreatic head. Exclusion of malignancy frequently requires surgical resection to ensure a reliable histopathological examination. In 10% of patients, the diagnosis of pancreatic cancer is only established by histological proof at the time of operation.

7. Serum ANA antibodies + IgG4 levels. Positive testing for serum ANA antibodies and IgG4 levels suggests autoimmune pancreatitis. These tests are an alternative to biopsy, but should only be used by specialists.

8. Therapeutic trial of corticosteroids. A positive response suggests autoimmune pancreatitis. This test is an alternative to biopsy, but requires follow up and should only be used by a specialist.

DIFFERENTIAL DIAGNOSIS

- Pancreatic cancer.
- Acute pancreatitis.
- Biliary colic.
- Peptic ulcer disease.
- Mesenteric ischaemia.
- Aneurysm, abdominal aorta.
- Intestinal obstruction.
- Irritable bowel syndrome.
- Gastroparesis.
- Somatisation disorders.
- Radiculopathy.
- Post-herpetic neuralgia.
- Abdominal wall pain.
- Nephrolithiasis.

4.1.6. TREATMENT

Three components are essential to the optimal management of chronic pancreatitis: 1) control of pain; 2) improvement of maldigestion; and 3) management of complications.

Conservative treatment of pancreatic pain

The main goal of conservative treatment for chronic pancreatitis is to relieve pain and prevent or substitute functional insufficiency without surgery. Pain and functional deterioration in chronic pancreatitis is multifactorial. Intermittent attacks of pain with temporary functional deterioration may originate from recurrent tissue necrosis and inflammation provoked by alcohol consumption or other causes of recurrent pancreatitis, while chronic pain with progressive pancreatic insufficiency may be secondary to segmental hypertension due to ductular strictures and stones. The chronic inflammatory process may also involve increased intrapancreatic pressure with ischemia, neural inflammation and scarring, intra – and peripancreatic fluid collections and pseudocysts, common bile duct stenosis and/or duodenal compression and papillitis, all resulting in the precipitation of relapses and fluctuating pain. Both the inflammatory process and ductular hypertension can diminish with the development of severe pancreatic insufficiency and the pain may disappear in several cases. It seems that the "burned out" state of pancreatitis, if it occurs, takes more than 10 years and the balance is distorted with an almost total loss of exocrine and endocrine function with severe diabetic and/or alcoholic neuropathy and malnutrition.

Analgesics are indicated to treat patients with pain from chronic pancreatitis in order to achieve pain relief or reduction of pain until spontaneous improvement due to cessation of a relapse or definitive treatment (e.g. endoscopy or surgery).

The argument that morphine or its analogues possibly cause contraction of the duodenal papilla, thus creating an additional obstruction for pancreas secretion, is obsolete. This effect either does not occur when using the majority of analgesics of this group or is so inconsequential that it does not play any clinical role. Some morphine analogs are successfully used for pain control both in acute and chronic pancreatitis. Tramadol is generally not preferred because it often causes nausea and vomiting in patients with acute pancreatitis. However, the use of tramadol is associated with less gastrointestinal side effects. Some centers have achieved good results by the use of thoracic epidural analgesia. This does not only lead to rapid analgesia but, in addition, prevents or treats paralytic ileus.

The duration of medical therapy with various combinations of pain relievers can be decided on a case by case basis. However, re-evaluation should be made regularly in unsuccessful cases in order to augment the treatment with either an endoscopic or surgical procedure. There are no data to guide the duration of pain therapy using conservative means or when endoscopic or surgical treatment is indicated.

Non-narcotic analgesics (nonsteroidal anti-inflammatory drugs) are the next step in the management of painful chronic pancreatitis. If pain persists, low doses of mild narcotics (codeine, 15 to 60 mg/day, or propoxyphene 65 to 260 mg/day) may be added. Severe or recalcitrant pain may warrant the use of stronger opiates in select cases.

Pancreatic enzymes are presumed to improve pain by suppressing CCK release from the duodenum, leading to decreased pancreatic stimulation.

It is generally accepted that pain in chronic pancreatitis may result in part from obstruction of the main pancreatic duct from stones and strictures, leading to increased ductal and parenchymal pressure. Because obstruction contributes to pain, patients with large duct chronic pancreatitis may benefit from endoscopic or surgical duct decompression therapy. Endoscopic techniques include biliary or pancreatic sphincterotomy, or both, removal of pancreatic duct stones, and placement of pancreatic stents.

Maldigestion

Pancreatic enzymes are used for the treatment of maldigestion in chronic pancreatitis. Exogenous pancreatic enzymes are safe, well tolerated, and produce few side effects. There are a multitude of available pancreatic enzyme preparations; they differ based on enzyme content, the use of microspheres versus microtablets, and the presence of a coating for delayed release. Lipase is the most important determinant of the effectiveness of individual preparations. A minimum of 30,000 U lipase per meal allows adequate intraluminal digestion of fat and protein in most patients. The dose may need to be titrated to as much as 60,000 to 80,000 U lipase per meal, because not all the lipase may reach the proximal small intestine in active form. Enzymes may be taken entirely at the onset of each meal; however, dosing is more physiologic if one half the amounts is taken at the onset of the meal and the other half is taken approximately 15 minutes into the meal.

Because the enzyme "microspheres" contained in most coated preparations are typically released too distally in the small bowel, uncoated preparations are optimal for the management of maldigestion. Alternatively, patients may break open coated capsules and sprinkle the microspheres over food to ensure proper delivery to the proximal bowel. Because uncoated preparations are more easily denatured by gastric acid, acid suppression with a proton pump inhibitor (e.g., omeprazole, 20 mg once daily) or histamine-receptor antagonist (e.g., famotidine, 20 mg twice daily) is required. Response to enzyme therapy may be monitored through an assessment of symptoms or, more objectively, through 72-hour stool fat quantification. A poor response to pancreatic enzymes may suggest noncompliance, loss of enzyme potency, improper timing of enzymes in relation to meals, or coexisting mucosal disease. A daily proton pump inhibitor may be added for those refractory to therapy because gastric acid may denature exogenous enzymes.

Surgical management

There are a number of different surgical interventions available in the treatment of chronic pancreatitis.

Major goals of surgery are to:

• Eliminate or reduce intractable pain.

• Address associated complications, for example, biliary obstruction, duodenal obstruction, and pseudocyst compression.

• Exclude pancreatic carcinoma.

• Conserve functional tissue.

Predictors of surgical success are:

• Segmental fibrosis (distal or proximal).

• Diffuse ductal dilation (length >10 cm and diameter > 5 to 7 mm).

• Associated or adjacent organ complication, for example, biliary obstruction, duodenal obstruction, and pseudocyst compression.

The ideal procedure for treating pain in chronic pancreatitis should be the one which is simple, easy to perform, associated with a low morbidity/mortality rate and at the same time providing adequate drainage and not for augmenting its endo/exocrine insufficiency. Surgeries for chronic pancreatitis can be broadly classified as:

A. Drainage procedures:

1. Partial: draining the duct partially e.g. Duval, Puestow.

2. Complete: consists of draining the main duct completely e.g. Partington's, Bapat's.

B. Resectional procedure: resecting a part of pancreas with adjoining organs: e.g. Whipples, Child's.

C. Extended drainage procedure: adding a pancreatic sphincterotomy to the drainage procedure e.g. Rumpf's.

D. Resection with extended drainage: a combination e.g. Beger's, Frey's.

The rationales for various procedures are:

• Drainage procedures were developed on the basis that pain in chronic pancreatitis is due to ductal hypertension and proper drainage would decompress it.

• On the other hand, theory of perineural inflammation as the cause of pain led to development of resectional procedures.

Drainage Procedures

It has been more than 3/4th of a century since these procedures were proposed. Duval and Zollinger first applied this principle. These procedures provide pain relief in up to 60–80% of cases.

I. Partial Drainage Procedures

1. ***Duval' s procedure*** (1954): developed on the basis of presumption that a single stricture of duct of Wirsung near the ampulla was responsible for the obstructive pathology and terminal drainage would treat the condition. It consists of a distal pancreatectomy with splenectomy and retrograde drainage of the main duct into a defunctioned jejunal loop (*Fig. 4.11*).

2. ***Peustow-Gilesby's procedure*** (1958): these authors demonstrated that multiple strictures (chain – of – lake appearance) were the pathology involved in chronic pancreatitis. They recommended a longitudinal opening of pancreatic duct from site of transection of the pancreatic duct after resection of pancreatic tail and splenectomy, to a point just to the right of mesenteric vessels and invagination of the open duct with pancreas into a Roux-en-Y loop of jejunum (*Fig. 4.12*). This achieved wider drainage of the ductal system.

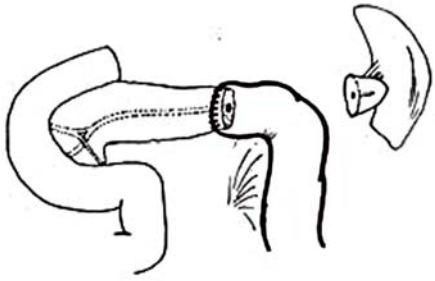


Figure 4.11. *Duval's procedure*

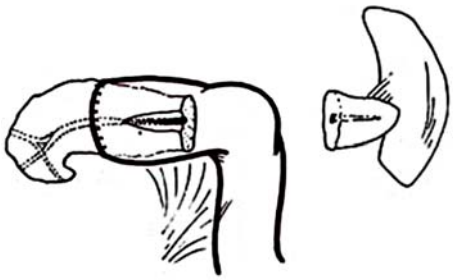


Figure 4.12. *Peustow–Gilesby's procedure*

3. ***Leger's procedure*** (1974): developed for distal stricture and consists of up to 40% distal pancreatectomy with splenectomy and opening of pancreatic duct into a loop of jejunum by a retrograde, lateral pancreatico-jejunostomy (*Fig. 4.13*).

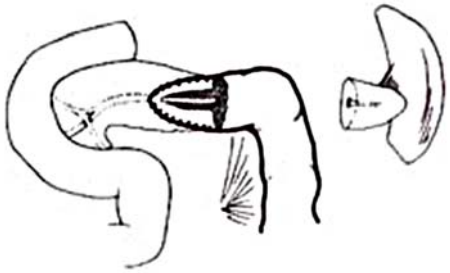


Figure 4.13. *Leger's procedure*

II. Complete Drainage Procedures

1. ***Partington-Rochelle's procedure*** (1960): suggested a refinement in Peustow's procedure. A dilated main pancreatic duct (minimum 8 mm) is a prerequisite for a good duct to mucosa anastomosis, however people have even reported a mucosa to capsule anastomosis when the duct size is 5 mm. It consists of a side to side, long, lateral pancreaticojejunostomy without resection of pancreatic tail or spleen (*Fig. 4.14*).

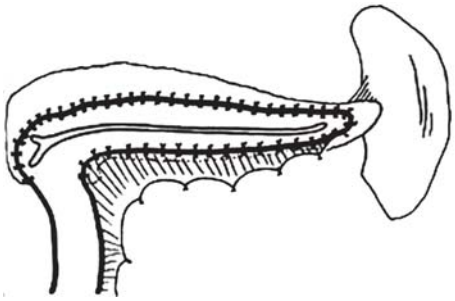


Figure 4.14. *Partington-Rochelle's procedure*

B. Resectional Procedures

These procedures were resorted to when lesser procedures failed especially when malignancy could not be ruled out.

1. ***Whipple's procedure*** (1935): described by Allen O. Whipple first in 1946, but published later for malignant lesions of head of pancreas, now used for benign, inflammatory mass in head of pancreas with a non-dilated pancreatic duct. It consists of a pancreaticoduodenectomy with reconstruction by a pancreatico – jejunostomy / gastrostomy + gastrojejunostomy + choledochojejunostomy (*Fig. 4.15*). This is a complex, challenging technical exercise with higher mortality rates as compared to a drainage procedure however with good results. This procedure involves excising normal organs much against the principles of surgery for a benign disorder and has led to more conservative approaches.

2. ***Traverso–Longmire's procedure*** (1978): it is a pylorus preserving pancreatico-duodenectomy (*Fig. 4.16*). To overcome the problems of postgastrectomy syndrome associated with classical Whipples, pylorus is preserved. Originally used for carcinoma of head of pancreas, now also used for the head related sequel of chronic pancreatitis.

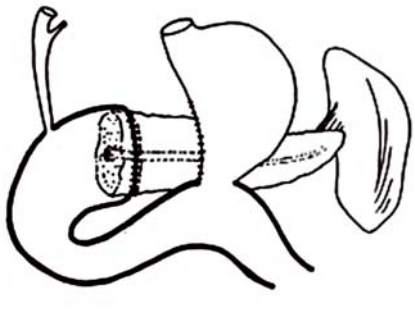


Figure 4.15. *Whipple's procedure*

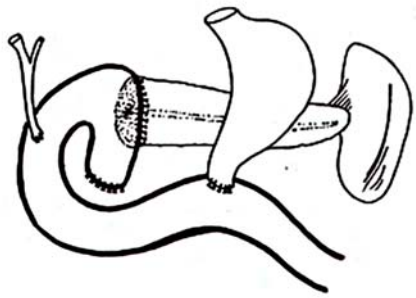


Figure 4.16. *Traverso-Longmire's procedure*

3. ***Subtotal Pancreatic resection:*** consists of resection less than 80% of pancreas. Spleen may be conserved. It is indicated when disease is confined to body and tail e.g. pseudocyst, failed pancreaticojejunostomy, non-dilated duct, pseudoaneurysm and when it is not possible to rule out a malignant lesion in body and tail.

4. ***Child's Resection*** (1965): it is a 95% distal pancreatectomy. First described by Barret and Bowers18 in 1957, Child popularized it. The spleen, the tail, the body and the uncinate process of pancreas are completely removed. A small cuff of head is preserved along the lesser curvature of the duodenum, no more than 5% of the entire gland. This cuff protects the vascularity and common bile duct during surgery.

Not frequently done and indicated when entire pancreas is uniformly and severely diseased and if previous or lesser procedures have failed. Following this procedure the incidence of insulin dependent diabetes mellitus raises up to 74% in non-diabetics.

6. ***Total Pancreatectomy:*** rarely indicated primarily as less radical procedure suffice. Indicated secondarily after a pancreatico-duodenectomy or distal subtotal resection has failed to provide pain relief. Duodenum preserving total pancreatectomy is also reported to be effective. Since patients require insulin and also there are significant alteration in digestive and absorptive function, 95%. Distal pancreatectomy is preferred which preserves normal GI and biliary continuity.

C. Extended Drainage Procedures

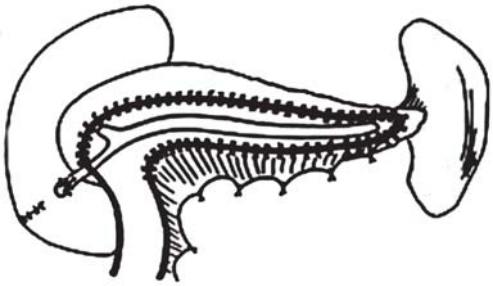


Figure 4.17. *Rumpf's extended drainage*

1. ***Rumpf's extended drainage*** (1983): it is a combination of Partingtons with a transduodenal pancreaticoplasty (*Fig. 4.17*). It is indicated when there is a prepapillary obstruction to the drainage of pancreatic duct due to stones or stricture. With the advent of endoscopy, the second half of the procedure has become unpopular.

D. Resection with extended drainage

As incidence of inflammatory mass in head of pancreas is about 30% of which only 10% are malignant, 21 resection with extended drainage provide cure in up to 94–95% of cases.

1. ***Hans Beger's resection:*** it is a duodenum preserving resection of pancreatic head. Two major steps are involved subtotal resection of pancreatic head conserving the duodenum and restitution of the exocrine pancreatic secretory flow (*Fig. 4.18,* and *Fig. 4.19*).

2. ***The Berne modification.*** The Berne modification spares the dissection of the pancreatic body from the portal vein. In this case, a single cavum results after the resection of the pancreatic head (*Fig. 4.20*), which can be anastomosed side-to-side with a Roux-en-Y jejunal loop (*Fig. 4.21*).

3. ***Frey's procedure.*** In 1985 Frey and Smith introduced a modification of duodenum preserving pancreatic head resection which combines a longitudinal pancreatico-jejunostomy with a local resection of the pancreatic head. This technique combines the principle of duodenum preserving pancreatic head resection with drainage of the ductus wirsungianus (*Fig. 4.22*). Compared to the original Beger procedure, this variant is simpler to perform as it spares the dissection of the pancreas from the portal vein and the division of the pancreatic body.

4. ***Izbicki's "V" Shaped Ventral Pancreatic Excision*** (1998): indicated for sclerosing ductal pancreatitis (small duct disease) with maximum diameter of Wirsung duct less than 3 mm. In this procedure, a long "V" shaped excision of ventral

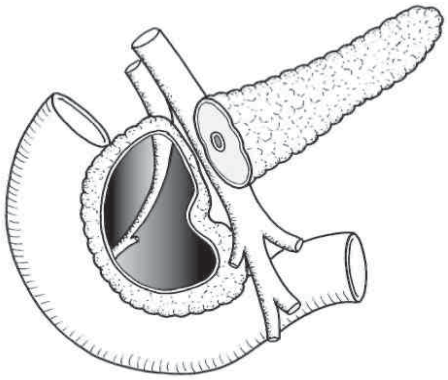


Figure 4.18. *Duodenum preserving pancreatic head resection according to Beger before reconstruction: decompression of common bile duct, Wirsungian duct, duodenum and retropancreatic vessels and division of the pancreatic body over the portal vein*

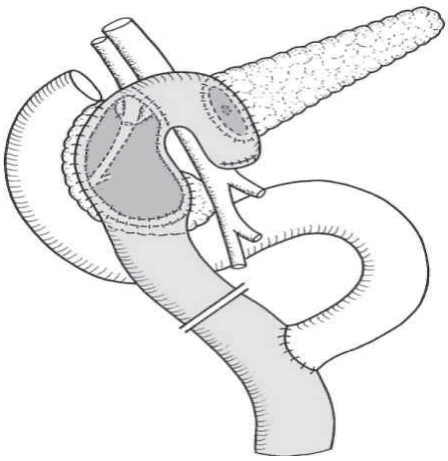


Figure 4.19. *Reconstruction after duodenum proserving pancreatic head resection according to Beger: end-to-side and side-to-side pancreatico-jejunostomy*

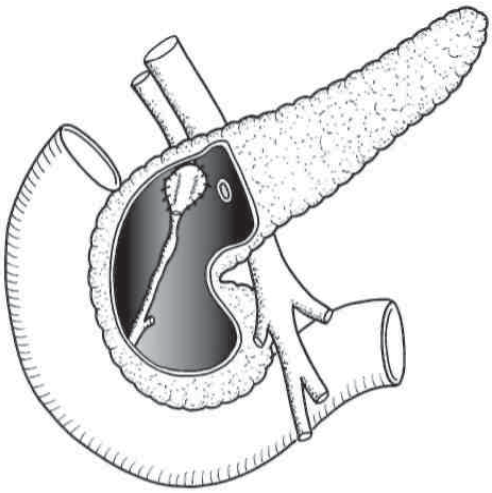


Figure 4.20. *Berne modification of the original Beger technique, in this case with additional opening of the intrapancreatic common bile duct. Division of the pancreatic body over the portal vein is omitted*

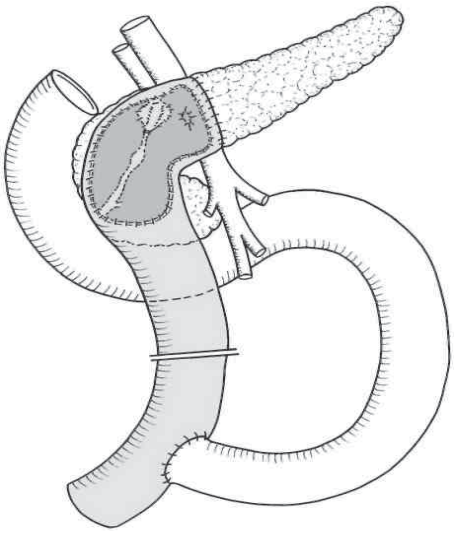


Figure 4.21. *Berne variation of duodeneum preserving pancreatec-tomy: reconstruction with Roux-en-Y jejunal loop and internal anastomosis of the opened intrapancreatic common bile duct*

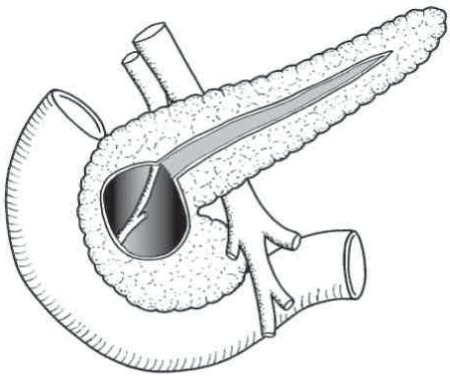


Figure 4.22. *Duodenum-preserving pancreatic head resection according to Frey: combinating of duodenum preserving pancreatic head resection and longitudinal drainage of the Wirsungian duct without division of the pancreatic body over the portal vein*

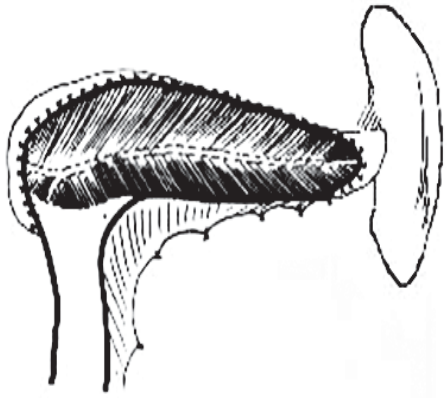


Figure 4.23. *Izbicki's "V" shaped ventral pancreatic excision*

aspect of pancreas is done with a lateral pancreaticojejunostomy by a mucosa to capsule anastomosis (*Fig. 4.23*). This procedure drains the main as well as second and third order ducts.

4.1.7. SURGICAL COMPLICATIONS OF CHRONIC PANCREATITIS

Duodenal obstruction. Obstruction of the duodenum is also quite common. This happens because the pancreatitis in the head of the pancreas can press on the duodenum and cause it to become partly blocked. This causes a feeling of sickness (nausea), vomiting after food and contribute to weight loss. The patients will usually need major surgery such as a Beger's operation. If this is not possible then the narrowing (or stricture) is "bypassed" connecting the small bowel to the stomach (gastro-jejunostomy).

Pancreatic ductal decompression. This option can be considered in patients with intractable pain and main pancreatic duct dilation (> 5 to 7 mm) to provide pain relief. Surgical decompression has better long-term results than endoscopic techniques, possibly because surgery addresses other hypothesized etiologies of pain by denervation pancreatic sensory nerves and reducing pancreatic tissue pressure, an endpoint that may predict the magnitude of pain resolution.

Pancreatic pseudocyst decompression. Decompression of pseudocysts is indicated for persistent pain, cyst enlargement, or complications of the pseudocyst. Drainage can be done surgically, endoscopically, or percutaneously. Thus, the surgical treatment of pancreatic pseudocysts against of chronic pancreatitis includes:

- Pancreatic resection.
- Internal drainage (*Fig. 4.24*).
- Endoscopic or percutaneous drainage (*Fig. 4.25*).

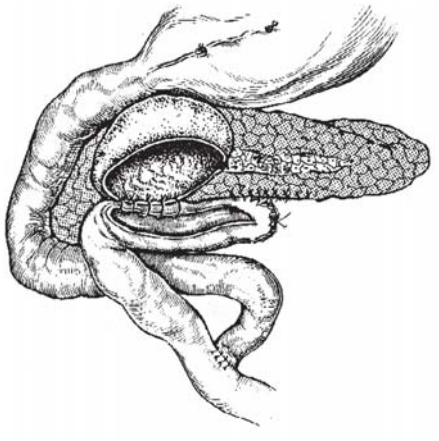


Figure. 4.24. *Internal drainage*

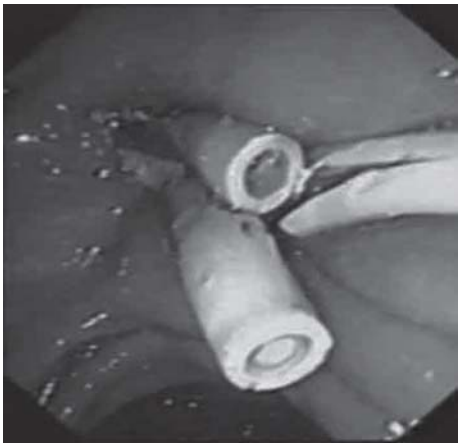


Figure. 4.25. *Endoscopic drainage*

Biliary decompression. No randomized controlled trials have assessed biliary decompression (surgical or endoscopic) for patients with biliary obstruction secondary to chronic pancreatitis. However, biliary decompression should be considered. Surgical options include Roux-en-Y choledochojejunostomy or choledochoduodenostomy. Surgery is usually definitive and long-lasting, but has a morbidity rate of around 30%.

Endoscopic therapy involves biliary sphincterotomy with placement of multiple simultaneous plastic. It is reserved for patients with severe jaundice and cholangitis, in the presence of a large inflammatory mass in the head of the pancreas, or if severe comorbidity is present.

Splenic vein thrombosis. In severe chronic pancreatitis the splenic vein may become blocked because of a clot. This is because the pancreatitis irritates the splenic vein to cause the clot and the blockage of the splenic vein usually becomes permanent.

Hepatic portal vein thrombosis. This is another serious complication of chronic pancreatitis. The pancreatitis irritates the hepatic portal vein to cause a clot and permanent blockage of the hepatic portal vein. This can then cause venous bleeding (bleeding from the system of veins) or a build of fluid in the abdomen (ascites).

Venous bleeding. If there is permanent splenic vein thrombosis and/or hepatic portal vein thrombosis then the blood pressure will build up in the tiny vessels that normally drain into these big veins. The tiny veins now become much larger and are called venous collaterals. These slowly increase in size over some months or years and become windy or tortuous. These are then referred to as varices (similar to varicose veins in the legs, but now inside the abdomen). The varices may appear in the stomach and in the lower gullet. There is a real danger that bleeding may occur from rupture of one of these varices. With conservative treatment patients will be given injections or a continuous infusion of special drugs that will reduce the pressure in the varices (vasopressin). This will then be followed by endoscopic sclerotherapy. These measures are usually successful.

Very occasionally the bleeding will keep recurring and in this case surgery is required. The operation will involve removal of the spleen and disconnection of the

varices from the stomach. This operation is called gastric devascularisation and splenectomy.

Arterial bleeding. This can sometimes happen during the natural course of severe chronic pancreatitis because the pancreatitis causes an irritation and erosion of the outer wall of an artery near the pancreas. Sometimes this may cause a pulsating sac to be created next to the artery. This is called a pseudo-aneurysm. The treatment is to perform angiography and occlusion of the vessel that caused bleeding. Only rarely is it necessary to try to stop the bleeding with open surgery and is only performed if the selective arteriography has not identified the source of bleeding or if the selective arterial embolisation has failed.

External and internal pancreatic fistula. The term "fistula" is an old medical term meaning an abnormal connection between one surface and another. When there is a connection between the pancreatic duct and some other surface in the body this is called an internal fistula. An example is when pancreatic fluid leaks into the abdomen to cause pancreatic ascites. If the pancreatic fluid leaks into the chest cavity this is sometimes called a pleural fistula. This fluid as such is not harmful as the enzymes in the pancreatic juice are not activated. When there is connection between the pancreatic duct and the skin this is known as an external pancreatic fistula.

Many pancreatic fistulas dry up with no special measures except by using external drainage tube inserted in the X-ray department. Only in exceptional circumstances is it necessary to encourage closure of the fistula by pancreatic stenting or the use of octreotide injections to reduce pancreatic secretions. In even more exceptional circumstances surgery is needed to control the fistula such as using a small bowel channel to drain the fistula internally. This operation is called a Roux-en-Y fistulo-jejunostomy.

Ascites. This refers to the buildup of straw colored fluid in the abdomen. Normally this condition will slowly improve but sometimes you will need treatment with a special water tablet (called spironolactone) and tablets or injections (often using a drug called octreotide) to reduce the pressure in the varices and venous collaterals as well as paracentesis of the fluid by inserting a tube into the abdomen (usually in the X-ray department or in the operating room) under local anaesthetic.

Another rare cause of ascites is specifically called pancreatic ascites. This is because the fluid instead of being straw colored is white and contains a large amount of pancreatic juice. The pancreatic fluid escapes from the main pancreatic duct because of direct damage to the duct by the pancreatitis or indirectly by a small hole in a pancreatic pseudocyst. This is therefore called an internal pancreatic fistula.

Summary

• Alcohol remains the most common cause of chronic pancreatitis; however, genetic, autoimmune, and environmental factors may also contribute.

• Abdominal radiography and computed tomography scanning allow for the detection of advanced chronic pancreatitis.

• Endoscopic retrograde pancreatography, endoscopic ultrasound, and direct pancreatic function tests allow for the detection of early, or minimal change, chronic pancreatitis.

• Management strategies for chronic pancreatic pain include analgesics, pancreatic enzyme supplementation, celiac plexus blockade, endoscopic or surgical duct decompression therapy, surgical resection, and thorascopic splanchnicectomy.

4.2. SPLEEN DISEASE

The spleen is an organ found in virtually all vertebrate animals with important roles in regard to red blood cells and the immune system. In humans, it is located in the left upper quadrant of the abdomen. It removes old red blood cells and holds a reserve of blood in case of hemorrhagic shock while also recycling iron. It synthesizes antibodies in its white pulp and removes antibody-coated bacteria along with antibody-coated blood cells by way of blood and lymph node circulation. The spleen is purple and gray. Recently, it has been found to contain in its reserve half of the body's monocytes within the red pulp. These monocytes, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages while promoting tissue healing. It is one of the centers of activity of the reticuloendothelial system and can be considered analogous to a large lymph node, as its absence leads to a predisposition toward certain infections.

4.2.1. ANATOMY AND FUNCTION

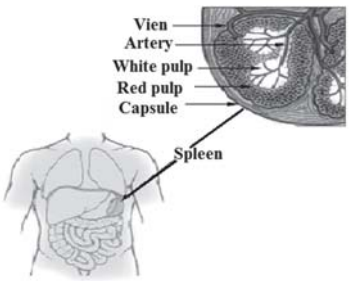


Figure 4.26. *Spleen*

The spleen, in healthy adult humans, is approximately 4 centimeters (4.3 in) in length. It usually weighs 150 grams (5.3 oz.) and lies beneath the 9th to the 12th thoracic ribs (*Fig. 4.26*).

• Like the thymus, the spleen possesses only efferent lymphatic vessels.

• The spleen is part of the lymphatic system.

• The germinal centers are supplied by arterioles called penicilliary radicles.

Function

• The function of the human spleen is to filter abnormal RBCs, stores platelets, produce tuftsin and properdin (opsins) produces antibodies (IgM) and is site of phagocytosis .

• During fetal development the spleen produces red blood cells.

• By the fifth month of gestation the spleen no longer has hematopoietic function but retains the capacity throughout life.

• Red cells that pass through the spleen undergo a "cleaning" or repair (*Table 4.1*).

Other functions of the spleen are less prominent, especially in the healthy adult:

• Production of opsonins, properdin, and tuftsin.

• Creation of red blood cells. While the bone marrow is the primary site of hematopoiesis in the adult, the spleen has important hematopoietic functions up until the fifth month of gestation. After birth, erythropoietic functions cease, except in some hematologic disorders. As a major lymphoid organ and a central player in the

Table 4.1 – Function of the spleen

Area	Function	Composition
Red pulp	Mechanical filtration of red blood cells. Reserve of monocytes.	• "sinuses" (or "sinusoids") which are filled with blood; • "splenic cords" of reticular fibers; • "marginal zone" bordering on white pulp.
White pulp	Active immune response through humoral and cell–mediated pathways.	Composed of nodules, called Malpighian corpuscles. These are composed of: • "lymphoid follicles" (or "follicles"), rich in B–lymphocytes; • "periarteriolar lymphoid sheaths" (PALS), rich in T–lymphocytes.

reticuloendothelial system, the spleen retains the ability to produce lymphocytes and, as such, remains a hematopoietic organ.

• Storage of red blood cells and other formed elements. In horses roughly 30% of the red blood cells are stored there. The red blood cells can be released when needed. In humans, it does not act as a reservoir of blood cells. It can also store platelets in case of an emergency.

• Storage of half the body's monocytes so that upon injury they can migrate to the injured tissue and transform into dendritic cells and macrophages and so assist wound healing.

4.2.2. SPLENIC TRAUMA

The management of splenic trauma has changed considerably in the last few decades especially in favor of non-operative management (NOM). NOM ranges from observation and monitoring alone to angiography/angioembolization with the aim to preserve the spleen and its function, especially in children. These considerations were carried out considering the immunological function of the spleen and the high risk of immunological impairment in splenectomized patients. In contrast with liver traumatic injuries, splenic injuries can be fatal not only at the admission of the patient to the Emergency Department, but also due to delayed subcapsular hematoma rupture or pseudoaneurism rupture. Lastly, overwhelming post-splenectomy infections are a late cause of complications due to the lack of the immunological function of the spleen. For these reasons, standardized guidelines in the management of splenic trauma are necessary.

The existing classification of splenic trauma is considering the anatomical lesions (*Table 4.2*).

The World Society of Emergency Surgery (WSES) position paper suggested to group splenic injury into minor, moderate, and severe. This classification has not previously been clearly defined by the literature. Frequently low-grade AAST lesions (i.e., grades I–III) are considered as minor or moderate and treated with NOM. However, hemodynamically stable patients with high-grade lesions could be successfully treated non-operatively, especially exploiting the more advanced tools for bleeding management. On the other hand, "minor" lesions associated with hemodynamic instability often must be treated with OM. This demonstrates that the classification of spleen injuries into minor and major must consider both the anatomic AAST classification (*Table 4.2*) and the hemodynamic status.

Table 4.2 – Spleen Trauma Classification
(American Association for Surgery for Trauma - AAST)

Grade	Injury description	
I	Hematoma	Subcapsular, < 10% surface area
	Laceration	Capsular tear, < 1 cm parenchymal depth
II	Hematoma	Subcapsular, 10–50% surface area
		Intraparenchymal, < 5 cm diameter
	Laceration	1–3 cm parenchymal depth not involving a perenchymal vessel
III	Hematoma	Subcapsular, > 50% surface area or expanding
		Ruptured subcapsular or parenchymal hematoma
		Intraparenchymal hematoma > 5 cm
	Laceration	> 3 cm parenchymal depth or involving trabecular vessels
IV	Laceration	Laceration of segmental or hilar vessels producing major devascularization (> 25% of spleen)
V	Laceration	Completely shatters spleen
	Vascular	Hilar vascular injury which devascularized spleen

The WSES classification divides spleen injuries into three classes:

- Minor (WSES class I).
- Moderate (WSES classes II and III).
- Severe (WSES class IV).

Physiopathology of injuries

Some mechanisms of injuries are similar between children and adults like motor vehicle crashes and pedestrian accidents, while others like motorcycle accidents, sport injuries, gunshot or stab-related injuries, and assaults are more frequent in adults.

A few authors consider a normal hemodynamic status in adults when the patient does not require fluids or blood to maintain blood pressure, without signs of hypoperfusion; hemodynamic stability in adults as a counterpart is the condition in which the patient achieve a constant or an amelioration of blood pressure after fluids with a blood pressure > 90 mmHg and heart rate <100 bpm; hemodynamic instability in adults is the condition in which the patient has an admission systolic blood pressure < 90 mmHg, or > 90 mmHg but requiring bolus infusions/transfusions and/or vasopressor drugs and/or admission base excess (BE) > –5 mmol/l and/or transfusion requirement of at least 4–6 units of packed red blood cells within the first 24 h. The 9th edition of the Advanced Trauma Life Support definition considers as "unstable" the patient with the following: blood pressure < 90 mmHg and heart rate > 120 bpm, with evidence of skin vasoconstriction (cool, clammy, decreased capillary refill), altered level of consciousness and/or shortness of breath. Moreover, transient responder patients (those showing an initial response to adequate fluid resuscitation and then signs of ongoing loss and perfusion deficits) and, more in general, those responding to therapy but not amenable of sufficient stabilization to be undergone to interventional radiology treatments, are to be considered as unstable patients. In the management of severe bleeding, the early evaluation and correction of the trauma-induced coagulopathy remains a main cornerstone. Physiologic impairment is frequently associated with aggressive resuscitation and the activation and deactivation of several procoagulant and anticoagulant factors contributes to the insurgence of trauma-induced coagulopathy. The application of massive transfusion protocols is of paramount

importance. The advanced tailored evaluation of the patient's coagulate asset is clearly demonstrated as fundamental in driving the administration of blood products, coagulation factors, and drugs.

Clinical features depend on:

- degree of hypovolaemia;
- presence of associated injuries.

• Clinical features range from left upper quadrant pain to shock and peritonitis.

• 30 to 60% of patients have other assocaited intraperitoneal injuries.

Diagnosis

The choice of diagnostic technique at admission must be based on the hemodynamic status of the patient.

• If cardiovascularly unstable requires resuscitation and early surgery.

• If cardiovascularly stable consider either ultrasound, CT scan etc.

Extended focused assessment sonography for trauma (E-FAST) and ultrasonography (US) have replaced diagnostic peritoneal lavage management of abdominal trauma in present days. Contrast-enhanced US increase the visualization of a variety of splenic injuries and complications. Doppler US and contrast-enhanced US are useful to evaluate splenic vascularization and in follow-up. Contrast tomography (CT) scan is considered the gold standard in trauma with a sensitivity and specificity for splenic injuries near to 96–100%. CT must be rapidly available and must be performed only in hemodynamically stable patients or in those responding to fluid resuscitation. However, in some centers, there is the possibility to perform a fast-track CT scan that seems to permit to expand the criteria for performing CT scan in trauma patients. Delayed-phase CT helps in differentiating patients with active bleeding from those with contained vascular injuries. Injury grade on CT scan, extent of free fluid, and the presence of pseudoaneurism do not predict non-operative management failure or the need of operative management.

Management of splenic injury

• Overall 20–40% of patients are suitable for conservative management.

• Children can often be managed conservatively as they have increased proportion of low grade injuries.

• Multiple injuries should be monitored in high dependency unit.

• Require cardiovascular and haematological monitoring.

Non-operative management (NOM)

Blunt and penetrating trauma:

Patients with hemodynamic stability and absence of other abdominal organ injuries requiring surgery should undergo an initial attempt of NOM irrespective of injury grade.

NOM of moderate or severe spleen injuries should be considered only in an environment that provides capability for patient intensive monitoring, angiography/ angioembolization (AG/AE), an immediately available operating room and immediate access to blood and blood product or alternatively in presence of a rapid centralization system and only in patients with stable or stabilized hemodynamic and absence of other internal injuries requiring surgery.

NOM in splenic injuries is contraindicated in the setting of unresponsive hemodynamic instability or other indicates for laparotomy (peritonitis, hollow organ injuries, bowel evisceration, impalement).

In patients being considered for NOM, CT scan with intravenous contrast should be performed to define the anatomic spleen injury and identify associated injuries.

AG/AE may be considered the first-line intervention in patients with hemodynamic stability and arterial blush on CT scan irrespective from injury grade.

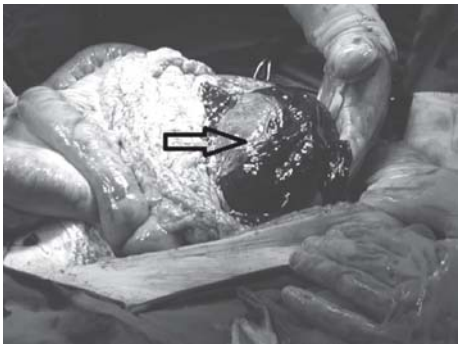


Figure 4.27. *Splenectomy – posttraumatic spleen (arrow)*

Blunt trauma: NOM is considered the gold standard for the treatment of patients with blunt splenic trauma who are hemodynamically stable after an initial resuscitation, in the absence of peritonitis and associated injuries requiring laparotomy.

Penetrating trauma: laparotomy is the gold standard in penetrating abdominal trauma. Surgical management can involve either splenectomy or splenic repair (*Fig. 4.27*).

4.2.3. SPLENOMEGALY

Enlargement of the spleen is known as splenomegaly. It may be caused by sickle cell anemia, sarcoidosis, malaria, bacterial endocarditis, leukemia, pernicious anaemia, Gaucher's disease, leishmaniasis, Hodgkin's disease, Banti's disease, hereditary spherocytosis, cysts, glandular fever (mononucleosis or 'Mono' caused by the Epstein-Barr Virus), and tumors. Primary tumors of the spleen include hemangiomas and hemangiosarcomas. Marked splenomegaly may result in the spleen occupying a large portion of the left side of the abdomen. The spleen is the largest collection of lymphoid tissue in the body.

Splenomegaly can result from antigenic stimulation (e.g., infection), obstruction of blood flow (e.g., portal vein obstruction), underlying functional abnormality (e.g., hemolytic anemia), or infiltration (e.g., leukemia or storage disease, such as Gauche's disease). Basic work-up for acute splenomegaly includes a complete blood count with differential, platelet count, and reticulocyte and atypical lymphocyte counts to exclude hemolytic anemia and leukemia. Assessment of IgM antibodies to viral capsid antigen (a rising titer) is indicated to confirm Epstein-Barr virus or cytomegalovirus. Other infections should be excluded if these tests are negative.

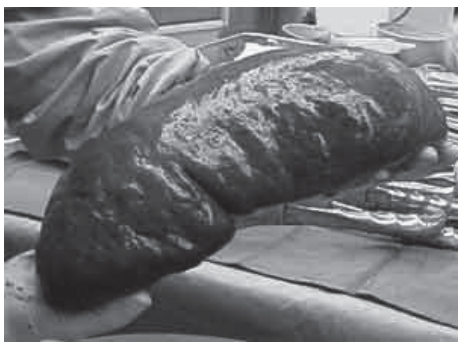


Figure 4.28. *Splenomegaly*

Splenomegaly (*Fig. 4.28*) may lead to hypersplenism (pancytopenia as cells become trapped in an overactive spleen and are destroyed). So anemia, infection, or hemorrhage may result.

4.2.4. HYPERSPLENISM

Hypersplenism is a type of disorder which causes the spleen to rapidly and prematurely destroy blood cells.

Causes and symptoms

Hypersplenism may be caused by a variety of disorders. Sometimes, it is brought on by a problem within the spleen itself and is referred to as **primary hypersplenism. Secondary hypersplenism** results from another disease such as chronic malaria, rheumatoid arthritis, tuberculosis, or polycythemia vera, a blood disorder.

Symptoms of hypersplenism include easy bruising, easy contracting of bacterial diseases, fever, weakness, heart palpitations, and ulcerations of the mouth, legs and feet. Individuals may also bleed unexpectedly and heavily from the nose or other mucous membranes, and from the gastrointestinal or urinary tracts. Most patients will develop an enlarged spleen, anemia, leukopenia, or abnormally low white blood cell counts, or thrombocytopenia, a deficiency of circulating platelets in the blood. Other symptoms may be presents that reflect the underlying disease that has caused hypersplenism.

An enlarged spleen is one of the symptoms of Malaria, Cirrhosis of the liver, leukemia, lymphoma, Hodgkin's disease, polycythemia, etc. Spleen enlarges when called on to remove massive numbers of red blood cells, defective cells, or bacteria from circulation. Splenomegaly occurs in about 10% of systemic lupus erythematosus patients. Sometimes, it is caused by recent viral infection, such as mononucleosis.

Summary

- Refers to a variety of ill effects resulting from increased splenic function that may be improved by splenectomy.
- The criteria for diagnosis included:
  - Anemia, leukopenia, thrombocytopenia or a combination of the three.
  - Compensatory bone marrow hyperplasia.
  - Splenomegaly.
- Hypersplenism can be categorized as primary or secondary.

BANTI'S SYNDROME

Banti's syndrome (also known as Banti's disease) is a chronic congestive enlargement of the spleen resulting in premature destruction of the red blood cells by the spleen. However, the term Banti's syndrome is a term that was used in the past (but isn't any longer) to describe patients with splenomegaly, hypersplenism and portal hypertension without cirrhosis and without occlusion of the portal venous system. It is named for Guido Banti (1882).

Pathogenesis

The basic pathology is some kind of obstructive pathology in the portal, hepatic or splenic vein that causes obstruction of venous blood flow from the spleen towards the heart. The cause of such obstruction may be abnormalities present at birth (congenital) of certain veins, blood clots, or various underlying disorders causing inflammation and obstruction of veins (vascular obstruction) of the liver.

Clinical presentation

Enlargement of spleen, ascites, jaundice, and the result of destruction of various blood cells by spleen – anemia, leukopenia, thrombocytopenia, gastrointestinal tract bleeding – may constitute the presenting symptoms.

GAUCHER'S DISEASE

Gaucher's disease is a genetic disease in which a fatty substance (lipid) accumulates in cells and certain organs. Gaucher's disease is the most common of the lysosomal storage diseases. It is caused by a hereditary deficiency of the enzyme glucocerebrosidase (also known as acid β-glucosidase). The enzyme acts on a fatty substance glucocerebroside (also known as glucosylceramide). When the enzyme is defective, the substance accumulates, particularly in cells of the mononuclear cell lineage. Fatty material can collect in the spleen, liver, kidneys, lungs, brain and bone marrow.

Symptoms may include enlarged spleen and liver, liver malfunction, skeletal disorders and bone lesions that may be painful, severe neurologic complications, swelling of lymph nodes and (occasionally) adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelets and yellow fatty deposits on the white of the eye (sclera). Persons affected most seriously may also be more susceptible to infection.

The disease is caused by a recessive mutation in a gene located on chromosome 1 and affects both males and females. About 1 in 100 people in the United States are carriers of the most common type of Gaucher disease, while the carrier rate among Ashkenazi Jews is 8.9% while the birth incidence is 1 in 450.

The disease is named after the French doctor Philippe Gaucher, who originally described it in 1882.

Classification

Gaucher's disease has three common clinical subtypes.

• **Type I** (or non-neuropathic type) is the most common form of the disease, occurring in approximately 1 in 50,000 live births. It occurs most often among persons of Ashkenazi Jewish heritage. Symptoms may begin early in life or in adulthood and include enlarged liver and grossly enlarged spleen (together hepatosplenomegaly); the spleen can rupture and cause additional complications. Skeletal weakness and bone disease may be extensive. Spleen enlargement and bone marrow replacement cause anemia, thrombocytopenia and leukopenia. The brain is not affected pathologically, but there may be lung and, rarely, kidney impairment. Patients in this group usually bruise easily (due to low levels of platelets) and experience fatigue due to low numbers of red blood cells. Depending on disease onset and severity, type 1 patients may live well into adulthood. Many patients have a mild form of the disease or may not show any symptoms.

• **Type II** (or acute infantile neuropathic Gaucher's disease) typically begins within 6 months of birth and has an incidence rate of approximately 1 in 100,000 live births. Symptoms include an enlarged liver and spleen, extensive and progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow. Affected children usually die by age 2.

• **Type III** (the chronic neuropathic form) can begin at any time in childhood or even in adulthood, and occurs in approximately 1 in 100,000 live births. It is characterized by slowly progressive but milder neurologic symptoms compared to the acute or type 2 version. Major symptoms include an enlarged spleen and/or liver, seizures, poor coordination, skeletal irregularities, eye movement disorders, blood disorders including anemia and respiratory problems. Patients often live into their early teen years and adulthood.

Signs and symptoms

• Painless hepatomegaly and splenomegaly; the size of the spleen can be 1500–3000 ml, as opposed to the normal size of 50–200 ml.

• Hypersplenism: the rapid and premature destruction of blood cells, leading to anemia, neutropenia and thrombocytopenia (with an increased risk of infection and bleeding).

• Cirrhosis of the liver is rare.

• Neurological symptoms occur only in some types of Gaucher's:

‣ Type II: serious convulsions, hypertonia, mental retardation, apnea.

‣ Type III: muscle twitches known as myoclonus, convulsions, dementia, ocular muscle apraxia.

• Osteoporosis: 75% develop visible bony abnormalities due to the accumulated glucosylceramide. A deformity of the distal femur in the shape of an Erlenmeyer flask is commonly described (aseptic necrosis of the femur joint).

• Yellowish-brown skin pigmentation.

Genetics

The three types of Gaucher's disease are inherited in an autosomal recessive fashion. Both parents must be carriers in order for a child to be affected. If both parents are carriers, there is a one in four, or 25%, chance with each pregnancy for an affected child. Each type has been linked to particular mutations. In all, there are about 80 known mutations, grouped into three main types:

• Type I (N370S homozygote), the most common, also called the "non-neuropathic" type occurs mainly in Ashkenazi Jews, at 100 times the occurrence in the general populace. The median age at diagnosis is 28 years of age, and life expectancy is mildly decreased. There are no neurological symptoms.

• Type II (1 or 2 alleles L444P) is characterized by neurological problems in small children. The enzyme is hardly released into the lysosomes. Prognosis is dismal: most die before reaching the third birthday.

• Type III (also 1–2 copies of L444P, possibly delayed by protective polymorphisms) occurs in Swedish patients from the Norrbotten region. This group develops the disease somewhat later, but most die before their 30th birthday.

Diagnosis

A definitive diagnosis is made with genetic testing. As there are numerous different mutations, sequencing of the beta-glucosidase gene is sometimes necessary to confirm the diagnosis. Prenatal diagnosis is available, and is useful when there is a known genetic risk factor.

A diagnosis can also be implied by biochemical abnormalities such as high alkaline phosphatase, angiotensin-converting enzyme (ACE) and immunoglobulin levels, or by cell analysis showing "crinkled paper" cytoplasm and glycolipid-laden macrophages.

Some lysosomal enzymes are elevated, including tartrate-resistant acid phosphatase, hexosaminidase, and a human chitinase, chitotriosidase. This latter enzyme has proved to be very useful for monitoring Gaucher's disease activity in response to treatment, and may reflect the severity of the disease.

Treatment

For type 1 and most type 3 patients, enzyme replacement treatment with intravenous recombinant glucocerebrosidase (imiglucerase) can dramatically decrease liver and spleen size, reduce skeletal abnormalities, and reverse other manifestations.

Successful bone marrow transplantation cures the non-neurological manifestations of the disease, because it introduces a monocyte population with active beta-glucosidase. However, this procedure carries significant risk and is rarely performed in Gaucher patients. Surgery to remove the spleen (splenectomy) may be required on rare occasions if the patient is anemic or when the enlarged organ affects the patients comfort. Blood transfusion may benefit some anemic patients. Other patients may require joint replacement surgery to improve mobility and quality of life. Other treatment options include antibiotics for infections, antiepileptics for seizures, bisphosphonates for bone lesions, and liver transplants. Substrate reduction therapy may prove to be effective in stopping Type 2, as it can cross through the blood barrier into the brain. There is currently no effective treatment for the severe brain damage that may occur in patients with types 2 and 3 Gaucher disease. Gene therapy may be a future step.

4.2.5. HYPOSPLENISM AND ASPLENIA

- Is a potentially lethal syndrome characterized by diminished splenic function.
- The patient peripheral blood smears appear as if they are asplenic.
- Hyposplenism can occur in the presence of abnormal sized or enlarged spleen.
- The danger of hyposplenism is the risk of developing potentially lethal sepsis.
- Sickle cell anemia is the most common disease associated with hyposplenism.

Asplenia is the absence of normal spleen function. It predisposes to some septicaemia infections. Therefore, vaccination and antibiotic measures are essential in such cases. There are multiple causes:

- Some people congenitally completely lack a spleen, although this is rare.
- Sickle-cell disease can cause a functional asplenia (or autosplenectomy) by causing infarctions of the spleen during repeated sickle-cell crises.
- It may be removed surgically (known as a splenectomy), but this is rarely performed, as it carries a high risk of infection and other adverse effects. Indications include following abdominal injuries with rupture and hemorrhage of the spleen, or in the treatment of certain blood diseases (Idiopathic thrombocytopenic purpura, hereditary spherocytosis, etc.), certain forms of lymphoma or for the removal of splenic tumors or cysts.

4.2.6. ANEMIA

• Hemolytic anemia results from an increase in the rate of red blood cell destruction.

• Many hemolytic anemias have a hereditary basis:

‣ congenital hemolytic anemias have defects in the cell membrane, cell structure or problems with hemoglobin structure or synthesis (G-6-PD);

‣ acquired hemolytic anemias have factors attached to the outside cell structure.

Sickle Cell Anemia

Symptoms

• Severe abdominal pain.

• Signs of peritoneal irritation.

Chronic features

• Retarded growth and development, bone and joint problems , cardiovascular, pulmonary, hepatobiliary, genitourinary, and neurologic manifestations, hematuria, priapism and ulcerations over the distal portions of the legs.

• The incidence of pigmented gallstones increases with age.

Diagnosis

• Characteristic sickle cells on blood smear.

• Hemoglobin electrophoresis.

Treatment

• Palliative-directed towards minimizing complications of the disease.

• Many patients die during childhood from infections, renal failure and heart failure.

Thalassemia

• These hereditary hemolytic anemia's result from a defect in hemoglobin synthesis.

• Beta thalassemia is the most common type.

• Hemoglobin electrophoresis in thalassemia major reveals a absence of hemoglobin A and an increase in hemoglobin F.

• Treatment includes transfusions, iron chelation and splenectomy.

Autoimmune Hemolytic Anemia

• Is an acquired hemolytic anemia resulting from antibodies that are produced by the body against its own red cells.

• Patients have hemolysis with anemia, reticulocytosis, shortened erythrocyte lifespan, fluctuating jaundice and splenomegaly.

• The distinguishing feature is a positive direct Coombs test-this identifies antibodies on the red cell surface.

• Drugs can be associated or related to this anemia.

‣ Penicillin, cephalothin, streptomycin, methyldopa, quinidine, aspirin, phenacetin and several sulfonamides.

• Pallor and splenomegaly are the main physical findings.

• Treatment is directed towards the hemolytic anemia and any underlying disease.

Treatment

Blood transfusion, steroids and splenectomy are often used.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) – WERLHOF'S DISEASE

Werlhof's disease – purpura associated with a reduction in circulating blood platelets which can result from a variety of factors. Thrompocytopenia results from immune destruction of platelets. The features of ITP is shown in the *Table 4.3*.

Table 4.3 – Idiopathic Thrombocytopenic Purpura

Features	Acute ITP	Chronic ITP
Peak age	2–6 years	20–40 years
Sex predilection	none	F > M (3:1)
Hx of recent infection	Common (Often viral(	rare
Onset of bleed	abrupt	insidious
Platelet count	<20 10^9/L	30–80 10^9/L
Duration	Usually weeks	months to years
Spontanous remission	80% or more	uncommon

Acute ITP

This form of ITP lasts for less than six months and typically affects children, most commonly those between the ages of 2 and 6. It usually appears shortly after a viral infection. Most children with acute ITP recover without treatment, and their platelet counts eventually rise to normal levels. However, 7 percent to 28 percent of people with acute ITP go on to develop chronic ITP.

Chronic (adult – type) ITP

- Most common cause of isolated thrombocytopenia
  - diagnosis of exclusion;
- Idiopathic but may occur with autoimmune disorders e.g: SLE, thyroid disease, chronic lymphocytic leukemia, HIV or the same drugs that cause autoimmune hemolytic anemia.

Pathophysiology

- IgG autoantibody.
- Spleen :
  - site of antibody production & platelet destruction.
- Usually not palpable (enlarged in 10%).

Clinical presentation

- Insidious onset.
- May be seen after mild viral illness or after immunization.
- Mucosal or skin bleeding.
- Petechia and easy bruising.
- Hematuria.
- Melena.
- Epistaxis.
- Female with menorrhea.

Laboratory results

- Peripheral blood film: ↓ platelet, large platelets.

• Bone marrow: plentiful megakaryocytes critical test to rule out other causes of thrombocytopenia.

• Anti-platelet antibodies present in most.

• ↑ bleeding time.

• PT and PTT normal.

Management

• Conservative if mild:

‣ steroids;

‣ splenectomy if steroids fail has 60 % cure rate.

• IV gamma globulin if steroids and splenectomy fail or rapid response is required.

• Others: prednisolone, platelets, plasma exchange, danazol.

Prognosis

• Fluctuating course.

• Overall relatively benign, mortality 1–2 %.

• Major concern is cerebral hemorrhage at platelets count < 5×10^9/L.

4.2.7. CYSTS AND TUMORS OF THE SPLEEN

• The differential diagnosis of splenomegaly should include splenic masses and primary tumors (these conditions are rare however they must be considered).

• Cystic lesions comprise parasitic and nonparasitic cysts:

‣ parasitic cysts are due almost exclusively to echinococcal disease (rare disease);

‣ nonparasitic cysts are classified as primary (true) which have an epithelial lining or pseudocysts (more common).

• Symptoms of splenic cysts are vague and are caused primarily by mass effect (compression of adjacent viscera).

Diagnosis

• Ultrasound (*Fig. 4.29*).

• CT scan (*Fig. 4.30*).

• Laparoscopy.

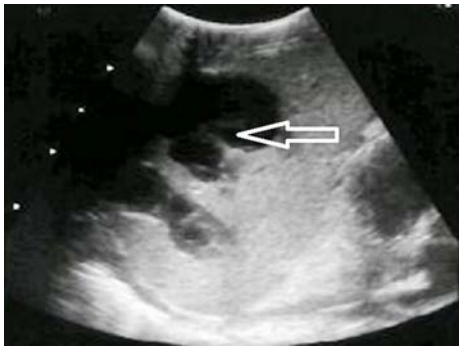


Figure. 4.29. *Ultrasound: cyst of the spleen (arrow)*

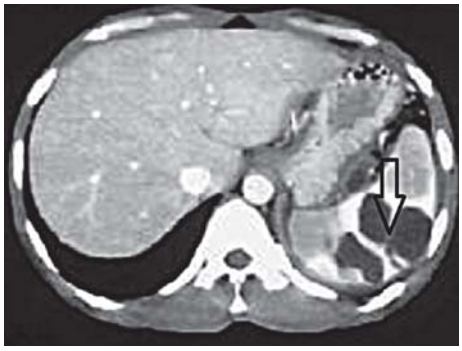


Figure. 4.30. *CT: cyst of the spleen (arrow)*

Selected and treatment

• Selected nonparasitic cyst may be managed by aspiration.

• Splenectomy should be performed for all large cyst and those with an uncertain diagnosis.

• Malignant and benign primary tumors of the spleen are rare.

• Most primary malignant tumors are angiosarcomas.

4.2.8. SPLENIC INFARCTION

In medicine, splenic infarction is a condition in which oxygen supply to the spleen is interrupted, leading to partial or complete infarction (tissue death due to oxygen shortage) in the organ.

Splenic infarction occurs when the splenic artery or one of its branches are occluded, for example by a blood clot. Although it can occur asymptomatically, the typical symptom is severe pain in the left upper quadrant of the abdomen, sometimes radiating to the left shoulder. Fever and chills develop in some cases. It has to be differentiated from other causes of acute abdomen.

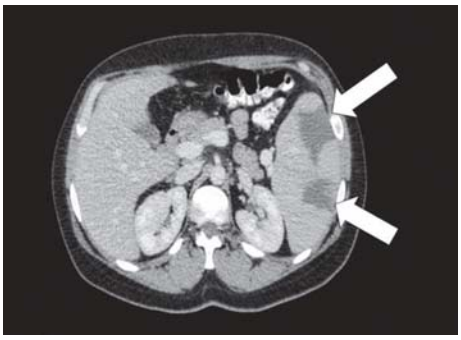


Figure 4.31. *CT scan: two large splenic infarcts, as demonstrated on an abdominal CT scan (white arrows)*

An abdominal US and CT scan is the most commonly used modality to confirm the diagnosis, although abdominal ultrasound can also contribute (*Fig. 4.31*).

There is no specific treatment, except treating the underlying disorder and providing adequate pain relief. Splenectomy is only required if complications ensue. Complications include a ruptured spleen, hemorrhage, splenic abscess (for example, if the underlying cause is endocarditis) or pseudocyst formation. Splenectomy may be warranted for persistent pseudocysts due to the high risk of subsequent rupture.

Causes

Several factors may increase the tendency for clot formation, such as specific infections (such as infectious mononucleosis, cytomegalovirus infection, malaria or babesiosis), inherited clotting disorders (thrombophilia, such as Factor V Leiden, antiphospholipid syndrome), malignancy (such as pancreatic cancer) or metastasis, or a combination of these factors.

In some conditions, blood clots form in one part of the circulatory system and then dislodge and travel to another part of the body, which could include the spleen. These emboligenic disorders include atrial fibrillation, patent foramen ovale, endocarditis or cholesterol embolism.

Splenic infarction is also more common in hematological disorders with associated splenomegaly, such as the myeloproliferative disorders. Other causes of splenomegaly (for example, Gaucher's disease or hemoglobinopathies) can also

predispose to infarction. Splenic infarction can also result from a sickle cell crisis in patients with sickle cell anemia. Both splenomegaly and a tendency towards clot formation feature in this condition. In sickle cell disease, repeated splenic infarctions lead to a non-function spleen (autosplenectomy).

Any factor that directly compromises the splenic artery can cause infarction. Examples include abdominal traumas, aortic dissection, torsion of the splenic artery (for example, in wandering spleen) or external compression on the artery by a tumor. It can also be a complication of vascular procedures.

Splenic infarction can be due to vasculitis or diffuse intravascular coagulation. Various other conditions have been associated with splenic infarction in case reporters, for example Wegener's granulomatosis or treatment with drugs that predispose to vasospasm or thrombosis, like vasoconstrictors used to treat esophageal varices, sumatriptan or bevacizumab.

Splenic infarction can be induced for the treatment of such conditions as portal hypertension or splenic injury. It can also be used prior to splenectomy for the prevention of blood loss.

Treatment

Splenectomy (open or laparoscopic) is performed in all complications with a splenic infarction.

4.2.9. SPLENIC ABSCESSES

Abscesses of the spleen have been reported periodically since the time of Hippocrates. He postulated that 1 of 3 courses was followed by a patient with a splenic abscess: 1) the patient might die; 2) the abscess might heal; or 3) the abscess might become chronic and the patient may live with the disease (*Fig. 4.32, 4.33*).

Splenic abscess is a rare entity, with a reported frequency of 0.05–0.7%. Its reported mortality rate is still high, up to 47%, and can potentially reach 100% among

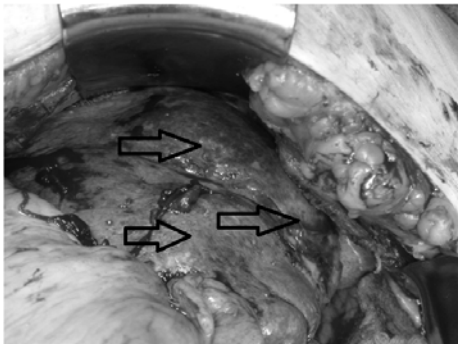


Figure 4.32. Splenic abscess (arrows)

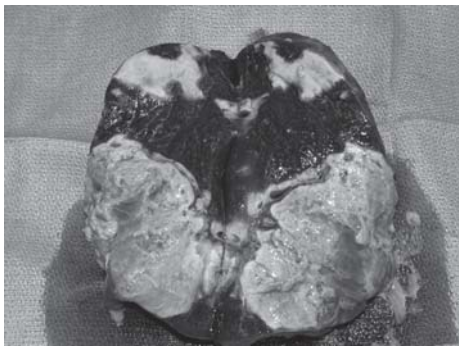


Figure 4.33. *Resected spleen (same as in the above image) with abscesses caused by pneumococcal bacteremia. Note the discrete abscesses adjacent to normal parenchyma*

patients who do not receive antibiotic treatment. Appropriate management can decrease the mortality to less than 10%.The timely and widespread use of imaging methods (e.g., computed tomography scanning, ultrasonography) facilitates early diagnosis and guides treatment, thus improving the prognosis.

Etiology

Splenic abscesses have diverse etiologies. The most common is hematogenous spread originating from an infective focus elsewhere in the body. Infective endocarditis, a condition associated with systemic embolization in 22–50% of cases, has a 10–20% incidence of associated splenic abscess. Other infective sources include typhoid, paratyphoid, malaria, urinary tract infection, pneumonias, osteomyelitis, otitis, mastoiditis, and pelvic infections. Pancreatic, other retroperitoneal, and subphrenic abscesses, as well as diverticulitis, may contiguously involve the spleen. Splenic trauma is another well-recognized etiologic factor. Splenic infarction resulting from systemic disorders, such as hemoglobinopathies (especially sickle cell disease), leukemia, polycythemia, or vasculitis, can become infected and evolve into splenic abscesses.

Alcoholics, diabetics, and patients who are immunosuppressed are among the most susceptible to splenic abscesses.

Microbiology:

• Aerobes (in most published cases).

• Gram-positive cocci – Streptococcus, Staphylococcus, Enterococcus (predominant in most reports).

• Gram-negative bacilli – Escherichia coli, Klebsiella pneumoniae, Proteus, Pseudomonas species, Salmonella species (occasionally predominant).

• Anaerobes – Peptostreptococcus, Bacteroides, Fusobacterium, Clostridium, Propionibacterium acnes .

• Polymicrobial (up to 50% of cases).

• Fungal – Candida.

• Unusual flora – Burkholderia pseudomallei (occasionally reported in melioidosis), actinomycotic and mycobacterial abscesses, most typically seen in immunosuppressed patients.

Pathophysiology

Hematogenous embolization to a previously normal spleen - typical examples include patients with septic endocarditis who have antibiotics of the latest generation and patients undergoing chemotherapy who develop fungemia, resulting in a splenic abscess. Typically, patients in this category either are immunosuppressed or have an overwhelming bacteremia. This group of patients is expected to expand and include analogous groups from the domains of transplantation and HIV/AIDS.

Hematogenous spread in the presence of previously altered splenic architecture – this group includes patients with single splenic infarcts (from trauma) or multiple splenic infarcts (from sickle cell disease or vasculitis). Bacteremia from an intercurrent infection (e.g., pneumonia, cholecystitis, central line sepsis) can colonize a splenic avascular area and form an abscess. Contiguous spread – this includes direct involvement from a pancreatic abscess, gastric or colonic perforations, or subphrenic abscesses.

History

The signs and symptoms of splenic abscess have been well described but are not very specific. Therefore, splenic abscess remains a substantial diagnostic challenge. The classical triad of fever, left upper quadrant pain, and splenomegaly is seen in only about one third of patients.

The symptoms of splenic abscess can acute, subacute, or chronic. Deep-seated, small abscesses can be painless and accompanied by septic symptoms.

• Fever (>90%) can be moderate, continuous, intermittent, or even absent.

• Abdominal pain (>60%) typically occurs suddenly, with a punctum maximum in the left hypochondrium (>39%). Remember that pain usually signifies perisplenitis.

• Involvement of the diaphragmatic pleura can cause shoulder pain.

• Pleuritic chest pain around the left lung base (>15%) is aggravated by coughing or forced expiration.

• General malaise and other constitutional and dyspeptic symptoms can be included, all of which can also be seen in a variety of other septic conditions.

Physical examination

• Abdominal tenderness (>50%) may or may not be accompanied by muscle guarding in the left upper quadrant. There may be edema of the soft tissues overlying the spleen. Costovertebral tenderness may also be noted.

• Splenomegaly (<50%) is less frequently observed, probably because of early diagnosis resulting from the widespread use of imaging methods.

• Chest findings are nonspecific and reportedly include dullness at the left lung base (>30%), left basilar rales (>21%), or elevation of the left hemidiaphragm (>15%).

Diagnosis

• Ultrasound.

• CT scan.

• Laparoscopy.

Treatment

Early supportive care and parenteral broad-spectrum antibiotics are of paramount importance while further diagnostic and therapeutic arrangements are made. Antibiotic coverage should target the presumed bacterial strains. The published literature suggests that most patients in this category have contiguous infections in the abdomen; the mortality in this group has been reported to be approximately 50%.

Besides the more common organisms isolated from splenic abscesses, mycobacteria, Candida, and Aspergillus should also be considered; these organisms account for a small but significant number of splenic abscesses in patients who are immunocompromised. Fungal abscesses are known to respond more favorably to antifungal treatment, because they result more often from a disseminated infection.

Invasive treatment of splenic abscess includes the following three options:

• Percutaneous drainage.

• Open or laparoscopic splenectomy.

• Open drainage.

Percutaneous drainage

Percutaneous drainage is indicated for easily accessible uniloculated or biloculated abscesses and also for surgical patients at very high risk who cannot tolerate general anesthesia or surgery. The procedure includes a risk of iatrogenic injury of the spleen, colon (splenic flexure), stomach, left kidney, and diaphragm.

Calcified walls of the abscess, the presence of other intra-abdominal cysts with intraluminal daughter cysts, and an origin from endemic areas (e.g., the Mediterranean basin, Eastern Europe) should raise a suspicion for Echinococcus granulosus. Percutaneous drainage of such suppurative cysts increases the risk of hydatid seeding and anaphylaxis and is therefore **contraindicated**.

Other iatrogenic complications resulting from percutaneous drainage include hemorrhage, pleural empyema, pneumothorax, and enteric fistula.

Splenectomy

Splenectomy has long been considered the standard treatment of splenic abscess. Depending on the patient population, open splenectomy has a mortality of 0–17% and a morbidity of 28–43%. The procedure removes the septic source and the diseased organ. The surgeon can explore and manage coexisting septic collections.

Laparoscopic splenectomy is safe and effective in selected patients.

Open drainage

Open drainage is used when the abscess cannot be drained percutaneously. Depending on the location of the abscess, one of the following three access routes can be employed:

Transpleural: this usually requires resection of the 12th rib in the posterior axillary line and drainage of the abscess through the diaphragm.

Abdominal extraperitoneal: this accesses the abscess through the lateral abdominal wall and between the peritoneum and the flat abdominal muscles.

Retroperitoneal: this is used when the abscess extends to the flank.

4.2.10. TROPICAL SPLENOMEGALY SYNDROME

After excluding known causes of splenomegaly, tropical splenomegaly syndrome was defined as a separate entity. This condition was later defined as hyperreactive malarial syndrome (HMS) using clear diagnostic criteria. Overall, HMS is more common in female individuals, especially lactating mothers, than in male individuals, with a female-to-male ratio of 2:1. HMS is most common in young and middle-aged adults, although the process probably commences during childhood. HMS is rare in children younger than 8 years but was reported in a 3-year-old patient. These observations support the theory that chronic antigenic stimulation is an important factor in the development of HMS.

HMS is restricted to native residents of and visitors to the malaria belt which roughly encompasses equatorial regions of South America, Africa, the Middle East, South Asia, and Southeast Asia (*Fig. 4.34*).

HMS has been reported in the following countries: Algiers, Congo, Madagascar, Ivory Coast, Sudan, New Guinea, Nigeria, India, Philippines, Brazil, China, Uganda, Yemen, Bangladesh, Ethiopia, Hong Kong, Ghana, Somalia, Zambia, Chile.

Accurate assessment of the incidence of HMS is difficult because many conditions that cause splenomegaly are prevalent in areas where malaria is endemic. These conditions include hemoglobinopathies, lymphoreticular disorders, schistosomiasis, hepatic cirrhosis, leishmaniasis, typhoid, and tuberculosis.

The incidence of massive splenomegaly is estimated to be 1–2% in rural Nigeria, and HMS accounts for 4–45% of massive splenomegaly cases in Africa. The incidence of HMS is highest among the people of the Upper Watut Valley in Papua New Guinea, where the rate is estimated to be 80%.

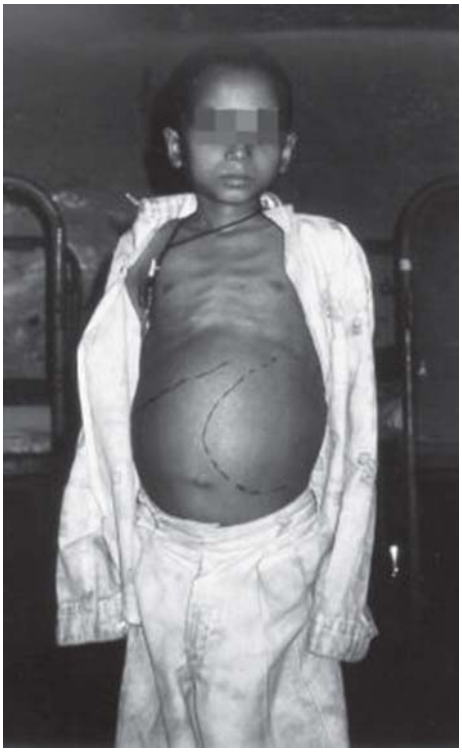


Figure 4.34. *Young patient with hepatomegaly and massive splenomegaly*

Pathophysiology

HMS is prevalent in native residents of regions where malaria is endemic and visitors to those regions. Patients with HMS have high levels of antibody for *Plasmodium falciparum*, *Plasmodium vivax*, or *Plasmodium ovale*.

Genetic factors, pregnancy, and malnutrition may play a role in the etiology of HMS. Relative protection against HMS is observed in patients with sickle cell trait, as it is with malaria. In experimental models, animals developed a similar syndrome after malarial infection.

Although the exact mechanism is uncertain, evidence suggests that exposure to malaria elicits exaggerated stimulation of polyclonal B lymphocytes, leading to excessive and partially uncontrolled production of immunoglobulin M (IgM) as the initiating event. IgM is polyclonal and is not specific for any particular malarial species.

Defective immunoregulatory control of B lymphocytes by suppressor or cytotoxic T lymphocytes causes the increase in B lymphocytes, although the mechanism by which malarial parasitemia drives these changes is unclear. T-cell infiltration of the hepatic and splenic sinusoids accompanies this process. Serum cryoglobulin and autoantibody levels increase, as does the presence of high molecular weight immune complexes. The result is anemia, deposition of large immune complexes in Kupffer cells in the liver and spleen, reticuloendothelial cell hyperplasia, and hepatosplenomegaly.

Antimalarial treatment is effective in decreasing the size of the spleen, but premature discontinuation of treatment may lead to relapse.

History

• The most common presenting symptoms of hyperreactive malarial syndrome (HMS), or tropical splenomegaly syndrome, are chronic abdominal swelling (64%) and pain (52%).

• Abdominal swelling may wax and wane.

• Almost all patients (97%) report weight loss.

• Many patients do not have any symptoms and are capable of normal daily activity.

• Rarely, patients have intermittent fever. Persistent, severe fevers should raise the possibility of an alternative diagnosis.

• Some patients present with acute abdominal pain.

• Patients physiologically adapt well to the chronic evolution of anemia and are symptomatic only when anemia is severe.

• Weakness and loss of energy may reflect the degree of anemia.

• Nonspecific symptoms include cough, dyspnea, epistaxis, and headache.

• Pressure on the abdominal contents may lead to hernias and leg swelling.

• A history of chronic splenic enlargement differentiates HMS from simple malarial splenomegaly.

• Bleeding complications are uncommon because thrombocytopenia is usually not severe.

• Susceptibility to infections, especially skin and respiratory infections, is slightly increased.

• Pregnant women are susceptible to episodes of massive Coombs-negative hemolysis, which are usually preceded by febrile episodes; the basis for hemolysis remains uncertain.

Physical

• The hallmark of HMS is splenomegaly, which is usually moderate to massive.

• Most spleens are not tender (63%).

• The spleen has a smooth surface (99%), soft consistency (91%), and sharp border (93%). The enlarged spleen may be seen to protrude against the abdominal wall.

• A splenic bruit may be audible.

• Despite the size of the spleen, splenic rupture is rare.

• Pallor is common.

• Patients are usually afebrile at presentation.

• In general, tachycardia is absent. If tachycardia is present, it indicates a concurrent complication.

• Dilatation of the veins, cardiomegaly, low blood pressure, and flow murmurs reflect hypervolemia.

• Lymphadenopathy is absent.

• The patient may be malnourished and jaundiced.

• Ascites is uncommon.

Treatment

Therapy is based on the use of antimalarial drugs. In such patients, according to the study, elimination of the infection effectively cures the splenomegaly. The patients who continue to be exposed to malaria-endemic regions require intermittent therapy or possibly lifelong treatment.

The most frequent anti-malarial treatments administered in endemic countries were weekly chloroquine or daily proguanil. Other regimens were chloroquine plus primaquine, mefloquine, quinine, pyrimethamine, artemether, and sulphadoxine/ pyrimethamine.

The management of HMS in non-endemic areas has been heterogeneous. Overall, the drugs used were: chloroquine, quinine plus clindamycin or doxycycline or pyrimethamine-sulphadoxine, proguanil, mefloquine, atovaquone-proguanil, halofantrine, and artemisinin derivatives.

Splenectomy in HMS is generally suggested for patients with huge splenomegaly and disabling symptoms, who do not respond to medical treatments. The most frequent peri-operative complications described were major bleeding and infections. The latter were the main cause of death in the following months.

Conclusion

Lifelong effective malaria prophylaxis or intermittent treatments are probably necessary for those who remain exposed to malaria transmission. Chloroquine seems to still be partially effective, even if *P. falciparum* resistance has developed. Possibly this regimen acts not only as an anti-malarial, but also as an immunomodulating and immunosuppressant therapy, as it is suggested by the regression of the spleen size even in patients with lymphoproliferative disorders. The choice of the drug should consider the local pattern of *P. falciparum* drug susceptibility, as well as the availability and cost of the different regimens.

Splenectomy is potentially associated with high mortality, therefore it should be strictly limited to cases that do not respond to medical treatment.

REFERENCES

1. Amikura K, Tsai J, Akaishi S, et al. A case of mucin producing adenocarcinoma of the pancreas. Journal of Japanese Pancreatic Society 1988; 3 : 52–7.

2. Aghdassi A, Mayerle J, Kraft M, et al. Diagnosis and treatment of pancreatic pseudocysts in chronic pancreatitis. Pancreas. 2008;36:105–112.

3. Ammann RW, Muellhaupt B, Meyenberger C, et al. Alcoholic nonprogressive chronic pancreatitis: prospective long-term study of a large cohort with alcoholic acute pancreatitis (1976–1992). Pancreas. 1994;9:365–373

4. Ammann RW, Muellhaupt B. Progression of alcoholic acute to chronic pancreatitis. Gut. 1994;35:552–556.

5. Ammann RW. Idiopathic "senile" chronic pancreatitis and pancreatic lithiasis in the aged. Gas-troenterology 1984; 86: 253.

6. Archibald E. Experimental Production of pancreatitis in animals as a result of common duct sphincter. Sugery, Gynecology and Obstetrics 1919; 28: 529.

7. Augusto JB, Niederhuber JE. The pancreas. In Niederhuber JE, Dunwoody S Leditor. Fundamentals of surgery. 1st Edition. Stamford : Appleton and Langue. 1998; 375–89.

8. Baghdadi S, Abbas MH, Albouz F, et al. Systematic review of the role of thoracoscopic splanchnicectomy in palliating the pain of patients with chronic pancreatitis. Surg Endosc. 2008;22:580–588.

9. Bapat RD, Jadhav RN, Mohite JD, Rohandia OS. Modified Partingtons procedure for pancreatico-jejunostomy in chronic pancreatitis. Indian Journal of Gastroenterology 1997; 16 (3) : 122–5.

10. Baron TH. Endoscopic therapy with multiple plastic stents for benign biliary strictures due to chronic calcific pancreatitis: the good, the bad, and the ugly. J Clin Gastroenterol. 2004;38:96–98.

11. Barret O, Bowers WF. Total pancreatectomy for chronic relapsing and calcinosis of the pancreas. USAF Medical Journal 1957; 8 : 1037–41.

12. Beger HG, Witte C, Krautzberger W, et al. Erfahrung mit einer das duodenum erhaltenden pankreaskopfresektion bei chronischer pancreatitis. Chirurg 1980; 51 : 303–7.

13. Bhardwaj P, Garg PK, Maulik SK, et al. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. Gastroenterology. 2009;136:149–159.e2.

14. Bockmann DE, Buechler M, Maltertheimer P, et al. Analysis of nerves in chronic pancreatitis. Gastroenterology 1988; 94 : 1459–69.

15. Bordalo O et al. Newer concept for the pathogenesis of chronic alcoholic pancreatitis. Am J Gastroenterol 1977; 68(3): 278–85.

16. Braganza JM. The pathogenesis of chronic pancreatitis. Qjm 1996; 89(4): 243–50.

17. Buchler MW, Friess H, Muller MW, et al. Randomized trial of duodenum-preserving pancreatic head resection versus pylorus-preserving Whipple in chronic pancreatitis. Am J Surg. 1995;169:65–69.

18. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007;356:676–684.

19. Cahen DL, Rauws EA, Fockens P, et al. Endoscopic drainage of pancreatic pseudocysts: long-term outcome and procedural factors associated with safe and successful treatment. Endoscopy. 2005;37:977–983.

20. Cahen DL, van Berkel AM, Oskam D, et al. Long-term results of endoscopic drainage of common bile duct strictures in chronic pancreatitis. Eur J Gastroenterol Hepatol. 2005;17:103–108.

21. Catalano MF, Linder JD, George S, et al. Treatment of symptomatic distal common bile duct stenosis secondary to chronic pancreatitis: comparison of single vs. multiple simultaneous stents. Gastrointest Endosc. 2004;60:945–952.

22. Cawley T. A singular case of diabetes, consisting entirely in the quantity of urine with an inquiry into the different theories of that disease. Lond Med J 1788; 9: 286.

23. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4:1010–1016.

24. Chowdhury RS, Forsmark CE, Davis RH, et al. Prevalence of gastroparesis in patients with small duct chronic pancreatitis. Pancreas. 2003;26:235–238.

25. Clark E. Pancreatitis in acute and chronic alcoholism. Am J Dig Dis. 1942;9:428.

26. Clemens DL, Jerrells TR. Ethanol consumption potentiates viral pancreatitis and may inhibit pancreas regeneration: preliminary findings. Alcohol. 2004;33:183–189.

27. Coffey R. Pancreaticojejunostomy and pancreatostomy. Annals of Surgery 1909; 50 : 1238–64

28. Comfort M, Gambill E, Baggenstoss AH. Chronic relapsing pancreatitis: A study of 29 cases without associated disease of the biliary or gastrointestinal tract. Gastroenterology 1946; 6: 238–76.

29. Copenhagen pancreatitis study. An interim report from a prospective epidemiological multicentre study. Scand J Gastroenterol. 1981;16:305–312.

30. Corrao G, Bahnardi V, Zambon A, et al. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med. 2004;38:613–619.

31. Daremberg C, Ruelle E. Oeuvres de Rufus d'Ephese. Paris, 1879.

32. Deaver JB. Chronic Pancreatitis: Its Symptomatology, Diagnosis and Treatment. Journal of American Medical Association 1911; 56: 1079.

33. DeCaro A, Lohse J, Sarles H. Characterization of a protein isolated from pancreatic calculi of men suffering from chronic calcifying pancreatitis. Biochem Biophys Res Commun 1979; 87: 1176–82.

34. Diener M K, Rahbari NN, Fischer L, et al. Duodenum-preserving pancreatic head resection versus pancreatoduodenectomy for surgical treatment of chronic pancreatitis: a systematic review and meta-analysis. Ann Surg. 2008;247:950–961.

35. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol. 2005;21:544–554.

36. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol. 2004;20:444–451.

37. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol. 2006;22:487–497.

38. Dite P, Ruzicka M, Zboril V, et al. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy. 2003;35:553–558.

39. Dufour MC, Adamson MD. The epidemiology of alcohol-induced pancreatitis. Pancreas. 2003;27:286–290.

40. Dumasy V, Delhaye M, Cotton F, et al. Fat malabsorption screening in chronic pancreatitis. Am J Gastroenterol. 2004;99:1350–1354.

41. Dumonceau JM, Costamagna G, Tringali A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic therapy. A randomised controlled trial. Gut. 2006;56:545–552.

42. Durbec JP, Sarles H. Multicenter survey of the etiology of pancreatic diseases. Relationship between the relative risk of developing chronic pancreaitis and alcohol, protein and lipid consumption. Digestion. 1978;18:337–350.

43. Duval MK. Caudal pancreatico jejunostomy for chronic relapsing pancreatitis. Annals of Surgery 1954; 140 : 775–85.

44. Ebbehoj N, Svendsen LB, Madsen P. Pancreatic tissue pressure in chronic obstructive pancreatitis. Scandinavian Journal of Gastroenterology 1984; 19 : 1066–8.

45. Ellis I, Lerch MM, Whitcomb DC. Genetic testing for hereditary pancreatitis: guidelines for indications, counselling, consent and privacy issues. Pancreatology. 2001;1:405–415.

46. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120:682–707.

47. Farkas G, Leindler L, Daroczi M, et al. Prospective randomised comparison of organ-preserving pancreatic head resection with pylorus-preserving pancreaticoduodenectomy. Langenbecks Arch Surg. 2006;391:338–342.

48. Fitz RH. Acute pancreatitis: a consideration of pancreatic hemorrhage, hemorrhagic, suppura-tive, and gangrenous pancreatitis, and of disseminated fat-necrosis. Medical monographs, no. 2. Boston: Cupples and Hurd, 1889: 91.

49. Freedman S, Sakamoto K, Venu R. GP2, the homologue to the renal cast protein uromodulin, is a major component of intraductal plugs in chronic pancreatitis. J Clin Invest 1993; 92: 83.

50. Fregni F, DaSilva D, Potvin K, et al. Treatment of chronic visceral pain with brain stimulation. Ann Neurol. 2005;58:971–972.

51. Frey CF, Katsumi Amikura. Local resection of the head of pancreas combined with longitudinal pancreatico-jejunostomy in the management of patients with chronic pancretitis. Annals of Surgery 1994; 220 (4) : 492–507.

52. Frey CF, Smith GJ. Description and rationale of a new operation for chronic pancreatitis. Pancreas 1987; 2 : 701–7.

53. Frey CF, Suzuki M, Isaji S. Treatment of chronic pancreatitis complicated by obstruction of the common bile duct or duodenum. World J Surg. 1990;14:59–69.

54. Frey CF. The surgical management of chronic pancreatitis : The Frey procedure. Advances in surgery. 1999; 32 : 41–85.

55. Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. J Gastroenterol Hepatol. 2004;19:998–1004.

56. George HS, Michael BF, David MN, et al. Pancreaticoduodenectomy for chronic pancreatitis : Long term results in 105 patients. Archives of Surgery May, 2000; 135 : 517–24.

57. Govil S, Imrie CG. Value of splenic preservation during distal pancreatectomy for chronic pancreatitis. British Journal of Surgery 1999; 86 (7) : 895–8.

58. Guda NM, Partington S, Freeman ML. Extracorporeal shock wave lithotripsy in the management of chronic calcific pancreatitis: a meta-analysis. JOP. 2005;6:6–12.

59. Hahn JU, Bochnig S, Kerner W, et al. A new fecal elastase 1 test using polyclonal antibodies for the detection of exocrine pancreatic insufficiency. Pancreas. 2005;30:189–191.

60. Hahn JU, Kerner W, Maisonneuve P, et al. Low fecal elastase 1 levels do not indicate exocrine pancreatic insufficiency in type-1 diabetes mellitus. Pancreas. 2008;36:274–278.

61. Ichikawa T, Nakao K, Hamasaki K, et al. An autopsy case of acute pancreatitis with a high serum IgG4 complicated by amyloidosis and rheumatoid arthritis. World J Gastroenterol. 2005;11:2032–2034.

62. Izbicki JR, Bloechle C, Knoefel WT, et al. Duodenum preserving resection of the head of pancreas in chronic pancreatitis. Annals of Surgery 1995; 221 (4) : 350–8.

63. Izbicki JR, Bloechle C, Knoefel WT, et al. Longitudinal V shaped excision of the ventral pancreas for small duct disease in severe chronic pancreatitis. Annals of Surgery 1998; 227 (2) : 213–21.

64. Jacobson BC, Baron TH, Adler DG, et al. ASGE guideline: The role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. Gastrointest Endosc. 2005;61:363–370.

65. James O, Agnew JE, Bouchier IA. Chronic pancreatitis in England: a changing picture? Br Med J. 1974;2:34–38.

66. Jerrells TR, Chapman N, Clemens DL. Animal model of alcoholic pancreatitis: role of viral infections. Pancreas. 2003;27:301–304.

67. Jia T, Pamer EG. (2009). Dispensable But Not Irrelevant. Science, 325:549–550.

68. Kahl S, Glasbrenner B, Leodolter A, et al. EUS in the diagnosis of early chronic pancreatitis: a prospective follow-up study. Gastrointest Endosc. 2002;55:507–511

69. Kamisawa T, Yoshiike M, Egawa N, et al. Chronic pancreatitis in the elderly in Japan. Pancreatology. 2004;4:223–227.

70. Kaufman M, Singh G, Das S, et al. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol. 2009.

71. Kawa S, Hamano H. Clinical features of autoimmune pancreatitis. J Gastroenterol. 2007;18:9–14.

72. Kloeppel G. Pathology of chronic pancreatitis and pancreatic pain. Acta Chir Scand 1990; 156(4): 261–5.

73. Kloepper G, Maillet B. Pathology of acute and chronic pancreatitis. Pancreas 1993; 8 : 659–70.

74. Lankisch PG, Lohr-Happe A, Otto J, et al. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. Digestion. 1993;54:148–155.

75. Layer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994;107:1481–1487.

76. Leger L, Lenriot JP, Lemaigre G. Five to 25 year follow up after surgery for chronic pancreatitis in 148 patients. Annals of Surgery 1974; 180 : 185–191.

77. Levy P, Barthet M, Mollard BR, et al. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. Gastroenterol Clin Biol. 2006;30:838–844.

78. Link G. Treatment of chronic pancreatitis by pancreatostomy. Annals of Surgery 1911; 53 : 768–82.

79. Loscalzo, Joseph; Fauci, Anthony S.; Braunwald, Eugene; Dennis L. Kasper; Hauser, Stephen L; Longo, Dan L. (2008). Harrison's principles of internal medicine. McGraw-Hill Medical.

80. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89:442–446.

81. Lowenfels AB, Sullivan T, Fiorianti J, et al. The epidemiology and impact of pancreatic diseases in the United States. Curr Gastroenterol Rep. 2005;7:90–95.

82. Lu CL, Chen CY, Luo JC, et al. Impaired gastric myoelectricity in patients with chronic pancreatitis: role of maldigestion. World J Gastroenterol. 2005;11:372–376.

83. Maisonneuve P, Lowenfels AB, Mullhaupt B, et al. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. Gut. 2005;54:510–514.

84. Maras WB, Helmut Friess, Michael W, et al. Randomized trial of duodenum preserving pancreatic head resection versus pylorus preserving whipple in chronic pancreatitis. American Journal of Surgery 1995; 169 : 65–70.

85. Mebius RE, Kraal G. (2005). Structure and function of the spleen. Nat Rev Immunol. 5(8) : 606–16.

86. Metter CC. History of Medicine. Philadelphia: The Blakiston Co., 1947.

87. Mizushima T, Ochi K, Ichimura M, et al. Pancreatic enzyme supplement improves dysmotility in chronic pancreatitis patients. J Gastroenterol Hepatol. 2004;19:1005–1009.

88. Modlin IM, Kidd M, Farhadi F. Bayliss and Starling and the nascence of endocrinology. Regul Pept 2000; 93(1-3): 109–23.

89. Moon SH, Kim MH, Park DH, et al. Is a 2-week steroid trial after initial negative workup for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. Gut. 2008;57:1704–1712.

90. Morton C, Klatsky AL, Udaltsova N. Smoking, coffee, and pancreatitis. Am J Gastroenterol. 2004;99:731–738.

91. Mullhaupt B, Truninger K, Ammann R. Impact of etiology on the painful early stage of chronic pancreatitis: a long-term prospective study. Z Gastroenterol. 2005;43:1293–1301.

92. Nakamura Y, Ohmori T, Higuchi S, et al. Certain background factors exhibit an association with an increased risk for pancreatic calcification among Japanese male alcoholics. Pancreas. 2005;31:225–231.

93. Nealon WH, Walser E. Surgical management of complications associated with percutaneous and/or endoscopic management of pseudocyst of the pancreas. Ann Surg. 2005;241:948–957.

94. Nishimori I, Tamakoshi A, Otsuki M, and the Research Committee on Intractable Disease of the Pancreas (Ministry of Health, Labour, and Welfare of Japan). Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. J Gastroenterol. 2007;42(suppl. 18):6–8.

95. Nordback I, Pelli H, Lappalainen-Lehto R, et al. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology. 2009;136:848–855.

96. Ockenga J, Vogel A, Teich N, et al. UDP glucuronosyltransferase (UGT1A7) gene polymorphisms increase the risk of chronic pancreatitis and pancreatic cancer. Gastroenterology. 2003;124:1802–1808.

97. Okazaki K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol. 2006;41:626–631.

98. Olsen TS. The incidence and clinical relevance of chronic inflammation in the pancreas in autopsy material. Acta Pathol Microbiol Scand A. 1978;86A:361–365.

99. Opie EL. The Etiology of Acute Hemorrhagic Pancreatitis. Bull Johns Hopkins Hosp 1901; 12: 182–88.

100. Ostrowski SE, Reilly AA, Collins DN, et al. Progression or resolution of coxsackievirus B4-induced pancreatitis: a genomic analysis. J Virol. 2004; 78:8229–8237.

101. Otsuki M. Chronic pancreatitis. The problems of diagnostic criteria. Pancreatology. 2004;4:28–41.

102. Partington RF, Rochelle REL. Modified Puestow procedure for retrograde drainage of the pancreatic duct. Annals of Surgery 1960; 152 : 1037–42.

103. Pitchumoni CS, Viswanathan KV, GeeVarghese PJ. Ultrastructure and elemental composition of human pancreatic calculi. Pancreas 1987; 2: 152.

104. Puestow CB, Gillesby WT. Retrograde surgical drainage of pancreas for chronic pancreatitis. Archives of Surgery 1958; 76 : 898–906.

105. Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci. 2009;54:2330–2337.

106. Raimondo M, Imoto M, DiMagno EP. Rapid endoscopic secretin stimulation test and discrimination of chronic pancreatitis and pancreatic cancer from disease controls. Clin Gastroenterol Hepatol. 2003;1:397–403.

107. Raimondo M, Wallace MB. Diagnosis of early chronic pancreatitis by endoscopic ultrasound. Are we there yet? JOP. 2004;5:1–7

108. Rumpf KD, Pichlmayr R. Eine method zur chirurgischen behand lung der chronischen pankreatitis. Die transduodenal pancreaticoplastik. Chirurg 1983; 54 : 722–7.

109. Safdi M, Bekal PK, Martin S, et al. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas. 2006;33:156–162.

110. Sahel J, Sarles H. Modifications of pure human pancreatic juice induced by chronic alcohol consumption. Dig Dis Sci 1979; 24(12): 897–905.

111. Sarles H, Bernard JP, Johnson C. Pathogenesis and epidemiology of chronic pancreatitis. Annu Rev Med 1989; 40: 453–68.

112. Sarles H. An international survey on nutrition and pancreatitis. Digestion. 1973;9:389–403.

113. Sarles H. Definitions and classifications of pancreatitis. Pancreas. 1991;6:470–474.

114. Seicean A, Tantau M, Grigorescu M, et al. Mortality risk factors in chronic pancreatitis. J Gastrointest Liver Dis. 2006; 15: 21–26.

115. Shiratori K, Takeuchi T, Satake K, et al. Clinical evaluation of oral administration of a cholecystokinin-A receptor antagonist (loxiglumide) to patients with acute, painful attacks of chronic pancreatitis: a multicenter dose-response study in Japan. Pancreas. 2002;25:e1–e5.

116. Spielmann, Audrey L.; David M. DeLong, Mark A. Kliewer (1 January 2005). "Sonographic Evaluation of Spleen Size in Tall Healthy Athletes". American Journal of Roentgenology (American Roentgen Ray Society) 2005 (184): 45–49.

117. Strate T, Bachmann K, Busch P, et al. Resection vs drainage in treatment of chronic pancreatitis: long-term results of a randomized trial. Gastroenterology. 2008;134:1406–1411.

118. Strate T, Taherpour Z, Bloechle C, et al. Long-term follow-up of a randomized trial comparing the Beger and Frey procedures for patients suffering from chronic pancreatitis. Ann Surg. 2005;241:591–598.

119. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, Figueiredo J-L, Kohler RH, Chudnovskiy A, Waterman P, Aikawa E, Mempel TR, Libby P, Weissleder R, Pittet MJ. (2009). Identification of Splenic Reservoir Monocytes and Their Deployment to Inflammatory Sites. Science, 325: 612–616.

120. Tolstrup JS, Kristiansen L, Becker U, et al. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. Arch Intern Med. 2009;169:603–609.

121. Traverso LW, Longmire WP. Preservation of pylorus in pancreatico-duodenectomy. Surgery Gynecology Obstetrics 1978; 156 : 954–62.

122. Vecht J, Symersky T, Lamers CB, et al. Efficacy of lower than standard doses of pancreatic enzyme supplementation therapy during acid inhibition in patients with pancreatic exocrine insufficiency. J Clin Gastroenterol. 2006;40:721–725.

123. Vellguth, Swantje; Brita von Gaudecker, Hans-Konrad Müller-Hermelink. "The development of the human spleen". Cell and Tissue Research (Springer Berlin / Heidelberg) 242 (3): 579–592.

124. Warren WD, Millikan W Jr, Henderson JM, et al. A denervated pancreatic flap for control of chronic pain in pancreatitis. Surgery Gynecology Obstetrics 1984; 159 : 581–6.

125. William JF, Charles G. Child 95% distal pancreatectomy for chronic pancreatitis. Annals of Surgery Oct., 1965; 162 (4) : 534–49.

126. Wittingen J, Frey CF. Islet concentration in the head, body, tail and uncinate process of the pancreas. Annals of Surgery 1974; 179 : 412–8.

127. Worning H. Chronic pancreatitis: pathogenesis, natural history and conservative treatment. Clin Gastroenterol. 1984;13:871–894.

128. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169:1035–1045.

129. Yasuda H, Takada T, Uchiyama K, et al. Resection of the head of the pancreas with preservation of biliary tract and duodenum. Journal of Biliary Tract and Pancreas 1990; 11 : 967–73.(Japanese)

130. Ziemssen H v. Cyclopaedia of the practice of Medicine. New York: William Wood & Co., 1878.

131. Zollinger RM, Keith LM, Ellison EH. Pancreatitis.New England Journal of Medicine 1994; 251 : 497–502

132. Zuideman P. Calcification and cirrhosis of the pancreas in patients with deficient nutrition. Doc Med Geograph Trop Amsterdam 1955; 5: 229–31.

Chapter 5

DISEASES OF THE SMALL AND LARGE INTESTINE

5.1. ANATOMY AND PHYSIOLOGY

The small intestine is a convoluted tube, extending from the pylorus to the colic valve, where it ends in the large intestine. It is about 7 meters long, and gradually diminishes in size from its commencement to its termination. It is contained in the central and lower part of the abdominal cavity, and is surrounded above and at the sides by the large intestine; a portion of it extends below the superior aperture of the pelvis and lies in front of the rectum. It is in relation, in front, with the greater omentum and abdominal parietes, and is connected to the vertebral column by a fold of peritoneum, the mesentery. The small intestine is divisible into three portions: the duodenum, the jejunum, and the ileum (*Fig. 5.1*). The wall of the small intestine is composed of four coats: serous, muscular, areolar, and mucous.

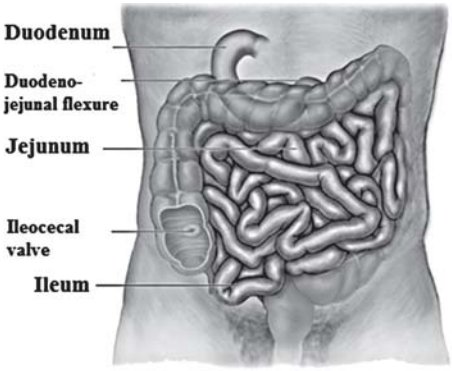


Figure 5.1. *Anatomy of the small intestine*

The *duodenum* has received its name from being about equal in length to the breadth of twelve fingers (25 cm). It is the shortest, the widest, and the most fixed part of the small intestine, and has no mesentery, being only partially covered by peritoneum. Its course presents a remarkable curve, somewhat of the shape of an imperfect circle, so that its termination is not far removed from its starting-point. The duodenum divided into four portions: superior, descending, horizontal, and ascending.

Jejunum and ileum. The remainder of the small intestine from the end of the duodenum is named jejunum and ileum; the former term being given to the upper two-fifths and the latter to the lower three-fifths. There is no morphological line of distinction between the two, and the division is arbitrary; but at the same time the character of the intestine gradually undergoes a change from the commencement of the jejunum to the end of the ileum, so that a portion of the bowel taken from these two situations would present characteristic and marked differences.

Meckel's diverticulum (diverticulum ilei). This consists of a pouch which projects from the lower part of the ileum in about 2 percent of subjects. Its average position is about 1 meter above the colic valve, and its average length about 5 cm. Its caliber is generally similar to that of the ileum, and its blind extremity may be free or may be connected with the abdominal wall or with some other portion of the intestine by a fibrous band. It represents the remains of the proximal part of the vitelline duct, the duct of communication between the yolk-sac and the primitive digestive tube in early fetal life.

Vessels and nerves. The jejunum and ileum are supplied by the superior mesenteric artery, the intestinal branches of which, having reached the attached border of the bowel, run between the serous and muscular coats, with frequent inosculations to the free border, where they also anastomose with other branches running around the opposite surface of the gut. From these vessels numerous branches are given off, which pierce the muscular coat, supplying it and forming an intricate plexus in the submucous tissue. From this plexus minute vessels pass to the glands and villi of the mucous membrane. The veins have a similar course and arrangement to the arteries. The lymphatics of the small intestine (lacteals) are arranged in two sets, those of the mucous membrane and those of the muscular coat. The lymphatics of the villi commence in these structures in the manner described above. They form an intricate plexus in the mucous and submucous tissue, being joined by the lymphatics from the lymph spaces at the bases of the solitary nodules, and from this pass to larger vessels at the mesenteric border of the gut. The lymphatics of the muscular coat are situated to a great extent between the two layers of muscular fibers, where they form a close plexus; throughout their course they communicate freely with the lymphatics from the mucous membrane, and empty themselves in the same manner as these into the origins of the lacteal vessels at the attached border of the gut.

The nerves of the small intestines are derived from the plexuses of sympathetic nerves around the superior mesenteric artery. From this source they run to the mesenteric plexus (Auerbach's plexus) of nerves and ganglia situated between the circular and longitudinal muscular fibers from which the nervous branches are distributed to the muscular coats of the intestine. From this a secondary plexus, the plexus of the submucosa (Meissner's plexus) is derived, and is formed by branches which have perforated the circular muscular fibers. This plexus lies in the submucous coat of the intestine; it also contains ganglia from which nerve fibers pass to the muscularis mucosæ and to the mucous membrane. The nerve bundles of the submucous plexus are finer than those of the mesenteric plexus.

PHYSIOLOGY

Digestion and Absorption. The complex process of digestion and eventual absorption of nutrients, water, electrolytes, and minerals is the main role of the small intestine. Liters of water and hundreds of grams of food are delivered to the small intestine daily; and, with remarkable efficiency, nearly all food is absorbed, except for indigestible cellulose. The stomach initiates the process of digestion with the breakdown of solids to particles 1 mm or smaller, which are then delivered to the duodenum, where pancreatic enzymes, bile, and brush border enzymes continue the process of digestion and eventual absorption through the small intestinal wall. The small bowel is primarily responsible for absorption of the dietary components (carbohydrates, proteins, and fats), as well as ions, vitamins, and water.

Food particles are propelled through the small bowel by a complex series of muscular contractions. Peristalsis consists of intestinal contractions passing aborally at a rate of 1 to 2 cm/sec. The major function of peristalsis is the movement of intestinal chyme through the intestine. Motility patterns in the small bowel vary greatly

between the fed and fasted states. Pacesetter potentials, which are thought to originate in the duodenum, initiate a series of contractions in the fed state that propel food through the small bowel. During the interdigestive (fasting) period between meals, the bowel is regularly swept by cyclical contractions that move aborally along the intestine every 75 to 90 minutes. These contractions are initiated by the migrating myoelectric complex (MMC), which is under the control of both neural and humoral pathways. Extrinsic nerves to the small bowel are vagal and sympathetic. The vagal fibers have two functionally different effects: one is cholinergic and excitatory, and the other is peptidergic and probably inhibitory. Sympathetic activity inhibits motor function, whereas parasympathetic activity stimulates it. Although intestinal hormones are known to affect small intestinal motility, the one peptide that has been clearly shown to function in this regard is motilin, which is found at its peak plasma level during phase III (intense bursts of myoelectrical activities resulting in regular, high-amplitude contractions) of MMCs.

Immune function. During the course of a normal day, we ingest a number of bacteria, parasites, and viruses. The large surface areas of the small bowel mucosa represent a potential major portal of entry for these pathogens; the small intestine serves as a major immunologic barrier in addition to its important role in digestion and endocrine function. As a result of constant antigenic exposure, the intestine possesses abundant lymphoid cells (i.e., B and T lymphocytes) and myeloid cells (macrophages, neutrophils, eosinophils, and mast cells). To deal with the constant barrage of potential toxins and antigens, the gut has evolved into a highly organized and efficient mechanism for antigen processing, humoral immunity, and cellular immunity. The gut-associated lymphoid tissue is localized in three areas: Peyer patches, lamina propria lymphoid cells, and intraepithelial lymphocytes.

The gastrointestinal barrier. The gastrointestinal mucosa forms a barrier between the body and a luminal environment which not only contains nutrients, but is laden with potentially hostile microorganisms and toxins. The challenge is to allow efficient transport of nutrients across the epithelium while rigorously excluding passage of harmful molecules and organisms into the animal. The exclusionary properties of the gastric and intestinal mucosa are referred to as the "gastrointestinal barrier".

It is clear that a number of primary gastrointestinal diseases lead to disruption of the mucosal barrier, allowing escalation to systemic disease. It is equally clear that many systemic disease processes result in damage to the gastrointestinal barrier, thereby adding further insult to an already compromised system. Understanding the nature of the barrier can assist in predicting such events and aid in prophylactic or active therapies.

The gastrointestinal barrier is often discussed as having two components:

1. The intrinsic barrier is composed of the epithelial cells lining the digestive tube and the tight junctions that tie them together.

2. The extrinsic barrier consists of secretions and other influences that are not physically part of the epithelium, but which affect the epithelial cells and maintain their barrier function.

The large intestine extends from the end of the ileum to the anus. It is about 1.5 meters long, being one-fifth of the whole extent of the intestinal canal (*Fig. 5.2*).

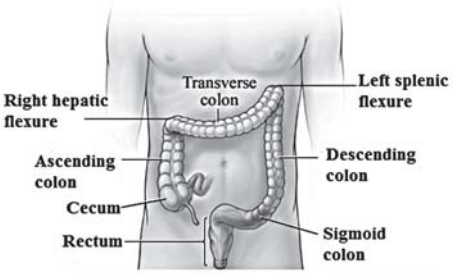


Figure 5.2. *Anatomy of the large intestine*

Its caliber is largest at its commencement at the cecum, and gradually diminishes as far as the rectum, where there is a dilatation of considerable size just above the anal canal. It differs from the small intestine in its greater caliber, its more fixed position, its sacculated form, and in possessing certain appendages to its external coat, the appendices epiploicæ. Further, its longitudinal muscular fibers do not form a continuous layer around the gut, but are arranged in three longitudinal bands or tæniæ. The large intestine, in its course, describes an arch which surrounds the convolutions of the small intestine. It commences in the right iliac region, in a dilated part, the cecum. It ascends through the right lumbar and hypochondriac regions to the under surface of the liver; it here takes a bend, the right colic flexure, to the left and passes transversely across the abdomen on the confines of the epigastric and umbilical regions, to the left hypochondriac region; it then bends again, the left colic flexure, and descends through the left lumbar and iliac regions to the pelvis, where it forms a bend called the sigmoid flexure; from this it is continued along the posterior wall of the pelvis to the anus. The large intestine is divided into the cecum, colon, rectum, and anal canal.

Vessels and Nerves. The arteries supplying the colon are derived from the colic (right, middle and left) and sigmoid branches of the upper and lower mesenteric arteries. They give off large branches, which ramify between and supply the muscular coats, and after dividing into small vessels in the submucous tissue, pass to the mucous membrane. The rectum is supplied by the superior hemorrhoidal branch of the inferior mesenteric, and the anal canal by the middle hemorrhoidal from the hypogastric, and the inferior hemorrhoidal from the internal pudendal artery. The superior hemorrhoidal, the continuation of the inferior mesenteric, divides into two branches, which run down either side of the rectum to within about 12.5 cm of the anus; they here split up into about six branches which pierce the muscular coat and descend between it and the mucous membrane in a longitudinal direction, parallel with each other as far as the Sphincter ani internus, where they anastomose with the other hemorrhoidal arteries and form a series of loops around the anus. The veins of the rectum commence in a plexus of vessels which surrounds the anal canal. In the vessels forming this plexus are smaller saccular dilatations just within the margin of the anus; from the plexus about six vessels of considerable size are given off. These ascend between the muscular and mucous coats for about 12.5 cm, running parallel to each other; they then pierce the muscular coat, and, by their union, form a single trunk, the superior hemorrhoidal vein. This arrangement is termed the hemorrhoidal plexus; it communicates with the tributaries of the middle and inferior hemorrhoidal veins, at its commencement, and thus a communication is established between the systemic and portal circulations.

The nerves are derived from the sympathetic plexuses around the branches of the superior and inferior mesenteric arteries. They are distributed in a similar way to those found in the small intestine.

The large intestine performs the vital functions of converting food into feces, absorbing essential vitamins produced by gut bacteria, and reclaiming water from feces. A slurry of digested food, known as chyme, enters the large intestine from the small intestine via the ileocecal sphincter. Chyme passes through the cecum where it is mixed with beneficial bacteria that have colonized the large intestine throughout a person's lifetime. The chyme is then slowly moved from one haustra to the next through the four regions of the colon. Most of the movement of chyme is achieved by slow waves of peristalsis over a period of several hours, but the colon can also be emptied quickly by stronger waves of mass peristalsis following a large meal.

While chyme moves through the large intestine, bacteria digest substances in the chyme that are not digestible by the human digestive system. Bacterial fermentation converts the chyme into feces and releases vitamins including vitamins K, B_1, B_2, B_6, B_{12}, and biotin. Vitamin K is almost exclusively produced by the gut bacteria and is essential in the proper clotting of blood. Gases such as carbon dioxide and methane are also produced as a byproduct of bacterial fermentation and lead to flatulence, or gas passed through the anus.

The absorption of water by the large intestine not only helps to condense and solidify feces, but also allows the body to retain water to be used in other metabolic processes. Ions and nutrients released by gut bacteria and dissolved in water are also absorbed in the large intestine and used by the body for metabolism. The dried, condensed fecal matter is finally stored in the rectum and sigmoid colon until it can be eliminated from the body through the process of defecation.

5.2. DIVERTICULAR DISEASE

Diverticular disease of the small intestine is relatively common. It may present as either true or false diverticula. A true diverticulum contains all layers of the intestinal wall and is usually congenital. False diverticula consist of mucosa and submucosa protruding through a defect in the muscle coat and are usually acquired defects. Small bowel diverticula may occur in any portion of the small intestine. Duodenal diverticula are the most common acquired diverticula of the small bowel, and Meckel's diverticulum is the most common true congenital diverticulum of the small bowel.

5.2.1. Duodenal diverticula

First described by Chomel, a French pathologist, in 1710, diverticula of the duodenum are relatively common, representing the second most common site for diverticulum formation after the colon. The incidence of duodenal diverticula is varied depending on the age of the patient and the method of diagnosis. Upper gastrointestinal radiographic studies identify duodenal diverticula in 1 to 5% of all studies, whereas some autopsy series report the incidence as being as high as 15 to 20%.

Duodenal diverticula occur twice as often in women as in men and are rare in patients younger than age 40 years. They have been classified as congenital or acquired,

true or false, and intraluminal or extraluminal. Two thirds to three fourths of duodenal diverticula are found in the periampullary region (within a 2 cm radius of the ampulla) and project from the medial wall of the duodenum (*Fig. 5.3*).

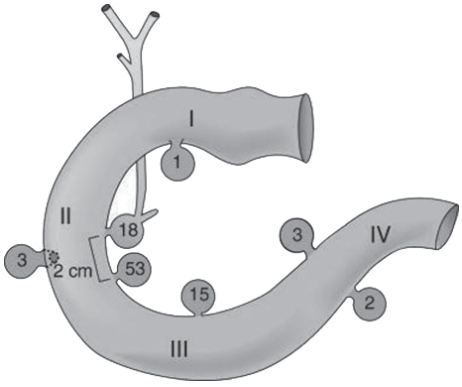


Figure 5.3. *Distribution of duodenal diverticula within the four portions of the duodenum*

Only those diverticula associated with the ampulla of Vater are significantly related to complications of cholangitis and pancreatitis. In these patients, the ampulla most often enters the duodenum at the superior margin of the diverticulum rather than through the diverticulum itself. The mechanism proposed for the increased incidence of complications of the biliary tract is the location of the perivaterian diverticula that may produce mechanical distortion of the common bile duct as it enters the duodenum, resulting in partial obstruction and stasis. Hemorrhage can be caused by inflammation, leading to erosion of a branch of the superior mesenteric artery. Perforation of duodenal diverticula has been described but is rare. Finally, stasis of intestinal contents within a distended diverticulum can result in bacterial overgrowth, malabsorption, steatorrhea, and megaloblastic anemia (i.e., blind loop syndrome). Symptoms related to duodenal diverticula in the absence of any other demonstrable disease usually are nonspecific epigastric complaints that can be treated conservatively and may actually prove to be the result of another problem not related to the diverticulum itself.

Clinical manifestations

The important thing to remember is that the overwhelming majority of duodenal diverticula is asymptomatic and are usually noted incidentally by an upper gastrointestinal series for an unrelated problem. Diagnosis may also be obtained by upper gastrointestinal endoscopy or suggested by plain abdominal films showing an atypical gas bubble; CT can identify large diverticula. Less than 5% of duodenal diverticula will require surgery because of a complication of the diverticulum itself. Major complications of duodenal diverticula include obstruction of the biliary or pancreatic ducts that may contribute to cholangitis and pancreatitis, respectively; hemorrhage; perforation; and rarely, "blind loop" syndrome.

Treatment

As stated previously, the vast majority of duodenal diverticula are asymptomatic and benign; and when they are found incidentally, they should be left alone. Several operative procedures have been described for the treatment of the symptomatic duodenal diverticulum. The most common and most effective treatment is diverticulectomy, which is most easily accomplished by performing a wide Kocher maneuver that exposes the duodenum. The diverticulum is then excised, and the duodenum is closed in a transverse or longitudinal fashion, whichever produces the least amount of luminal obstruction. Because of the close proximity of the ampulla,

careful identification of the ampulla is essential to prevent injury to the common bile duct and the pancreatic duct. For diverticula that are embedded deep within the head of the pancreas, a duodenotomy is performed with invagination of the diverticulum into the lumen, which is then excised, and the wall is closed. Alternative methods that have been described for duodenal diverticula associated with the ampulla of Vater include an extended sphincteroplasty through the common wall of the ampulla in the diverticulum.

The treatment of a perforated diverticulum may require procedures similar to those described in patients with massive trauma-related defects of the duodenal wall. The perforated diverticulum should be excised and the duodenum closed with a serosal patch from the jejunal loop. If the surrounding inflammation is severe, it may be necessary to divert the enteric flow away from the site of the perforation with a gastrojejunostomy or duodenojejunostomy. Interruption of duodenal continuity proximal to the perforated diverticulum may be accomplished with a row of staples. Great care should be taken if the perforation is adjacent to the papilla of Vater. Intraluminal duodenal diverticula have been described but are highly uncommon and, if symptomatic, can be completely excised if they arise at a site distant from the ampulla. However, if a symptomatic intraluminal diverticulum is encountered associated with the ampulla of Vater, subtotal resection of the diverticulum should be carried out to protect the entry of the biliary-pancreatic ducts.

5.2.2. Jejunal and ileal diverticula

Diverticula of the small bowel are much less common than duodenal diverticula, with an incidence ranging from 0.1 to 1.4% noted in autopsy series and 0.1 to 1.5% noted in upper gastrointestinal studies. Jejunal diverticula are more common and are larger than those in the ileum. These are false diverticula, occurring mainly in an older age group (after the sixth decade of life). These diverticula are multiple, usually protrude from the mesenteric border of the bowel, and may be overlooked at surgery because they are embedded within the small bowel mesentery. The cause of jejunoileal diverticulosis is thought to be a motor dysfunction of the smooth muscle or the mesenteric plexus, resulting in disordered contractions of the small bowel, generating increased intraluminal pressure, and resulting in herniation of the mucosa and submucosa through the weakest portion of the bowel (i.e., the mesenteric side).

Clinical manifestations

Jejunoileal diverticula are usually found incidentally at laparotomy or during the performance of an upper gastrointestinal study; the great majority remain asymptomatic. Acute complications such as intestinal obstruction, hemorrhage, or perforation can occur but are rare. Chronic symptomatology includes vague chronic abdominal pain, malabsorption, functional pseudo-obstruction, and chronic low-grade gastrointestinal hemorrhage. Acute complications are diverticulitis, with or without abscess or perforation; gastrointestinal hemorrhage; and intestinal obstruction. Stasis of intestinal flow with bacterial overgrowth (i.e., blind loop syndrome), owing to the jejunal dyskinesia, may lead to deconjugation of bowel salts and uptake of vitamin B_{12}

by the bacterial flora, resulting in steatorrhea and megaloblastic anemia, with or without neuropathy.

Treatment

For incidentally noted, asymptomatic jejunoileal diverticula, no treatment is required. Treatment of complications of obstruction, bleeding, and perforation is usually by intestinal resection and end-to-end anastomosis. Patients presenting with malabsorption secondary to the blind loop syndrome and bacterial overgrowth within the diverticulum can usually be given antibiotics. Obstruction may be caused by enteroliths that form in a jejunal diverticulum and are subsequently dislodged and obstruct the distal intestine. This condition may be treated by enterotomy and removal of the enterolith, or sometimes the enterolith can be milked distally into the cecum. When the enterolith causes obstruction at the level of the diverticulum, bowel resection is necessary. When a perforation of a jejunoileal diverticulum is encountered, resection with reanastomosis is required, because lesser procedures such as simple closure, excision, or invagination are associated with greater mortality and morbidity rates. In extreme cases, such as diffuse peritonitis, enterostomies may be required if judgment dictates that reanastomosis may be risky.

5.2.3. Meckel's diverticulum

Meckel's diverticulum is the most commonly encountered congenital anomaly of the small intestine, occurring in approximately 2% of the population. It was reported initially in 1598 by Hildanus and then described in detail by Johann Meckel in 1809. Meckel's diverticulum is located on the antimesenteric border of the ileum 45 to 60 cm proximal to the ileocecal valve and results from incomplete closure of the omphalomesenteric, or vitelline, duct. An equal incidence is found among men and women. The Meckel diverticulum may exist in different forms, ranging from a small "bump" that may be easily missed to a long projection that communicates with the umbilicus by a persistent fibrous cord or, much less commonly, a patent fistula. The usual manifestation is a relatively wide-mouth diverticulum measuring approximately 5 cm in length, with a diameter of up to 2 cm. Cells lining the vitelline duct are pluripotent; therefore, it is not uncommon to find heterotopic tissue within the Meckel diverticulum, the most common of which is gastric mucosa (present in 50% of all Meckel's diverticula). Pancreatic mucosa is encountered in approximately 5% of diverticula; less commonly, these diverticula may harbor colonic mucosa.

Clinical manifestations

The vast majority of Meckel's diverticula is entirely benign and are incidentally discovered during autopsy, laparotomy, or barium studies. The most common clinical presentation of a Meckel diverticulum is gastrointestinal bleeding, which occurs in 25 to 50% of patients who present with complications; hemorrhage is the most common symptomatic presentation in children aged 2 years or younger. This complication may present as acute massive hemorrhage, as anemia secondary to chronic bleeding, or as a self-limiting recurrent episodic event. The usual source of the bleeding is a chronic acid-induced ulcer in the ileum adjacent to a Meckel diverticulum that contains gastric mucosa.

Another common presenting symptom of Meckel's diverticulum is intestinal obstruction, which may occur as a result of a volvulus of the small bowel around a diverticulum associated with a fibrotic band attached to the abdominal wall, intussusception, or, rarely, incarceration of the diverticulum in an inguinal hernia (Littre's hernia). Volvulus is usually an acute event and, if allowed to progress, may result in strangulation of the involved bowel. In intussusception, a broad-based diverticulum invaginates and then is carried forward by peristalsis. This may be ileoileal or ileocolic and present as acute obstruction associated with an urge to defecate, early vomiting, and, occasionally, the passage of the classic currant-jelly stool. A palpable mass may be present. Although reduction of an intussusception secondary to a Meckel diverticulum can sometimes be performed by barium enema, the patient should still undergo resection of the diverticulum to negate subsequent recurrence of the condition.

Diverticulitis accounts for 10 to 20% of symptomatic presentations. This complication is more common in adult patients. Meckel's diverticulitis, which is clinically indistinguishable from appendicitis, should be considered in the differential diagnosis of a patient with right lower quadrant pain. Progression of the diverticulitis may lead to perforation and peritonitis. It is important to remember that when the appendix is found to be normal during exploration for suspected appendicitis, the distal ileum should be inspected for the presence of an inflamed Meckel diverticulum. Finally, much rarer complications of Meckel's diverticula include neoplasms, with the most common benign tumors reported as leiomyomas, angiomas, and lipomas. Malignant neoplasms include adenocarcinomas, which commonly originate from the gastric mucosa, sarcoma, and carcinoid tumor.

Diagnostic studies

The diagnosis of Meckel's diverticulum may be difficult. Plain abdominal radiographs, CT, and ultrasonography are rarely helpful. In children, the single most accurate diagnostic test for Meckel's diverticula is scintigraphy with sodium ^{99m}Tc-pertechnetate. The ^{99m}Tc-pertechnetate is preferentially taken up by the mucus-secreting cells of gastric mucosa and ectopic gastric tissue in the diverticulum. The diagnostic sensitivity of this scan has been reported as high as 85%, with a specificity of 95% and an accuracy of 90% in the pediatric age group.

In adults, however, ^{99m}Tc-pertechnetate scanning is less accurate because of the reduced prevalence of ectopic gastric mucosa within the diverticulum. The sensitivity and specificity can be improved by the use of pharmacologic agents such as pentagastrin and glucagon or H_2-receptor antagonists (e.g., cimetidine). Pentagastrin indirectly increases the metabolism of mucus-producing cells, whereas glucagon inhibits peristaltic dilution and washout of intraluminal radionuclide. Cimetidine may be used to increase the sensitivity of scintigraphy by decreasing the peptic secretion, but not the radionuclide uptake, and retarding the release of pertechnetate from the diverticular lumen, thus resulting in higher radionuclide concentrations in the wall of the diverticulum. In adult patients, when nuclear medicine findings are normal, barium studies should be performed. In patients with acute hemorrhage, angiography is sometimes useful.

Treatment

The treatment of a symptomatic Meckel diverticulum should be prompt surgical intervention with resection of the diverticulum or resection of the segment of ileum bearing the diverticulum. Segmental intestinal resection is required for treatment of patients with bleeding because the bleeding site usually is in the ileum adjacent to the diverticulum. Although the treatment for a complicated Meckel diverticulum is straightforward, controversy still exists regarding the optimal treatment of a Meckel diverticulum noted as an incidental finding. It is generally recommended that asymptomatic diverticula found during laparotomy be resected.

5.2.4. Diverticular disease of the large intestine

Colonic diverticulosis is among the most common diseases in developed Western countries. In the United States, diverticulosis occurs in approximately one third of the population older than age 45 and in up to two thirds of the population older than 85 years, and it also affects a significant proportion of younger adults.

A diverticulum is a saclike protrusion in the colonic wall that develops as a result of herniation of the mucosa and submucosa through points of weakness in the muscular wall of the colon. The colonic diverticulum is a false or pulsion diverticulum – that is, it does not contain all layers of the colonic wall. Diverticulosis indicates the presence of multiple diverticula and generally implies an absence of symptoms (*Fig. 5.4*). Diverticular disease implies any clinical state caused by diverticula, including hemorrhage, inflammation, or their complications. Diverticulitis describes the presence of an inflammatory process associated with diverticula. Its pathogenesis is attributed to genetic and environmental factor.

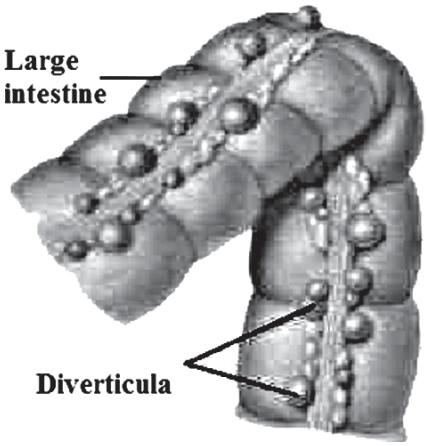


Figure 5.4. *Diverticula of the large intestine*

Factors involved in the pathogenesis of colonic diverticula

1. Genetic factors.
2. Environmental factors:

- Low-fiber diet.
- Obesity.
- Decreased physical activity.
- Corticosteroids.
- NSAIDs.
- Alcohol.
- Caffeine intake.
- Cigarette smoking.
- Polycystic kidney disease.

3. Epidemiologic factors:
• Age.
• Geography.
• Life style.
• Ethnicity.

Epidemiology

1. Incidence rises with age:
• 33% general population by 45 years.
• 66% general population by 85 years.
• Rare in patients < 40 years.
2. Male: Female ratio is equal.

Pathophysiology

Colonic diverticulosis in general is an acquired disease, developing as mucosal and submucosal herniations through the circular muscle layer at vulnerable weak points of the colonic wall. Diverticula are covered only by serosa, and tend to develop at four well-defined points around the circumference of the colon, where the vasa recta penetrate the muscular layer. These vessels enter the colonic wall on either side of the mesenteric teniae and on the mesenteric border of the two antimesenteric teniae. Diverticula do not develop in the rectum, presumably because of the coalescence of the teniae with the longitudinal muscle layer that marks the junction between the sigmoid colon and the rectum. In the colon, the presence of anatomic and physiologic changes contributes to the development of diverticula. Mycosis, a set of findings consisting of the thickening of the muscular layer, shortening of the teniae, and luminal narrowing, is found in most patients with sigmoid diverticula.

Physiologic and anatomic colonic changes in diverticula formation

• Mycosis.
• Changes in mechanical features of colonic wall.
• Changes in structural components of colonic wall.
• Elevated intraluminal pressure.
• Segmentation.

The mechanical features of the colonic wall change with increasing age. Combined barostat-manometry studies of the entire colon have demonstrated that compliance is lowest in the sigmoid and descending colon and greatest in the transverse and ascending colon. This difference in mechanical properties between the right and left sides might partly account for the left-sided predominance of diverticulosis.

Structural components of the extracellular matrix of the colonic wall, including collagen, elastin, and proteoglycans, are likely to be important in maintaining the strength and integrity of the colonic wall. Changes in these components of the bowel wall, such as damage and breakdown of mature collagen, and consequently its immature synthesis can lead to a change in bowel consistency These changes may be related to a genetic predisposition such as that seen in Ehlers-Danlos and Marfan's syndromes, which may be responsible for the occurrence of diverticula at an early age, or to the natural course of the aging process itself. In one study, it has been

reported that collagen fibrils in the left colon are smaller and more tightly packed than those in the right colon with increasing age, and that this difference is accentuated in diverticular disease.

The thickening of longitudinal and circular muscles in diverticular disease is neither hyperplastic nor hypertropic, but appears to be related to a contractile state. An increase in the number of elastic fibers has been observed only in the longitudinal muscle. It has been suggested that this process is responsible for longitudinal contraction, with subsequent thickening of both muscle layers. All these changes, along with elastin deposition in the teniae coli, lead to an irreversible state of contracture, with substantial bowel shortening, which may result in decreased resistance of the colon wall to persistent intraluminal pressure.

In addition to other predisposing factors, diverticula are believed to develop as a result of elevated intraluminal pressure generated by tonic and rhythmic contractions, resulting in segmentation. If contractions occur relatively close to each other and form an enclosed space, pressure within that intervening segment of colon may exceed 90 mm Hg. However, segmentation on its own separates the colonic lumen into a series of chambers, with each having a different amount of pressure that is closely related to the chamber's diameter. These isolated increases of intraluminal pressure are believed to predispose to herniation through the previously mentioned weak points of the colon.

The fiber content of the diet plays a large role in the pathogenesis of diverticular disease. Fiber has been found to be protective. Most fiber in the human diet is of plant origin and this type of fiber binds water and salt in the colon, leading to bulkier and more voluminous stools. Therefore, fiber decreases the frequency of contractions and prevents an exaggerated form of segmentation. In addition, dietary fiber influences the content of colonic bacterial flora, forms the main substrate for bacterial carbohydrate fermentation, and produces energy-yielding substrates-short-chain fatty acids-for growth and maintenance of colonic cellular function. Consequently, a fiber-deficient diet increases the chances of intense, more frequent segmentation, thus predisposing to herniation of mucosa by allowing isolated increases of intraluminal pressure.

After the development of colonic diverticula, a spectrum of inflammatory changes or bleeding caused by the traumatic injury to penetrating vessels may occur. Changes within these vessel walls, such as eccentric intimal thickening and thinning of the media of the vessel facing the bowel lumen, result in segmental weakness of these vessels and render them vulnerable to injury and bleeding.

The term *diverticulitis* represents a spectrum of inflammatory changes that ranges from localized subclinical inflammation to generalized peritonitis, with free perforation (*Fig. 5.5*). In turn, this leads to hyperplasia of the lymphoid tissue within the mucosa at the base of the diverticulum, one of the earliest signs of diverticulitis. Inflammation usually begins at the apex of the diverticulum and seldom involves the neck or mucosa proximal to the neck. However, there is active inflammation of the pericolic and mesenteric fat, with peridiverticular abscess formation. These

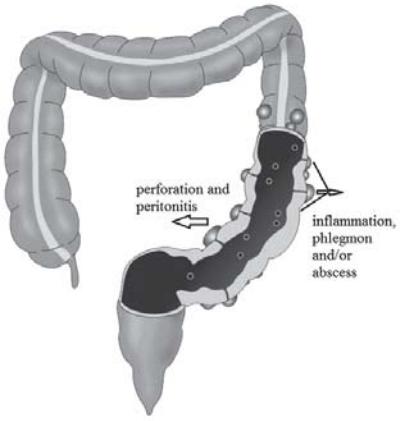


Figure 5.5. *The scheme of manifestations of diverticulitis*

peridiverticular abscesses often involve areas of subserosa and are closely related to the outer aspect of the muscularis propria; they can spread circumferentially and longitudinally and may be responsible for the pathologic picture of diverticular colitis. Longitudinal tracking, especially, may result in fissuring, along with the lymphoid aggregates, which resembles the distinctive feature of colonic colitis in Crohn's disease. This may cause misinterpretation of the pathologic study of the specimen. Therefore, the differential diagnosis of these two conditions in terms of pathologic interpretation of the resected specimen is important. Persistent localized inflammation after diverticular rupture results in a phlegmon, a thickened, firm segment of bowel wall, which ultimately may manifest as acute or subacute large bowel obstruction. If left untreated or treated inadequately, it may result in extensive fibrosis around the affected segment of the colon, giving it a mass appearance indistinguishable macroscopically from that of a neoplasm.

Another pathologic entity that may be encountered during progression of the disease, with recurrent attacks of diverticulitis, is the formation of a localized abscess with chronic inflammation and involvement of other neighboring luminal organs, such as the bladder, small and large bowel loops, uterus, and vagina. Fistulae may develop within this contained area, between involved segment(s) of colon and these organs. Fistulae occur in 2.4 to 20% of cases; 65% of these fistulae are colovesical and 20% are colovaginal fistulae.

Signs and symptoms

Most people with uncomplicated colonic diverticulosis are asymptomatic. A small fraction of these patients may have troublesome symptoms, such as colicky abdominal pain, bloating, flatulence, or altered bowel habit. The symptoms characteristically disappear after defecation or passage of flatus. On clinical examination, they may have tenderness in the left iliac fossa with no signs or symptoms of peritonitis or systemic illness, and all laboratory values may be within normal limits. The clinical picture of symptomatic uncomplicated diverticulosis often overlaps with that of irritable bowel syndrome (IBS), because these two clinical entities are usually diagnosed after other pathologies are excluded. IBS-type symptoms are independent of the presence or absence of diverticulosis on double-contrast barium enema studies. Bleeding alone can sometimes be the only sign of diverticulosis.

Signs and symptoms of acute diverticulitis may vary from local findings and manifestations to a wide variety of clinical pictures, with signs and symptoms of intra-abdominal sepsis, depending on the stage of disease.

Manifestation of acute diverticulitis:

- Acute left lower quadrant pain (93–100%).
- Fever, chills (57–100%).
- Leukocytosis (69–83%).
- Nausea, vomiting.
- Inflammatory mass.
- Constipation.
- Diarrhea.
- Urinary symptoms.

Patients with acute uncomplicated diverticulitis classically present with left-sided lower abdominal pain, fever, and leukocytosis. The site of pain often depends on the segment of colon affected. Right-sided symptoms may occur in the presence of right-sided diverticulosis, as well as in redundant sigmoid colon lying on the right side of the abdomen. Patients with left-sided pain may also have right-sided symptoms. Other common manifestations are frequently related to GI disturbances, with alteration in bowel habits, constipation, either alone or alternating with bouts of diarrhea, anorexia, and nausea and vomiting. Urinary symptoms such as dysuria, frequency, and urgency may develop in a minority of patients, probably because of the proximity of the bladder to the inflamed sigmoid colon. In acute presentations, fever is almost always present, but high fever must suggest the possibility of advanced disease and sepsis from generalized peritonitis caused by perforation and spreading of inflammation in the peritoneum.

Abdominal findings reflect the severity and localization of the disease. In cases of diffuse peritonitis, generalized tenderness, involuntary guarding, or decreased or absent bowel sounds are noted. Severe abdominal distention with nausea and vomiting suggests bowel obstruction. The presence of pneumaturia and fecaluria signifies the presence of a colovesical fistula.

Immunocompromised and immunosuppressed patients constitute the most important group needing special attention in diagnosis and treatment. This patient group may lack a normal inflammatory response and present with minimal classic signs and symptoms, which may delay the diagnosis and treatment. This may result in sepsis and death. It is preferable to operate semielectively on these patients during the first episode of their initial hospitalization.

Diagnosis

The initial assessment of patients with suspected acute diverticulitis is comprised of a thorough history and physical examination, including abdominal, rectal, and pelvic examinations. Useful initial examinations may include a complete blood cell count, urinalysis, and flat and upright abdominal radiography. If the clinical picture is clear enough to diagnose diverticulitis, no other tests are indicated. When the diagnosis is in question, other tests such as computed tomography (CT), water-soluble contrast enema, cystography, endoscopy, and ultrasound may be performed. The differential diagnosis of acute diverticulitis should also be considered, not only during examination of the patient but also while ordering the tests. In particular, the differential diagnosis of colorectal cancer, as well as the detection of its possible coexistence, is important.

A barium enema examination should be avoided in acute presentations in patients with suspected acute diverticulitis and localized peritoneal signs because of a possible extravasation of barium into the peritoneal cavity, which can increase the morbidity and mortality related to barium-induced chemical peritonitis. In the emergency setting, water-soluble enemas are safer.

Differential diagnosis of acute diverticulitis:

- Irritable bowel syndrome.
- Gastroenteritis.
- Cholecystitis.
- Bowel obstruction.
- Acute appendicitis.
- Ischemic colitis.
- Colorectal cancer.
- Urologic disorders.
- Gynecologic disorders.

Abdominal ultrasound is a noninvasive screening method. It is helpful, especially in female patients, to exclude pelvic and gynecologic pathology. CT is generally superior to contrast studies. In addition to the identification of complications such as phlegmon, abscess, adjacent organ involvement and distant septic complications, it also is a useful therapeutic tool for percutaneous drainage of intra-abdominal abscesses, providing the opportunity to downstage the intra-abdominal pathology so that it can be treated with a single-stage surgical procedure. Severity staging by CT scanning may allow not only the selection of patients most likely to respond to conservative treatment, but may also predict the risk of failure of medical therapy and of secondary complications after initial conservative treatment. The incidence of subsequent complications is highest in patients with severe disease on initial CT. CT is not useful in differentiating cancer from diverticulitis and must be supplemented by contrast enema studies or endoscopy. Although endoscopy is rarely indicated in an acute setting, if required, it should be done with gentle and cautious insufflation and manipulation because of the risk of perforation of an acutely inflamed colon, either by insufflation of air or by the instrument itself.

Treatment

Conservative treatment. Complicated diverticulitis refers to acute diverticulitis accompanied by abscess, fistula, obstruction, or free intra-abdominal perforation. In the absence of complications and systemic signs and symptoms, patients with mild abdominal tenderness may be treated conservatively. Conservative treatment typically includes dietary modification and oral or parenteral antibiotics.

Antibiotic selection should be based on appropriate coverage for gram-negative rods and anaerobic bacteria. Conservative treatment will resolve acute diverticulitis in 85% of patients, but approximately one third will have a recurrent attack, often within a year.

Approximately 15% of patients develop pericolonic or intramesenteric abscess. Abscesses smaller than 2 cm in diameter may resolve with antibiotic treatment without

any further intervention, whereas larger abscesses may require percutaneous drainage. This may prevent an emergency operation and multistaged surgeries involving the creation and closure of stoma.

After resolution of the initial acute attack, the colon should be thoroughly evaluated with colonoscopy or contrast enema radiography.

Surgical treatment. Surgical treatment of the disease can be evaluated emergently or electively, based on the stage of the disease and clinical presentation. Emergent sigmoid colectomy is required for patients with the following:

- Diffuse peritonitis.
- Failure of conservative treatment.
- Persistent sepsis despite percutaneous drainage.
- Very low threshold, immunosuppressed, and immunocompromised patients who are likely to fail medical treatment and present with perforation.

HINCHEY CLASSIFICATION:

- **Stage I:**
  - Ia: diverticulitis with phlegmon;
  - IIb: diverticulitis with pericolic or mesenteric abscess.
- **Stage II:** diverticulitis with walled off pelvic abscess.
- **Stage III:** diverticulitis with generalised purulent peritonitis.
- **Stage IV:** Diverticulitis with generalised fecal peritonitis.

Intraoperative surgical options are based on the status of the patient and the severity of intra-abdominal contamination (Hinchey classification). The desired surgical option is resection of the diseased segment with primary anastomosis, with or without intraoperative lavage or resection, and anastomosis with a temporary diverting ileostomy (*Fig. 5.6*). In advanced stages of peritonitis, Hartmann's procedure (sigmoid colectomy, end colostomy, and closure of the rectal stump; *Fig. 5.7*) is the preferred operation.

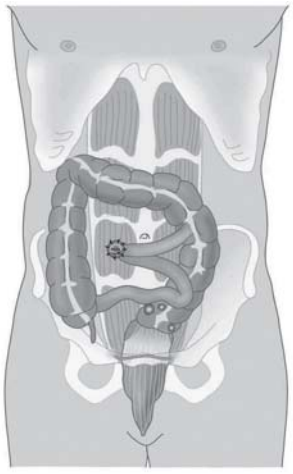


Figure 5.6. *Resection of large intestine with ileostomy*

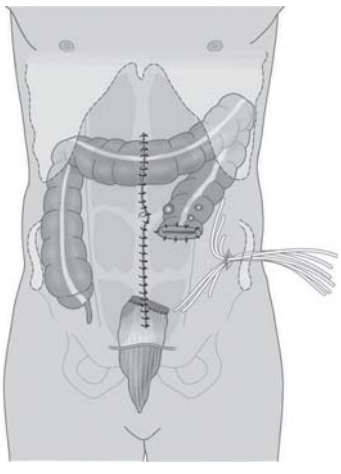


Figure 5.7. *Hartmann's procedure*

Prevention

Prevention can be achieved by elimination of the factors involved in the pathogenesis of this disease. Increasing the proportion of fiber in the diet, along with an increase in fluid intake, will help keep more diverticula from forming and also will help keep the existing condition from worsening. Additionally, alteration of lifestyle by weight reduction and exercise can limit the contribution of other causative factors.

Right-sided diverticulitis

Diverticulosis in Asia is predominantly a right-sided phenomenon. Diverticula of the right colon may be singular or multiple. The diagnosis of right-sided diverticulitis is difficult to differentiate from appendicitis with a similar clinical picture and presentation. An abdominal mass is usually found in 26 to 88% of cases. Surgical treatment is reserved for recurrent and complicated episodes if the diagnosis of right-sided diverticulitis has been made with confidence. If extensive inflammation is present or multiple diverticula are found, a right hemicolectomy with primary anastomosis is indicated.

Summary

1. The incidence of diverticular disease, particularly diverticulitis, has increased in industrialized countries.

2. Diverticular disease can be classified as symptomatic uncomplicated disease, recurrent symptomatic disease, and complicated disease.

3. Conservative or medical management is usually indicated for acute uncomplicated diverticulitis. Indications for surgery include recurrent attacks and complications of the disease.

4. Surgical treatment options have changed considerably over the years, along with the development of new diagnostic tools and surgical approaches (for example, laparoscopy).

5. Indications and timing for surgery of diverticular disease are determined mainly by the stage of the disease. In addition, individual patient risk factors, along with the course of the disease after conservative or operative therapy, play a significant role in decision making and treatment.

5.3. MESENTERIC ISCHEMIC

5.3.1. Acute mesenteric ischemic

Abrupt reduction in blood flow to intestinal circulation of sufficient magnitude to compromise metabolic requirements and potentially threaten the viability of affected organs.

"Occlusion of the mesenteric vessels is apt to be regarded as one of those conditions of which the diagnosis is impossible, the prognosis hopeless, and the treatment almost useless" (Cokkinis A.J., 1930).

This quote indicates some of the extreme difficulties faced by physicians treating acute mesenteric ischemia (AMI). Symptoms are nonspecific initially, before evidence of peritonitis presents. Thus, diagnosis and treatment are often delayed until the disease

is advanced. Fortunately, since this statement was written, many advances have been made that allow earlier diagnosis and treatment. While the prognosis is grave for patients in whom the diagnosis is delayed until bowel infarction has already occurred, patients who receive the appropriate treatment in a timely manner are much more likely to recover.

Epidemiology

1. Incidence as high as 1 in 1,000 pts.
2. Expected to increase c aging population.
3. Despite growing awareness, morbidity and mortality remain high.
4. Mortality 59–93%.

Pathophysiology

1. 10–30% resting C.O. devoted to intestinal blood flow.
2. Most directed towards mucosa, layer c greatest metabolic demand and highest rate of cell turnover.
3. Sudden reduction blood flow → organ ischemia specifically compromising mucosa.
4. Inflm cell infiltrate, loss of capillary integrity c bowel wall edema → bacterial translocation, endotoxemia, exudation of fluid from small bowel.
5. Injured mucosa sloughs → ulceration → necrosis of muscularis and serosa.
6. Septic shock, MSOF.

Etiology

AMI is a syndrome in which inadequate blood flow through the mesenteric circulation causes ischemia and eventual gangrene of the bowel wall. The syndrome can be classified generally as arterial or venous disease. Arterial disease can be subdivided into nonocclusive mesenteric ischemia (NOMI), shown in the image below, and occlusive mesenteric arterial ischemia (OMAI). Practically, AMI is divided into 4 different primary clinical entities:

1. Mesenteric arterial embolus.
2. Mesenteric arterial thrombosis.
3. Non occlusive mesenteric ischemia (NOMI).
4. Mesenteric venous thrombosis (MVT).

All 4 types of AMI have somewhat different predisposing factors, clinical pictures, and prognoses. A secondary clinical entity of mesenteric ischemia occurs because of mechanical obstruction, such as internal hernia with strangulation, volvulus, intussusception, tumor compression, and aortic dissection. Occasionally, blunt trauma may cause isolated dissection of the superior mesenteric artery and lead to intestinal infarction. Because all types of AMI share many similarities and a final common pathway (ie, bowel infarction and death, if not properly treated), they are discussed together.

History

Antonio Beniviene first described mesenteric ischemia in the 15th century. It became more intensely studied in the mid 19th century after case reports by Virchow and others. The first successful surgery to repair a case of AMI was performed by

Elliot, who, in 1895, resected a gangrenous portion of bowel and reanastomosed the viable bowel.

In the early 20th century, advances were made in diagnostic modalities, heparin was introduced for use in MVT, and residual arterial spasm was recognized. In the 1950s, vascular surgical repair to restore blood flow to ischemic bowel before gangrene occurred was introduced. The first successful embolectomy without bowel resection was performed in 1957.

NOMI was first recognized as a subtype of AMI in the 1950s. MVT was found to compose a much smaller portion of AMI than was originally thought. By 1960, the combination of heparin administration and bowel resection, when required, became the standard treatment of MVT. Hypercoagulable states were identified as the apparent cause of most cases of MVT.

In the 1970s, the use of angiography to diagnose and evaluate AMI, as well as the introduction of intra-arterial papaverine infusion, significantly improved the prognosis of patients by allowing early diagnosis and by combating residual arterial spasm. The increasing use of ultrasound and CT scan since the 1980s has helped achieve earlier diagnosis.

Anatomy

Typically, the celiac artery (CA) supplies the foregut, hepatobiliary system, and spleen; the superior mesenteric artery (SMA) supplies the midgut (i.e., small intestine and proximal mid colon); and the inferior mesenteric artery (IMA) supplies the hindgut (i.e., distal colon and rectum), but multiple anatomic variants are observed. Venous drainage is through the superior mesenteric vein (SMV), which joins the portal vein.

AMI arises primarily from problems in the SMA circulation or its venous outflow. Collateral circulation from the CA and IMA may allow sufficient perfusion if flow in the SMA is reduced because of occlusion, low-flow state (NOMI), or venous occlusion. The inferior mesenteric artery seldom is the site of lodgment of an embolus. Only small emboli can enter this vessel because of its smaller lumen. When lodgment occurs, the embolus lodges at the site of division of the inferior mesenteric artery into the left colic, sigmoidal, and superior hemorrhoidal arteries. In such instances, collateral flow from the middle colic and middle hemorrhoidal arteries (through the vascular arcades of the inferior mesenteric artery distal to the embolus) may sustain the perfusion of the left colon.

Pathophysiology

Insufficient blood perfusion to the small bowel and colon may result from arterial occlusion by embolus or thrombosis (AMAE or AMAT), thrombosis of the venous system (MVT), or nonocclusive processes such as vasospasm or low cardiac output (NOMI). Embolic phenomena account for approximately 50% of all cases, arterial thrombosis for about 25%, NOMI for roughly 20%, and MVT for less than 10%. Rarely, isolated spontaneous dissections of the SMA have been reported. Hemorrhagic infarction is the common pathologic pathway whether the occlusion is arterial or venous.

Injury severity is inversely proportional to the mesenteric blood flow and is influenced by the number of vessels involved, systemic mean pressure, duration of ischemia, and collateral circulation. The superior mesenteric vessels are involved more frequently than the inferior mesenteric vessels, with blockage of the latter often being silent because of better collateral circulation.

Damage to the affected bowel portion may range from reversible ischemia to transmural infarction with necrosis and perforation. The injury is complicated by reactive vasospasm in the SMA region after the initial occlusion. Arterial insufficiency causes tissue hypoxia, leading to initial bowel wall spasm. This leads to gut emptying by vomiting or diarrhea. Mucosal sloughing may cause bleeding into the gastrointestinal tract. At this stage, little abdominal tenderness is usually present, producing the classic intense visceral pain disproportionate to physical examination findings.

The mucosal barrier becomes disrupted as the ischemia persists, and bacteria, toxins, and vasoactive substances are released into the systemic circulation. This can cause death from septic shock, cardiac failure, or multisystem organ failure before bowel necrosis actually occurs. As hypoxic damage worsens, the bowel wall becomes edematous and cyanotic. Fluid is released into the peritoneal cavity, explaining the serosanguineous fluid sometimes recovered by diagnostic peritoneal lavage. Bowel necrosis can occur in 8–12 hours from the onset of symptoms. Transmural necrosis leads to peritoneal signs and heralds a much worse prognosis.

Embolic AMI is usually caused by an embolus of cardiac origin. Typical causes include mural thrombi after myocardial infarction, atrial thrombi associated with mitral stenosis and atrial fibrillation, vegetative endocarditis, mycotic aneurysm, and thrombi formed at the site of atheromatous plaques within the aorta or at the sites of vascular aortic prosthetic grafts interposed between the heart and the origin of the superior mesenteric artery. The vascular occlusion is sudden, so the patients have not developed a compensatory increase in collateral flow. As a result, they experience worse ischemia than patients with thrombotic AMI. The SMA is the visceral vessel most susceptible to emboli because of its small take-off angle from the aorta and higher flow. Most often, emboli lodge about 6–8 cm beyond the arterial origin, at a narrowing near the emergence of the middle colic artery.

Thrombotic AMI is a late complication of preexisting visceral atherosclerosis. Symptoms do not develop until 2 of the 3 arteries (usually the celiac and superior mesenteric arteries) are stenosed or completely blocked. Progressive worsening of the atherosclerotic stenosis before the acute occlusion allows time for development of additional collateral circulation.

Most patients with thrombotic AMI have atherosclerotic disease at other sites such as coronary artery disease, stroke, or peripheral arterial disease. A drop in cardiac output from myocardial infarction or congestive heart failure (CHF) may cause AMI in a patient with visceral atherosclerosis. Thrombotic AMI may also be a complication of arterial aneurysm or other vascular pathologies, such as dissection, trauma, and thromboangiitis obliterans. In inflammatory vascular disease, smaller vessels are affected. Thrombosis tends to occur at the origin of the SMA, causing

widespread infarction. These patients frequently present with a history of chronic mesenteric ischemia in the form of intestinal angina before the emergent event.

NOMI is precipitated by a severe reduction in mesenteric perfusion, with secondary arterial spasm from such causes as cardiac failure, septic shock, hypovolemia, or the use of potent vasopressors in patients in critical condition. Because bowel perfusion, similar to cerebral perfusion, is preserved in the setting of hypotension, NOMI represents a failure of autoregulation. Many vasoactive drugs may also cause regional vasoconstriction, such as digitalis, cocaine, diuretics, and vasopressin. Gross pathologic arterial or venous occlusions are not observed in patients with NOMI.

MVT often (i.e., >80% of the time) is the result of some processes that make the patient more likely to form a clot in the mesenteric circulation (i.e., secondary MVT). Primary MVT occurs in the absence of any identifiable predisposing factor. The list of causes for MVT is long and includes infection, usually from an intra-abdominal source; phlebitis or pylephlebitis (portal pyemia) secondary to inflammatory diseases of the bowel such as diverticulitis, appendicitis, and secondarily infected carcinoma of the bowel; hypercoagulable states such as those caused by polycythemia, oral contraceptives, or genetic abnormalities (protein C or S deficiency); mesenteric venous stasis from portal hypertension or mass effect of abdominal tumors; and direct trauma to the mesenteric veins from a surgical procedure. Increased intra-abdominal pressure from pneumoperitoneum during laparoscopic surgery can result in MVT. MVT may also occur after ligation of the splenic vein for a splenectomy or ligation of the portal vein or the superior mesenteric vein as part of "damage-control surgery" for severe penetrating abdominal injuries. Other associated causes include pancreatitis, sickle cell disease, and hypercoagulability caused by malignancy.

MVT often affects a much younger population. Symptoms may be present longer than in the typical cases of AMI, sometimes exceeding 30 days. Infarction from MVT is rarely observed with isolated SMV thrombosis, unless collateral flow in the peripheral arcades or vasa recta is compromised as well. Fluid sequestration and bowel wall edema are more pronounced than in arterial occlusion. The colon is usually spared because of better collateral circulation. The chronic form of SMV thrombosis may manifest as esophageal varices bleeding.

Clinical

History. All types of AMI have a similar presentation to some extent. Differences in clinical appearance for each type are discussed below. The most important finding is pain disproportionate to physical examination findings. Typically, pain is moderate to severe, diffuse, nonlocalized, constant, and sometimes colicky.

Onset varies from type to type. Nausea and vomiting are found in 75% of affected patients. Anorexia and diarrhea progressing to obstipation are also common. Abdominal distension and GI bleeding are the primary symptoms in up to 25% of patients. Pain may be unresponsive to narcotics. As the bowel becomes gangrenous, rectal bleeding and signs of sepsis (e.g., tachycardia, tachypnea, hypotension, fever, altered mental status) develop. A review of systems, looking for risk factors of AMI,

should be performed. This syndrome has a catastrophic outcome if not properly and rapidly treated. It should be considered in any patient with abdominal pain disproportionate to physical findings, gut emptying in the form of vomiting or diarrhea, and the presence of risk factors, especially age older than 50 years.

Embolic acute mesenteric ischemia (Fig. 5.8).

1. AMI from embolic causes typically has the most abrupt and painful presentation of all types. This is due to the rapid onset of occlusion and inability to form additional collateral circulation. It has been described as abdominal apoplexy.

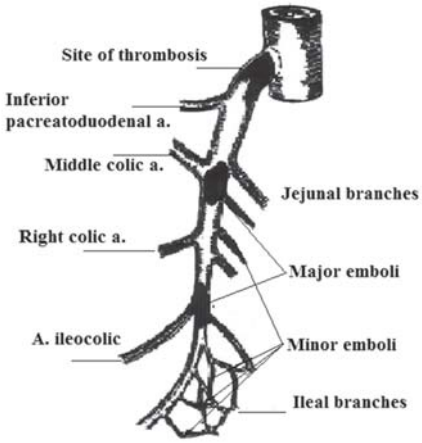


Figure 5.8. *The scheme of emboli of superior mesenteric artery*

2. Often, vomiting and diarrhea (gut emptying) are observed. Patients are usually found to have a source of embolization. Because most emboli are of cardiac origin, patients often have atrial fibrillation or a recent myocardial infarction (with mural thrombus). Infrequently, patients may report a history of valvular heart disease or previous embolic episode.

Thrombotic acute mesenteric ischemia

1. AMI caused by a thrombus, such as a myocardial infarction, typically happens when an artery already partially blocked by atherosclerosis becomes completely occluded.

2. Similarly to angina pectoris preceding a myocardial infarction, 20–50% of these patients have a history of abdominal angina. Abdominal angina is a syndrome of postprandial abdominal pain starting soon after eating and lasting for up to 3 hours. The digestion of food requires increased perfusion of the intestine, so the mechanism is similar to that of exercise-induced angina pectoris. Weight loss, "food fear," early satiety, and altered bowel habits may be present.

3. The precipitating event that initiates thrombotic AMI may be a sudden drop in cardiac output from myocardial infarction or CHF or a ruptured plaque. Dehydration from vomiting or diarrhea due to an unrelated illness may also precipitate thrombotic AMI. These patients have undergone a gradual progression of arterial occlusion and frequently have a better collateral supply. Bowel viability is better preserved, often leading to a less severe presentation than with embolic AMI. Symptoms tend to be less intense and of more gradual onset. As might be expected, these patients typically have a history of atherosclerotic disease at other sites, e.g., coronary artery disease, cerebral arterial disease, peripheral artery disease (especially aortoiliac occlusive disease), or a history of aortic reconstruction.

Pathogenesis

Transmural infarcts

• All layers due to sudden occlusion of major vessels.

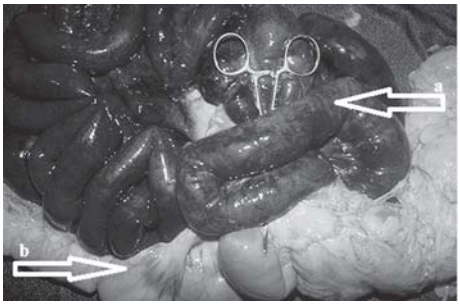


Figure 5.9. *Bowel gangrenous (arrow, a) and normal (arrow, b)*

• Bowel swollen, gangrenous and perforates in few days (*Fig. 5.9*).

• Clinical Presentation:

• Sudden severe abdominal pain and tenderness; sometimes nausea, vomiting and bloody diarrhea or melena.

• Shock and vascular collapse in hours.

• Peristalsis is diminished.

Mucosal and mural infarcts

• Most commonly due to hypoperfusion in watershed areas.

• Necrosis of mucosa only; mucosa hemorrhagic; serosa normal.

• Clinical Presentation:

– May not be fatal if cause corrected.

– Nonspecific abdominal complaints and intermittent bloody diarrhea, but may progress to extensive infarction and sepsis.

Nonocclusive mesenteric ischemia

1. Nonocclusive AMI occurs more frequently in older patients than other forms of AMI. These elderly patients are often already in an ICU setting with acute respiratory distress syndrome or severe hypotension from cardiogenic or septic shock, or they are taking vasopressive drugs. Most of these patients are taking digitalis.

2. Symptoms typically develop over several days, and patients may have had a prodrome of malaise and vague abdominal discomfort. When infarction occurs, the patients develop increased pain associated with vomiting. They may become hypotensive and tachycardic, with loose bloody stool.

Mesenteric venous thrombosis

1. MVT is often observed in a much younger patient population than other types of AMI. MVT patients can present with an acute or subacute abdominal pain syndrome related to involvement of the small intestine rather than the colon. The symptoms are frequently less dramatic. Diagnosis can be even more difficult, because symptoms may have been present for weeks (i.e., 27% have symptoms for >30 d). Typical symptoms of AMI may have been experienced for a prolonged period with gradual worsening. The chronic form may manifest as esophageal varices bleeding.

2. Many patients have a history of one or more of the risk factors for hypercoagulability. These include oral contraceptive use, congenital hypercoagulable states, deep vein thrombosis (DVT), liver disease, tumor, or portocaval surgery.

Physical. Despite different etiology, physical examination findings in patients with AMI are similar. The main distinction is between early and late presentation. Early in the course of the disease, in the absence of peritonitis, physical signs are few and nonspecific. Tenderness is minimal to nonexistent. Stool may be guaiac positive. Peritoneal signs develop late, when infarction with necrosis or perforation occurs. Tenderness becomes severe and may indicate the location of the infarcted bowel segment. A palpable tender mass may be present. Bowel sounds range from

hyperactive to absent. Voluntary and involuntary guarding appears. Fever, hypotension, tachycardia, tachypnea, and altered mental status are observed. Foul breath may be noted with bowel infarction, from the putrefaction of undigested alimentary material accumulated proximal to the pathologic site.

Signs reflecting risk factors for AMI may be noted. Patients with embolic AMI may have atrial fibrillation or heart murmurs. Those with thrombotic AMI or NOMI may have an abdominal murmur or a scar from a recent abdominal aortic repair with or without reimplantation of the SMA. Those with MVT may have evidence of tumor, cirrhosis, DVT, or recent abdominal surgery.

Causes

Embolic acute mesenteric ischemia

1. Cardiac emboli mural thrombus post-myocardial infarction, auricular thrombus associated with mitral stenosis and atrial fibrillation, septic emboli from valvular endocarditis (less frequent).
2. Emboli from fragments of proximal aortic thrombus due to a ruptured atheromatous plaque.
3. Atheromatous plaque dislodged by arterial catheterization.

Thrombotic acute mesenteric ischemia

1. Atherosclerotic vascular disease (most common).
2. Aortic aneurysm.
3. Aortic dissection.
4. Arteritis.
5. Decreased cardiac output from myocardial infarction or CHF (thrombotic AMI may cause acute decompensation).
6. Dehydration from other causes.

Nonocclusive mesenteric ischemia

1. Hypotension from CHF, myocardial infarction, sepsis, aortic insufficiency, severe liver or renal disease, or recent major cardiac or abdominal surgery.
2. Vasopressive drugs.
3. Ergotamines.
4. Cocaine.
5. Digitalis (whether a digitalis use causes NOMI or patients who develop NOMI are older and are more likely to have been prescribed digitalis is unclear).

Mesenteric venous thrombosis: more than 80% of patients with MVT are found to have predisposing conditions.

1. Hypercoagulability from protein C and S deficiency, antithrombin III deficiency, dysfibrinogenemia, abnormal plasminogen, polycythemia vera (most common), thrombocytosis, sickle cell disease, factor V Leiden mutation, pregnancy, and oral contraceptive use.
2. Tumor causing venous compression or hypercoagulability.
3. Infection, usually intra-abdominal, such as appendicitis, diverticulitis, or abscess.
4. Venous congestion from cirrhosis (portal hypertension).

5. Venous trauma from accidents or surgery, especially portocaval surgery.

6. Increased intra-abdominal pressure from pneumoperitoneum during laparoscopic surgery.

7. Pancreatitis.

8. Decompression sickness.

INVESTIGATIONS

Laboratory studies

In general, laboratory studies are not helpful in diagnosing AMI. No serum marker is sensitive or specific enough to establish or exclude the diagnosis of AMI. Waiting for laboratory results should not delay radiographic studies if serious suspicion of AMI exists.

1. CBC may be within the reference range initially, but the WBC count eventually rises as the disease progresses. Leukocytosis and/or leftward shift are observed in over 50% of cases. The hematocrit is elevated initially from hemoconcentration due to third spacing, but it decreases with GI bleeding.

2. Amylase levels are moderately elevated in over 50% of patients, but this finding is nonspecific.

3. Phosphate levels were initially thought to be sensitive, but later studies showed a sensitivity of only 25–33%.

4. ABG: Metabolic acidosis is observed late in disease course, but this is a nonspecific finding.

5. Lactate is elevated late in the clinical course. Levels that are persistently within the reference range strongly indicate a diagnosis other than AMI (sensitivity 96%, specificity 60%).

6. D-dimer has been suggested to possibly be helpful based on one small clinical study reported in 2001 and on one experimental study in rats.[7] Clinical experience is lacking to validate the role of D-dimer in the screening and diagnosis of AMI.

Imaging studies

Plain abdominal films

1. Findings on plain films of the abdomen often are normal in the presence of AMI. However, plain films are warranted to exclude identifiable causes of abdominal pain, such as perforated viscus with free intraperitoneal air.

2. Positive findings are usually late and nonspecific and include ileus, small bowel obstruction, edematous/thickened bowel walls, and paucity of gas in the intestines. More specific signs, such as pneumatosis intestinalis, that is, submucosal gas (see the image below); thumbprinting of the bowel wall; and portal vein gas, are late findings. In one study of 23 cases of bowel infarction, 30% of the patients demonstrated focally edematous bowel wall (thumbprinting) and/or pneumatosis intestinalis.

Computed tomography scan

1. CT scan helps exclude other causes of abdominal pain (*Fig. 5.10*).

2. CT angiography has a sensitivity of 71–96% and a specificity of 92–94% for AMI. In clinical practice, CT angiography is ordered much more frequently than

classic angiography. CT angiography is noninvasive, readily available, and the preferred modality for MVT (90% sensitivity).

3. CT scan may show pneumatosis intestinalis, portal vein gas, bowel wall and/or mesenteric edema, abnormal gas patterns, thumbprinting, streaking of mesentery, and solid organ infarction. Bowel wall edema is the most common finding on CT scan. It represents submucosal infiltration of fluid or hemorrhage into ischemic bowel. Arterial occlusion may show nonenhancement of the vessels. MVT usually shows a thrombus in the SMV or portal vein.

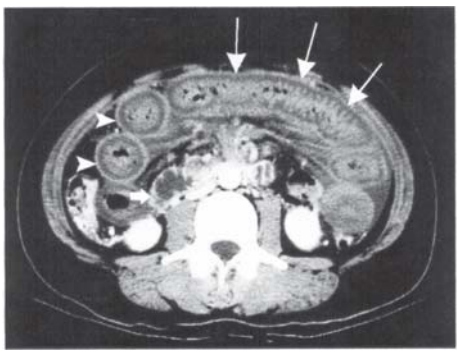


Figure 5.10. *CT scan: pneumatosis intestinalis (arrows)*

4. Serial CT angiograms can be used to monitor patients treated nonsurgically with anticoagulation.

Angiography

1. Angiography has been the criterion standard to aid in diagnosis and presurgical planning. It also plays an important role in pharmacologic infusion therapy. However, angiography is less and less resorted to in clinical practice. Sensitivity is reported to be 88% for AMI.

2. An embolus appears as a sharp cutoff of flow near the origin of the middle colic artery. Thrombus appears as a more tapered occlusion near the origin of the SMA. NOMI is characterized by narrowing of the origins of multiple SMA branches, alternating dilation and narrowing of the intestinal branches (ie, "string of sausages" sign), spasm of the mesenteric arcades, and impaired filling of the intramural vessels.

3. Angiography is actually a second-line study in patients with a strong suspicion of MVT because false-negative findings are common. Findings with MVT include thrombus in the SMV, reflux of contrast into the aorta, prolonged arterial phase with accumulation of contrast and thickened bowel walls, extravasation of contrast into bowel lumen, and filling defect in the portal vein or complete lack of venous phase.

Ultrasonography

1. Duplex sonography studies are highly specific (92–100%) but not as sensitive (70–89%) compared to angiography. The examination cannot detect clots beyond the proximal main vessels nor can it be used to diagnose NOMI. Ultrasound is considered a second-line study for AMI. It is often less useful in the presence of dilated fluid-filled loops of bowel.

2. Some studies show usefulness similar to CT scanning if duplex scanning is performed for MVT. It may show a thrombus or absent flow in the involved arteries or veins. Other possible findings include portal vein gas, biliary disease, free peritoneal fluid, thickened bowel wall, and intramural gas.

Magnetic resonance imaging/magnetic resonance angiography

1. MRI and MRA provide findings similar to CT scan in AMI. Sensitivity of MRA is 100% and specificity is 91%. MRA is particularly effective for evaluating MVT.

2. The main drawbacks are the expense and the time required. In the future, rapid MRA may supplant angiography.

Echocardiography findings may confirm the source of embolization or show valvular pathology.

Other tests

1. Intraoperative fluorescein administration: During laparotomy, 1 g of fluorescein is infused. Viable bowel fluoresces brightly under a Wood lamp. This allows the surgeon to better evaluate the segments that need resection. It may be performed at the primary operation or during a 24-hour second-look operation.

2. ECG may show myocardial infarction or atrial fibrillation.

Procedures

1. Nasogastric tube decompression helps relieve distension and allows evaluation for upper GI bleeding.

2. Diagnostic peritoneal lavage may recover the serosanguineous fluid associated with bowel infarction; this is not a preferred study if AMI is suspected.

3. Foley catheterization allows for monitoring of urinary output as an indicator for minimal fluid resuscitation.

4. In patients with intestinal angina, percutaneous transluminal angioplasty and stenting of the celiac and/or mesenteric arteries have been reported with variable short- and long-term patency rates. A multi-institutional, randomized, controlled clinical trial is needed to define the optimal conditions for their application.

TREATMENT

Medical care

Make all efforts to improve patients' cardiovascular status. Avoid use of vasopressors because they worsen ischemia. Provide oxygen at 100% or by intubation if needed. Fluid resuscitation is accomplished with isotonic sodium chloride solution, and blood products are provided as needed. Adequacy of resuscitation can be monitored by urinary output, central venous pressure, or Swan-Ganz pressure monitoring. Insert a nasogastric tube, and optimize cardiac status by treating arrhythmia, CHF, or myocardial infarction. Start broad-spectrum antibiotics early. Provide pain control while maintaining stable blood pressure.

Angiographically infused papaverine

1. Papaverine infused through the angiogram catheter at the affected vessel is useful for all arterial forms of AMI. It relieves reactive vasospasm in occluded arterial vessels and is the only treatment of NOMI other than resection of gangrenous bowel.

2. Start an infusion of 30–60 mg/h after angiogram, and adjust the dose for clinical response. Continue this for at least 24 hours.

3. If the catheter slips into the aorta, significant hypotension can occur. Papaverine is incompatible with heparin.

Angiographically infused thrombolytics

1. Thrombolytics infused through the angiogram catheter can be a life-saving therapy for selected patients with embolic AMI.

2. Bleeding is the main complication. Thrombolytic administration is risky and should only be undertaken if peritonitis or other signs of bowel necrosis are absent. It must be started within 8 hours of symptom onset.

3. If symptoms do not improve within 4 hours or if peritonitis develops, stop the infusion and perform surgery.

Angioplasty after thrombolysis

1. A very select group of patients who have atherosclerotic plaques at the origin of the SMA after thrombolysis are eligible for angioplasty. Angioplasty is technically difficult because of the anatomy of the SMA. Restenosis rates are 20–50%.

2. Limited study findings indicate a definite role for angioplasty in the treatment of AMI.

Heparin for MVT

1. Heparin anticoagulation is the main treatment of MVT. If no signs of bowel necrosis exist, the patient may not even need an operation. Heparin may increase the chance of bleeding complications. An avenue of study for possible future clinical trials may be the use of enoxaparin (Lovenox) or other low molecular weight heparins as a potential substitute for heparin in the treatment of MVT.

2. Administer heparin as a bolus of 80 U/kg, not to exceed 5000 U, and then as an infusion at 18 U/kg/h until full conversion to oral warfarin. Appropriate monitoring of anticoagulation using activated partial thromboplastin time (aPTT) is mandatory.

3. Percutaneous endovascular interventions.

4. Experience with percutaneous endovascular interventions has been accumulated.

5. In select cases, especially in isolated spontaneous dissection of the SMA, stent placement may offer the best option.

Surgical care

Recognition of AMI before permanent tissue damage occurs is the best way to improve patient survival, and only angiography or exploratory surgery makes early diagnosis possible. Experience with CT and MR angiography is rapidly changing the therapeutic approach, allowing for prompt laparotomy in patients with suspected AMI when expeditious formal angiography is not available. A second-look procedure is indicated whenever bowel of questionable viability is not resected.

• Preoperative care: stabilize patients using IV fluids, antibiotics covering the colonic flora, nasogastric tube decompression, and bladder catheterization, with heparin or papaverine administered as indicated. Blood should be available.

• Operative care: all types of AMI may require resection of necrotic bowel if signs of peritonitis develop. Differentiation of nonviable versus viable bowel can be enhanced by intraoperative fluorescein use. Because of fat absorption, fluorescein can be used only once. Most patients can benefit from a 24- to 48-hour second-look operation to assess for viability of the remaining bowel.

Embolic AMI

• Unless the involved bowel is clearly gangrenous, an attempt at reperfusion is necessary. The SMA is isolated, and the location of the blockage is determined by

palpation of pulses. Because most emboli are near the origin of the middle colic artery, note the proximal SMA pulse in embolic AMI.

• A transverse arteriotomy is made proximal to the point of occlusion, and a balloon-tipped Fogarty catheter (size 3 or 4) is passed distally. The balloon is then inflated and the clot extracted.

• The arteriotomy can be closed primarily or vein-patched to avoid lumen compromise. A bypass may be required if thrombectomy is unsuccessful.

• Observe the intestines for 10–15 minutes after restoration of flow to assess viability of bowel. This can be enhanced by intraoperative duplex ultrasound, fluorescein use, and palpation of pulses distal to the occlusion.

Thrombotic AMI

• Emergency surgical revascularization is indicated. Simple thrombectomy has little or no benefit because most patients have clinically significant atherosclerosis at the time of the acute decompensation. Unlike patients with embolic AMI, these patients have a lesion at the origin of the SMA and no SMA pulsation is detected at the origin.

• If the gut is not irreparably gangrenous, proceed with the revascularization procedure. An antegrade aortomesenteric bypass is the best technique. Transaortic endarterectomy is an alternative when no vein is suitable to harvest or a prosthetic graft is contraindicated (eg, massive fecal contamination). Endarterectomy is more time consuming than thrombectomy and bypass procedures.

• Reevaluate bowel viability after revascularization and thrombectomy.

Mesenteric venous thrombosis

• As for any patient with AMI and signs of peritonitis, including diagnosed NOMI, exploratory laparotomy and resection of infarcted bowel is indicated.

• Thrombectomy has little use in MVT because it can only be performed if the thrombus is fresh (i.e., 1–3 d). In MTV, thrombectomy has little proven effectiveness because the thrombus is usually too widespread and all the thrombi cannot be removed completely.

• Spontaneous dissection of the SMA: When diagnosed before the onset of intestinal infarction, percutaneous stent placement has been successful.

Surgical resection

1. Bowel returned to abdominal cavity and anesthesiologist maximize hemodynamic status for 30–45 min before making definitive assessment of intestinal viability and necessity for bowel resection.

2. Clinical signs (absence peristalsis, bowel wall edema, discoloration of bowel and mesentery, mucosal hemorrhage, absence of bleeding from cut edges) are imprecise markers and may lead to excessive resection.

3. Objective modalities: continuous wave Doppler ultrasound; fluorescein IV with Wood's lamp.

4. All nonviable bowel resected or long segments marginal bowel left in situ with continuity reestablished during second-look procedure 18–24 hrs. later.

Inpatient and outpatient medications

• Papaverine – for patients with arterial occlusive AMI or NOMI.

• Heparin – for patients with MVT or after revascularization.
• Warfarin – for long-term treatment of patients with MVT or atrial fibrillation.
• Broad-spectrum antibiotics and pain medications – for all patients.
• Thrombolytics – for selected patients with embolic AMI.
• Outpatient medications:
• Antiarrhythmics – for patients with atrial fibrillation.
• Warfarin – for long-term treatment of patients with MVT or atrial fibrillation.

Complications

• Bowel necrosis requiring bowel resection.
• Septic shock.
• Death.

Prognosis

The prognosis of AMI of any type is grave. Patients in whom the diagnosis is missed until infarction occurs have a mortality rate of 90%. Even with good treatment, up to 50–80% of patients die. Survivors of extensive bowel resection face lifelong disability. However, with rapid treatment, the mortality rate can be reduced considerably, and patients may be spared bowel resection.

5.3.2. Chronic mesenteric ischemia

Antonio Hodgson first described mesenteric ischemia (as shown in the following image) in the latter part of the 15th century.

During the middle of the 19th century, the medical profession became more interested in this condition. By the turn of the 20th century, many review articles and texts were produced describing the recent advances in both the characterization and treatment of mesenteric ischemia.

In 1901, Schnitzler described a patient with a long history of postprandial abdominal pain. He was found to have an atherosclerotic plaque with an overlying thrombus of the superior mesenteric artery. Schnitzler concluded that if a patient could develop pain in his or her lower extremities secondary to atherosclerosis, the assumption that a patient could present with postprandial pain due to narrowing of the mesenteric vessels would be reasonable.

By the middle of the 20th century, Dunphy hypothesized that mesenteric ischemia was a manifestation of visceral atherosclerosis. In 1958, Shaw and Maynard described the first thromboendarterectomy of the superior mesenteric artery for the treatment of both acute and chronic mesenteric ischemia.

Several other surgical procedures have since been attempted, ranging from reimplantation of the visceral branch into the adjacent aorta to using an autogenous vein graft. In 1972, Stoney and Wylie introduced transaortic visceral thromboendarterectomy and aortovisceral bypass, which have proven to be very effective techniques.

Pathophysiology

In more than 95% of patients, the cause of mesenteric ischemia is diffuse atherosclerotic disease, which decreases the flow of blood to the bowel. As the atherosclerotic disease progresses, symptoms worsen. Usually, all 3 major mesenteric

arteries are occluded or narrowed. Although the pathophysiologic mechanism by which ischemia produces pain is still not completely understood, current physiologic understanding of splanchnic perfusion suggests a key role for the splanchnic circulation in the regulation of cardiovascular homeostasis. Gastrointestinal perfusion is often compromised early relative to other vascular beds in situations including critical illness, major surgery, and exercise, all of which are characterized by increased demands on the circulation to maintain tissue oxygen delivery. Perhaps more importantly, this relative hypoperfusion often outlasts the period of the hypovolemic insult or low-flow state.

CLINICAL

History

Patients typically present with a history of the following:

- Weight loss.
- Postprandial pain, generally epigastric or periumbilical.
- Fear of eating (sitophobia).
- History of vascular disease involving other organs such as myocardial infarction (MI), cerebral vascular disease, or peripheral vascular disease.
- Other nonspecific symptoms include the following:
- Nausea.
- Vomiting.
- Diarrhea.
- Constipation.
- Flatulence.

Physical

Upon physical examination, the following may be found:

- Signs of malnutrition.
- Pain disproportionate to examination findings.
- Usually diffuse mild abdominal tenderness.
- No rebound or guarding.
- Abdominal bruit.
- Signs of peripheral vascular disease, such as carotid bruits, decreased pulses, and ischemic feet.

Causes

Factors that predispose to atherosclerosis are associated with increased risk for chronic mesenteric ischemia. These include the following: smoking, hypertension, diabetes mellitus, hypercholesterolemia (although patients may present with hypocholesterolemia because of their chronic malnourished state).

INVESTIGATIONS

Laboratory Studies

1. CBC count may demonstrate anemia, leukopenia, or lymphopenia secondary to chronic malnourishment.
2. Chemistries may show electrolyte abnormalities from malnutrition, vomiting, or diarrhea.

3. Urinalysis should be performed to rule out stones or infection.

4. Liver function tests may show hypoalbuminemia from malnutrition.

5. If a patient presents with steatorrhea, send stool fat for examination.

6. Preoperative considerations include the following:

- CBC count.
- Chemistries.
- Prothrombin time (PT).
- Activated partial thromboplastin time (aPTT).
- International normalized ratio (INR).

Imaging studies

1. Perform chest radiography to rule out pneumonia (see the image below).

2. Perform dipyridamole-thallium scanning if coronary artery disease is a suspected comorbidity.

3. Arteriography is the criterion standard and will show occlusion (as in the following image, *Fig. 5.11*) of 2 visceral branches of the aorta, with severe stenosis of the remaining visceral branch, usually the celiac or superior mesenteric artery.

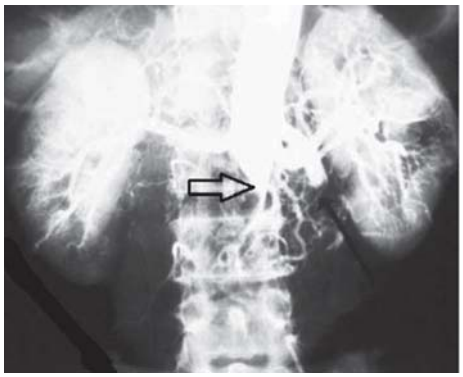


Figure 5.11. *Arteriography: stenosis of the superior mesenteric artery (arrow)*

4. Mesenteric duplex ultrasonography is a noninvasive method of analyzing flow through the vessels and also for assessing vascular patency following visceral bypass grafting or endovascular stenting. Visceral duplex testing of a bypass graft or stent-angioplasty site that shows peak systolic velocities >300 cm/s with end-diastolic velocities >50 to 70 cm/s, or a decreased graft velocity peak systolic velocity <40 cm/s should be considered for interrogation using angiography to confirm or exclude severe (>70%) stenosis. Unfortunately, intraperitoneal gas, respiratory movements, obesity, and any previous abdominal surgeries may limit the sensitivity of this test.

5. Multislice computerized tomography (MSCT) scanning is a noninvasive test which can also play a major role in diagnosing vascular disease of the celiac trunk and superior mesenteric artery in chronic mesenteric ischemia.

6. Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) appears to have great promise as a diagnostic tool. Until the use of fast contrast-enhanced (CE) techniques, an important limitation was the acquisition time of phase-contrast or time-of-flight imaging and the development of motion artifacts. Recent advances in MRA technology have shortened acquisition times, so it is now possible to obtain successive images in the arterial and then the portal phase. MRA can be used as an adjunct to any MR examination.7 Acute mesenteric ischemia is an emergency in which computed tomography scanning is the most appropriate imaging modality. Conversely, chronic mesenteric ischemia is best examined with CE-MRA,

which is almost as accurate as DSA. MRA can also be coupled with measurements of flow. With this functional approach, MRA is the only modality that can completely assess vascular diseases of the abdomen.

TREATMENT

Medical care

1. Because of the high rate of thrombosis, medical management as a sole treatment is warranted only in patients whose risk with surgery outweighs the benefits.

2. Some patients may find short-term relief with nitrate therapy; however, this treatment is not curative.

3. Medical management includes anticoagulation therapy with warfarin.

4. Once a diagnostic arteriogram is obtained and surgery is deemed appropriate, start intra-arterial papaverine to reduce the risk of arterial spasm.

Surgical care

1. After the diagnosis is made by arteriography, patients should undergo surgery because of the risk of continued weight loss, acute infarction, perforation, sepsis, and death.

2. Stenting of visceral vessels has been reported with some success and may be an alternative to surgery.

3. Surgical correction includes: 1) transaortic endarterectomy of the celiac or superior mesenteric artery, 2) retrograde bypass from the external iliac artery, and 3) anterograde bypass, which provides the best orientation of the graft to the aorta.

Mortality/Morbidity

• Chronic mesenteric ischemia by itself does not represent an important cause of mortality.

• Complications, which include acute thrombosis or embolus, are significant causes of increased mortality and are the main reason to revascularize these patients.

• Patients with chronic mesenteric ischemia often present with malnutrition secondary to their fear of postprandial abdominal pain. These patients may have a prolonged hospital course due to their chronic malnourished state.

5.4. INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) refers to chronic conditions that cause inflammation in some part of the intestines.

The intestinal walls become swollen, inflamed, and develop ulcers, which can cause discomfort and serious digestive problems. The exact symptoms depend on which part of the digestive tract is involved.

Types of IBD: Crohn's Disease and Ulcerative Colitis.

Crohn's disease is a form of IBD that can occur anywhere along the digestive tract – from the mouth to the anus. It affects the deeper layers of the digestive lining and can occur as "skip lesions" between healthy areas. Crohn's often involves the small intestine, the colon, or both. Internal tissues may develop shallow, crater-like areas or deeper sores and a cobblestone pattern, as seen here.

Unlike Crohn's disease, ulcerative colitis only involves the colon and rectum. Inflammation and ulcers typically affect only the innermost lining in these areas, compared with the deeper lesions seen in Crohn's disease. Often only the lower (sigmoid) colon is affected, but it can occur higher up, too. The more of the colon that is affected, the worse the symptoms will be.

5.4.1. Crohn's disease

Crohn's disease is a chronic inflammatory disease of the intestines (*Fig. 5.12*). It primarily causes ulcerations (breaks in the lining) of the small and large intestines, but can affect the digestive system anywhere from the mouth to the anus. It is named after the physician who described the disease in 1932. It also is called granulomatous enteritis or colitis, regional enteritis, ileitis, or terminal ileitis.

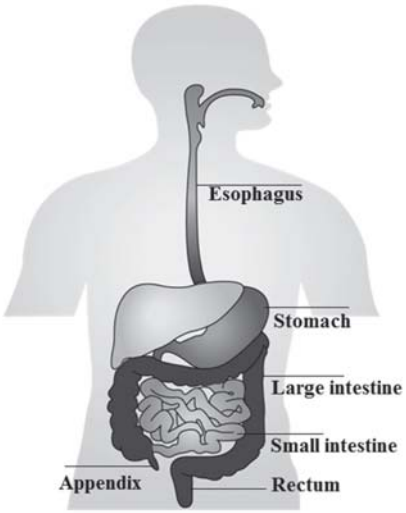


Figure 5. 12. *Crohn's disease is an inflammatory bowel disorder that may affect any part of the gastro-intestinal tract. The inflammation penetrates the lining of the gastro-intestinal tract and often causes ulcers to form*

Microscopy

• Characteristic granuloma of Crohn's disease composed of epithelioid histiocytes (*Fig. 5.13*).

• The granulomas are often found in lymph nodules.

• Giant cells are not necessary for the diagnosis of granuloma, and necrosis in the granuloma is not seen.

Causes of Crohn's disease

The cause of Crohn's disease is unknown. Some scientists suspect that infection by certain bacteria, such as strains of mycobacterium, may be the cause of Crohn's disease. To date, however, there has been no convincing evidence that the disease is caused by infection. Crohn's disease is not contagious. Although diet may affect the symptoms in patients with Crohn's disease, it is unlikely that diet is responsible for the disease.

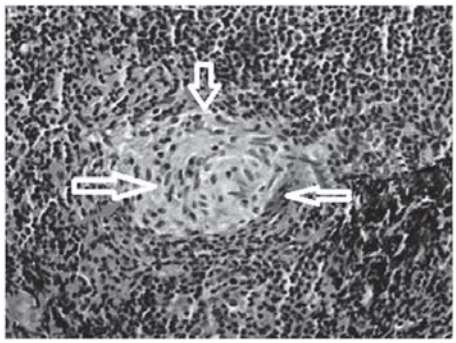


Figure 5.13. *Microscopy: granuloma of Crohn's disease (arrows)*

Activation of the immune system in the intestines appears to be important in IBD. The immune system is composed of immune cells and the proteins that these immune cells produce. Normally, these cells and proteins defend the body against harmful bacteria, viruses, fungi, and other foreign invaders. Activation of the immune system causes

inflammation within the tissues where the activation occurs. (Inflammation is an important mechanism of defense used by the immune system.)

Normally, the immune system is activated only when the body is exposed to harmful invaders. In patients with IBD, however, the immune system is abnormally and chronically activated in the absence of any known invader. The continued abnormal activation of the immune system results in chronic inflammation and ulceration. The susceptibility to abnormal activation of the immune system is genetically inherited. Thus, first degree relatives (brothers, sisters, children, and parents) of patients with IBD are more likely to develop these diseases. Recently a gene called NOD2 has been identified as being associated with Crohn's disease. This gene is important in determining how the body responds to some bacterial products. Individuals with mutations in this gene are more susceptible to developing Crohn's disease.

In the early stages, Crohn's disease causes small, scattered, shallow, crater-like areas (erosions) on the inner surface of the bowel. These erosions are called aphthous ulcers. With time, the erosions become deeper and larger, ultimately becoming true ulcers (which are deeper than erosions) and causing scarring and stiffness of the bowel. As the disease progresses, the bowel becomes increasingly narrowed, and ultimately can become obstructed. Deep ulcers can puncture holes in the wall of the bowel, and bacteria from within the bowel can spread to infect adjacent organs and the surrounding abdominal cavity.

When Crohn's disease narrows the small intestine to the point of obstruction, the flow of the contents through the intestine ceases. Sometimes, the obstruction can be caused suddenly by poorly-digestible fruit or vegetables that plug the already-narrowed segment of the intestine. When the intestine is obstructed, digesting food, fluid and gas from the stomach and the small intestine cannot pass into the colon. The symptoms of small intestinal obstruction then appear, including severe abdominal cramps, nausea, vomiting, and abdominal distention. Obstruction of the small intestine is much more likely since the small intestine is much narrower than the colon to begin with.

Deep ulcers can puncture holes in the walls of the small intestine and the colon, and create a tunnel between the intestine and adjacent organs. If the ulcer tunnel reaches an adjacent empty space inside the abdominal cavity, a collection of infected pus (an abdominal abscess) is formed. Patients with abdominal abscesses can develop tender abdominal masses, high fevers, and abdominal pain.

When the ulcer tunnels into an adjacent organ, a channel (fistula) is formed. The formation of a fistula between the intestine and the bladder (enteric-vesicular fistula) can cause frequent urinary tract infections and the passage of gas and feces during urination. When a fistula develops between the intestine and the skin (enteric-cutaneous fistula), pus and mucous emerge from a small painful opening on the skin of the abdomen. The development of a fistula between the colon and the vagina (colonic-vaginal fistula) causes gas and feces to emerge through the vagina. The presence of a fistula from the intestines to the anus (anal fistula) leads to a discharge of mucous and pus from the fistula's opening around the anus.

Summary

The etiology of Crohn's Disease is unknown. The search for an etiology has focused on the following areas:

1. Infectious agents – M.paratuberculosis has received the most attention although the findings are inconclusive.

2. Diet – a disordered immune response to some ingested antigen has been considered but no definite food antigen has been identified.

3. Genetic – the strong concordance in monozygotic twins and not in dizygotic in contrast to the lack of any association in Ulcerative Colitis has not resulted in any specific gene abnormality being identified. In addition there is a tenfold risk among first degree relatives.

4. Immune – there is increasing evidence that an abnormal immune response to unspecified and possible non-specific antigens, may result in abnormal up-regulation and down-regulation of inflammatory mediators leading to the inflammatory tissue changes which are the hallmark of the disease.

5. It is possible that the etiology of this disease is multifactorial with the common pathway being abnormal regulation of inflammatory mediators.

CLINICAL

Common symptoms of Crohn's disease include abdominal pain, diarrhea, and weight loss. Less common symptoms include poor appetite, fever, night sweats, rectal pain, and rectal bleeding. The symptoms of Crohn's disease are dependent on the location, the extent, and the severity of the inflammation. The different subtypes of Crohn's disease and their symptoms are:

Crohn's colitis is inflammation that is confined to the colon. Abdominal pain and bloody diarrhea are the common symptoms. Anal fistulae and peri-rectal abscesses also can occur.

Crohn's enteritis refers to inflammation confined to the small intestine (the first part, called the jejunum or the second part, called the ileum). Involvement of the ileum alone is referred to as Crohn's ileitis. Abdominal pain and diarrhea are the common symptoms. Obstruction of the small intestine also can occur.

Crohn's terminal ileitis is inflammation that affects only the very end of the small intestine (terminal ileum), the part of the small intestine closest to the colon. Abdominal pain and diarrhea are the common symptoms. Small intestinal obstruction also can occur.

Crohn's entero-colitis and ileo-colitis are terms to describe inflammation that involve both the small intestine and the colon. Bloody diarrhea and abdominal pain are the common symptoms. Small intestinal obstruction also can occur.

Crohn's terminal ileitis and ileo-colitis are the most common types of Crohn's disease. (Ulcerative colitis frequently involves only the rectum or rectum and sigmoid colon at the distal end of the colon. These are called ulcerative proctitis and procto-sigmoiditis, respectively).

Up to one third of patients with Crohn's disease may have one or more of the following conditions involving the anal area:

Swelling of the tissue of the anal sphincter, the muscle at the end of the colon that controls defecation.

1. Development of ulcers and fissures (long ulcers) within the anal sphincter. These ulcers and fissures can cause bleeding and pain with defecation.

2. Development of anal fistulae (abnormal tunnels) between the anus or rectum and the skin surrounding the anus). Mucous and pus may drain from the openings of the fistulae on the skin.

3. Development of peri-rectal abscesses (collections of pus in the anal and rectal area). Peri-rectal abscesses can cause fever, pain and tenderness around the anus.

INVESTIGATIONS

Laboratory Studies

The diagnosis of Crohn's disease is suspected in patients with fever, abdominal pain and tenderness, diarrhea with or without bleeding, and anal diseases. Laboratory blood tests may show elevated white cell counts and sedimentation rates, both of which suggest infection or inflammation. Other blood tests may show low red blood cell counts (anemia), low blood proteins, and low body minerals, reflecting loss of these elements due to chronic diarrhea.

X-ray

Barium X-ray studies can be used to define the distribution, nature, and severity of the disease (*Fig. 5.14*).

Barium is a chalky material that is visible by x-ray and appears white on X-ray films. When barium is ingested orally (upper GI series) it fills the intestine and pictures (X-rays) can be taken of the stomach and the small intestines. When barium is administered through the rectum (barium enema), pictures of the colon and the terminal ileum can be obtained. Barium X-rays can show ulcerations, narrowing, and, sometimes, fistulae of the bowel (*Fig. 5.15*).

Computerized axial tomography (CAT or CT) scanning is a computerized X-ray technique that allows imaging of the entire abdomen and pelvis (*Fig. 5.16*). It can be especially helpful in detecting abscesses.

Figure 5.14. *Barium X-ray*

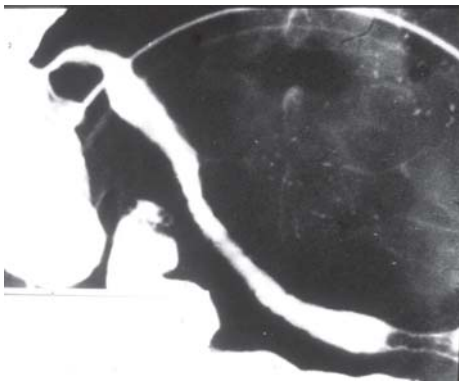


Figure 5.15. *"String sign" on X-ray from narrowed gut lumen*

Colonoscopy

Direct visualization of the rectum and the large intestine can be accomplished with flexible viewing tubes (colonoscopes). Colonoscopy is more accurate than barium X-rays in detecting small ulcers or small areas of inflammation of the colon and terminal ileum. Colonoscopy also allows for small tissue samples (biopsies) to be taken and sent for examination under the microscope to confirm the diagnosis of Crohn's disease. Colonoscopy also is more accurate than barium X-rays in assessing the degree (activity) of inflammation.

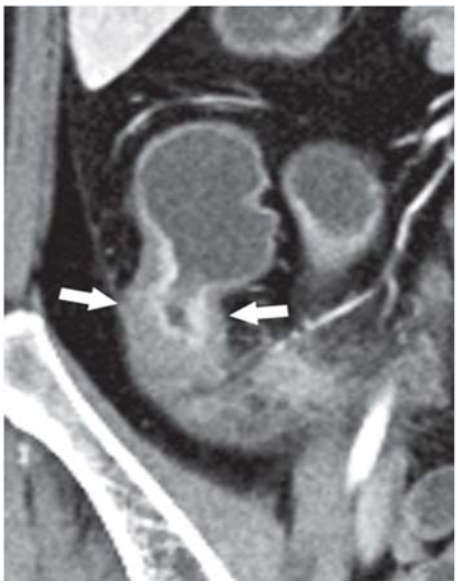


Figure 5.16. *Coronal enteric phase CT enterographic image shows mural hyperenhancement, mural stratification, and wall thickening in terminal ileum (arrows)*

Most recently, video capsule endoscopy has been added to the list of diagnostic tests for diagnosing Crohn's disease. For video capsule endoscopy, a capsule containing a miniature video camera is swallowed. As the capsule travels through the small intestine, it sends video images of the lining of the small intestine to a receiver carried on a belt at the waist. The images are downloaded and then reviewed on a computer. The value of video capsule endoscopy is that it can identify the early, mild abnormalities of Crohn's disease. Video capsule endoscopy may be particularly useful when there is a strong suspicion of Crohn's disease but the barium X-rays are normal. (Barium X-rays are not as good at identifying early, mild Crohn's disease.)

Video capsule endoscopy should not be performed in patients who have obstruction of the small intestine. The capsule may get stuck behind the obstruction and make the obstruction worse. Doctors usually also are reluctant to perform video-capsule endoscopy for the same reason in patients who they suspect of having small intestinal strictures (narrowed segments of small intestine that can result from prior surgery, prior radiation, or chronic ulceration, for example, from Crohn's disease).

Complications of Crohn's disease

Complications of Crohn's disease may be related or unrelated to the inflammation within the intestine (such as intestinal or extra-intestinal) (*Fig. 5.17*).

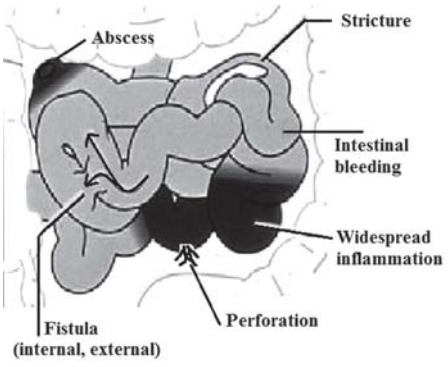


Figure 5.17. *Intestinal complications of Crohn's disease*

Intestinal complications of Crohn's disease include obstruction (*Fig. 5.18*) and perforation of the small intestine, abscesses (collections of pus), fistulae (*Fig. 5.19*), and intestinal bleeding. Massive distention or dilatation of the colon (megacolon), and rupture (perforation) of the intestine are potentially life-threatening complications. Both generally require surgery, but, fortunately, these two complications are rare. Recent data suggest that there is an increased risk of cancer of the small intestine and colon in patients with long-standing Crohn's disease.

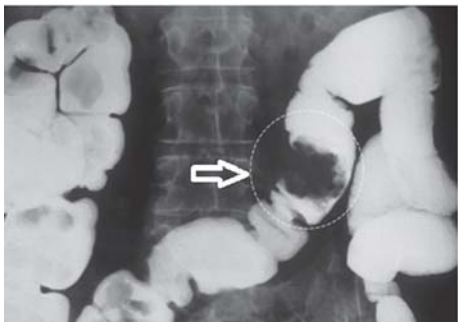


Figure 5.18. *The bowel obstruction (arrow)*

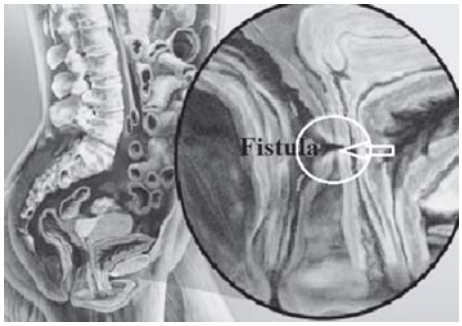


Figure 5.19. *The bowel fistula (arrow)*

Extra-intestinal complications involve the skin, joints, spine, eyes, liver, and bile ducts. Skin involvement includes painful red raised spots on the legs (erythema nodosum) and an ulcerating skin condition generally found around the ankles called pyoderma gangrenosum. Painful eye conditions (uveitis, episcleritis) can cause visual difficulties. Arthritis can cause pain, swelling, and stiffness of the joints of the extremities. Inflammation of the low back (sacroiliac joint arthritis) and of the spine (ankylosing spondylitis) can cause pain and stiffness of the spine. Inflammation of the liver (hepatitis) or bile ducts (primary sclerosing cholangitis) also can occur. Sclerosing cholangitis causes are narrowing and obstruction of the ducts draining the liver and can lead to yellow skin (jaundice), recurrent bacterial infections, and liver cirrhosis with liver failure. Sclerosing cholangitis with liver failure is one of the reasons for performing liver transplantation. Sclerosing cholangitis frequently is complicated by the development of cancer of the bile ducts.

Differential diagnosis

The differential diagnosis of Crohn's disease includes:

• *Ulcerative colitis*. In 10 to 20% of cases the two diseases cannot be differentiated. Distinguishing features include rectal involvement and bloody diarrhoea in UC, continuous disease pathology, but no strictures or fistulae. In UC there is a low plasma IL-6 in the active disease, and there is a stronger association with non-smokers. Also, UC patients are more often p-ANCA positive.

• *Irritable bowel syndrome*. This has no radiological abnormalities or weight loss.

• *Gastrointestinal malignancy*. The most important cancers here are lymphoma, right colonic cancer and small bowel cancer. These patients might be expected to have night sweats and anaemia. Radiologically there may be a mass and metastases.

• *Ileal tuberculosis*. This should be investigated for with a stool culture, and might be suspected in the immigrant population. Pathologically, after laparoscopic biopsy there will be caseating granulomas and mesenteric tubercules.

• *Anorexia nervosa*.

• *Coeliac disease* – this will cause a malabsorptive picture.

• *Chronic infection* with Giardia, Yersinia and Campylobacter.

• *Amyloidosis*.

• *Behcet's disease*.

• *Whipple's disease*.

TREATMENT

Medical care

The symptoms and severity of Crohn's disease vary among patients. Patients with mild or no symptoms may not need treatment. Patients whose disease is in remission (where symptoms are absent) also may not need treatment.

There is no medication that can cure Crohn's disease. Patients with Crohn's disease typically will experience periods of relapse (worsening of inflammation) followed by periods of remission (reduced inflammation) lasting months to years. During relapses, symptoms of abdominal pain, diarrhea, and rectal bleeding worsen. During remissions, these symptoms improve. Remissions usually occur because of treatment with medications or surgery, but occasionally they occur spontaneously without any treatment (*Fig. 5.20*).

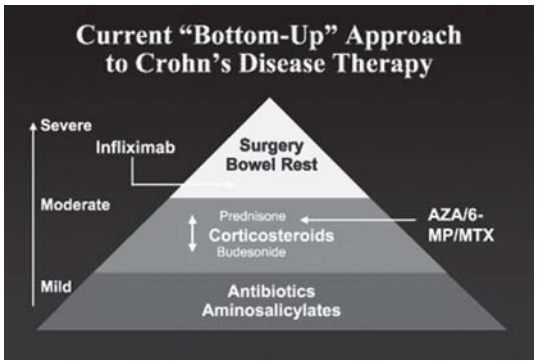


Figure 5.20. *Current "Bottom-up" approach to Crohn's disease therapy*

Since there is no cure for Crohn's disease, the goals of treatment are to 1) induce remissions, 2) maintain remissions, 3) minimize side effects of treatment, and 4) improve the quality of life. Treatment of Crohn's disease and ulcerative colitis with medications is similar though not always identical.

Medications for treating Crohn's disease include 1) antiinflammatory agents such as 5-ASA compounds, corticosteroids, topical antibiotics, 2) immuno-modulators, 3) other medications.

Antiinflammatory medications. Antiinflammatory medications that decrease intestinal inflammation are analogous to arthritis medications that decrease joint inflammation. Different types of antiinflammatory medications used in the treatment of Crohn's disease are:

5-ASA compounds such as sulfasalazine (Azulfidine) and mesalamine (Pentasa, Asacol, Dipentum, Colazal, Rowasa enema, Canasa suppository) that act via direct contact (topically) with the inflamed tissue in order to be effective.

Corticosteroids that act systemically (without the need for direct contact with the inflamed tissue) to decrease inflammation throughout the body. Systemic corticosteroids have important and predictable side effects if used long-term.

A new class of topical corticosteroid (for example, budesonide) that acts via direct contact (topically) with the inflamed tissue. This class of corticosteroids has fewer side effects than systemic corticosteroids which are absorbed into the body.

Antibiotics such as metronidazole (Flagyl) and ciprofloxacin (Cipro) that decrease inflammation by an unknown mechanism.

5-ASA (mesalamine) oral medications. 5-aminosalicylic acid (5-ASA), also called mesalamine, is similar chemically to aspirin. Aspirin has been used for many years for treating arthritis, bursitis, and tendonitis (conditions of tissue inflammation). Aspirin, however, is not effective in treating Crohn's disease and ulcerative colitis, and even may worsen the inflammation. On the other hand, 5-ASA can be effective in treating Crohn's disease and ulcerative colitis if the drug can be delivered topically onto the inflamed intestinal lining. For example, mesalamine (Rowasa) is an enema containing 5-ASA that is effective in treating inflammation in the rectum. However, the enema solution cannot reach high enough to treat inflammation in the upper colon and the small intestine. Therefore, for most patients with Crohn's disease involving both the ileum (distal small intestine) and colon, 5-ASA must be taken orally.

If pure 5-ASA is taken orally, however, most of the 5-ASA would be absorbed in the stomach and the upper small intestine, and very little 5-ASA would reach the ileum and colon. To be effective as an oral agent in treating Crohn's disease, 5-ASA has to be modified chemically to escape absorption by the stomach and the upper intestines.

Sulfasalazine (Azulfidine). Sulfasalazine (Azulfidine) was the first modified 5-ASA compound used in the treatment of Crohn's colitis and ulcerative colitis. It has been used successfully for many years to induce remissions among patients with mild to moderate ulcerative colitis. Sulfasalazine also has been used for prolonged periods for maintaining remissions.

Sulfasalazine consists of a 5-ASA molecule linked chemically to a sulfapyridine molecule. (Sulfapyridine is a sulfa antibiotic.) Connecting the two molecules together prevents absorption by the stomach and the upper intestines. When sulfasalazine reaches the ileum and the colon, the bacteria that normally are present break the link between the two molecules. After breaking away from 5-ASA, sulfapyridine is absorbed into the body and later eliminated in the urine. Most of the active 5-ASA, however, is available within the terminal ileum and colon to treat the colitis.

Most of the side effects of sulfasalazine are due to the sulfapyridine molecule. These side effects include nausea, heartburn, headache, anemia, skin rashes, and, in rare instances, hepatitis and kidney inflammation. In men, sulfasalazine can reduce the sperm count. The reduction in sperm count is reversible, and the count usually becomes normal after the sulfasalazine is discontinued or changed to a different 5- ASA compound.

Because the newer 5-ASA compounds [for example, mesalamine (Asacol and Pentasa)] do not have the sulfapyridine component and have fewer side effects than sulfasalazine, they are being used more frequently in treating Crohn's disease and ulcerative colitis.

Asacol. Asacol is a tablet consisting of the 5-ASA compound surrounded by an acrylic resin coating. Asacol is sulfa-free. The resin coating prevents the 5-ASA from being absorbed as it passes through the stomach and the small intestine. When the tablet reaches the terminal ileum and the colon, the resin coating dissolves, and the active 5-ASA drug is released.

Asacol is effective in inducing remissions in patients with mild to moderate ulcerative colitis. It also is effective when used in the longer term to maintain remissions. Some studies have shown that Asacol also is effective in treating Crohn's ileitis and ileo-colitis, as well as in maintaining remission in patients with Crohn's disease.

The recommended dose of Asacol for inducing remissions is two 400 mg tablets three times daily (a total of 2.4 grams a day). At least two tablets of Asacol twice daily (1.6 grams a day) is recommended for maintaining remission. Occasionally, the maintenance dose is higher.

As with Azulfidine, the benefits of Asacol are dose-related. If patients do not respond to 2.4 grams a day of Asacol, the dose frequently is increased to 3.6–4.8 grams a day to induce remission. If patients fail to respond to the higher doses of Asacol, then other alternatives such as corticosteroids are considered.

Pentasa. Pentasa is a capsule consisting of small spheres containing 5-ASA. Pentasa is sulfa-free. As the capsule travels down the intestines, the 5-ASA inside the spheres is released slowly into the intestine. Unlike Asacol, the active drug 5-ASA in Pentasa is released into the small intestine as well as the colon. Therefore, Pentasa can be effective in treating inflammation in the small intestine and is currently the most commonly used 5-ASA compound for treating mild to moderate Crohn's disease in the small intestine.

Patients with Crohn's disease occasionally undergo surgery to relieve small intestinal obstruction, drain abscesses, or remove fistulae. Usually, the diseased portions of the intestines are removed during surgery. After successful surgery, patients can be free of disease and symptoms (in remission) for a while. In many patients, however, Crohn's disease eventually returns. Pentasa helps maintain remissions and reduces the chances of the recurrence of Crohn's disease after surgery.

In the treatment of Crohn's ileitis or ileocolitis, the dose of Pentasa usually is four 250 mg capsules four times daily (a total of 4 grams a day). For maintenance of remission in patients after surgery, the dose of Pentasa is between 3–4 grams daily.

Olsalazine (Dipentum). Olsalazine (Dipentum) is a capsule in which two molecules of 5-ASA are joined together by a chemical bond. In this form, the 5-ASA cannot be absorbed from the stomach and intestine. Intestinal bacteria are able to break apart the two molecules releasing the active individual 5-ASA molecules into the intestine. Since intestinal bacteria are more abundant in the ileum and colon, most of the active 5-ASA is released in these areas. Therefore, olsalazine is most effective for disease that is limited to the ileum or colon. Although clinical studies have shown that olsalazine is effective for maintenance of remission in ulcerative colitis, up to 11% of patients experience diarrhea when taking olsalazine. Because of this, olsalazine is not often used. The recommended dose of olsalazine is 500 mg twice a day.

Balsalazide (Colazal). Balsalazide (Colazal) is a capsule in which the 5-ASA is linked by a chemical bond to another molecule that is inert (without effect on the intestine) and prevents the 5-ASA from being absorbed. This drug is able to travel through the intestine unchanged until it reaches the end of the small bowel (terminal ileum) and colon. There, intestinal bacteria break apart the 5-ASA and the inert molecule releasing the 5-ASA. Because intestinal bacteria are most abundant in the terminal ileum and colon, balsalazide is used to treat inflammatory bowel disease predominantly localized to the colon.

Side effects of oral 5-ASA compounds. The 5-ASA compounds have fewer side effects than Azulfidine and also do not reduce sperm counts. They are safe medications for long-term use and are well-tolerated.

Patients allergic to aspirin should avoid 5-ASA compounds because they are similar chemically to aspirin.

Rare kidney and lung inflammation has been reported with the use of 5-ASA compounds. Therefore, 5-ASA should be used with caution in patients with kidney disease. It also is recommended that blood tests of kidney function be done before starting and periodically during treatment.

Rare instances of worsening of diarrhea, cramps, and abdominal pain, at times accompanied by fever, rash, and malaise, may occur. This reaction is believed to represent an allergy to the 5-ASA compound.

5-ASA rectal medications (Rowasa Canasa). Rowasa is 5-ASA in enema form. 5-ASA by enema is most useful for treating ulcerative colitis involving only the distal colon since the enema easily can reach the inflamed tissues of the distal colon. Rowasa also is used in treating Crohn's disease in which there is inflammation in and near the rectum. Each Rowasa enema contains 4 grams of 5-ASA. The enema usually is administered at bedtime, and patients are encouraged to retain the enema through the night. The enema contains sulfite and should not be used by patients with sulfite allergy. Otherwise, Rowasa enemas are safe and well-tolerated.

Canasa is 5-ASA in suppository form. It is used for treating ulcerative proctitis. Each suppository contains 500 mg of 5-ASA and usually is administered twice daily.

Both enemas and suppositories have been shown to be effective in maintaining remission in patients with ulcerative colitis limited to the distal colon and rectum.

Corticosteroids. Corticosteroids (for example, prednisone, prednisolone, hydrocortisone, etc.) have been used for many years to treat patients with moderate to severe Crohn's disease and ulcerative colitis and to treat patients who fail to respond to 5-ASA. Unlike 5-ASA, corticosteroids do not require direct contact with the inflamed intestinal tissues to be effective.

Oral corticosteroids are potent antiinflammatory medications. After absorption, corticosteroids exert prompt antiinflammatory actions throughout the body, including the intestines. Consequently, they are used in treating Crohn's disease anywhere in the small intestine, as well as ulcerative and Crohn's colitis. In critically ill patients, intravenous corticosteroids (such as hydrocortisone) can be given in the hospital. For patients with proctitis, hydrocortisone enemas (Cortenema) can be used to deliver the corticosteroid directly to the inflamed tissue. By using the corticosteroid topically, less of it is absorbed into the body and the frequency and severity of side effects are lessened (but not eliminated) as compared with systemic corticosteroids.

Corticosteroids are faster-acting than 5-ASA, and patients frequently experience improvement in their symptoms within days of beginning them. Corticosteroids, however, do not appear to be useful in maintaining remission in Crohn's disease and ulcerative colitis or in preventing the return of Crohn's disease after surgery.

Side effects of corticosteroids. The frequency and severity of side effects of corticosteroids depend on the dose and duration of their use. Short courses of corticosteroids, for example, usually are well-tolerated with few and mild side effects. Long-term use of high doses of corticosteroids usually produces predictable and potentially serious side effects. Common side effects include: rounding of the face (moon face), acne, increased body hair, diabetes, weight gain, high blood pressure,cataracts, glaucoma, increased susceptibility to infections, muscle weakness, depression, insomnia, mood swings, personality changes, irritability, and thinning of the bones (osteoporosis) with fractures of the spine.

Children receiving corticosteroids experience stunted growth.

The most serious complication from long term corticosteroid use is aseptic necrosis of the hip joints. Aseptic necrosis is a condition in which there is death and degeneration of the hip bone. It is a painful condition that can ultimately lead to the need for surgical replacement of the hip. Aseptic necrosis also has been reported in the knee joints. It is not known how corticosteroids cause aseptic necrosis. The estimated incidence of aseptic necrosis among corticosteroid users is 3–4%. Patients on corticosteroids who develop pain in the hips or knees should report the pain to their doctors promptly. Early diagnosis of aseptic necrosis with cessation of corticosteroids might decrease the severity of the aseptic necrosis and the need for hip replacement surgery.

Prolonged use of corticosteroids can depress the ability of the body's adrenal glands to produce cortisol (a natural corticosteroid necessary for proper functioning of the body). Therefore, abruptly discontinuing corticosteroids can cause symptoms due to a lack of natural cortisol (a condition called adrenal insufficiency). Symptoms of adrenal insufficiency include nausea, vomiting, and even shock. Withdrawing corticosteroids too quickly also can produce symptoms of joint pain, fever, and malaise. Therefore, when corticosteroids are discontinued, the dose usually is tapered gradually rather than stopped abruptly.

Even after corticosteroids are discontinued, the adrenal glands' ability to produce cortisol can remain depressed from months up to two years. The depressed adrenal glands may not be able to produce increased amounts of cortisol to help the body handle the stress of accidents, surgery, and infections. Therefore, patients need additional corticosteroids during stressful situations to avoid developing adrenal insufficiency. Because corticosteroids are not useful in maintaining remission in ulcerative colitis and Crohn's disease, and because they have predictable and potentially serious side effects, they should be used for the shortest possible length of time.

Proper use of corticosteroids. Once the decision is made to use systemic corticosteroids, treatment usually is initiated with prednisone, 40–60 mg daily. The majority of patients with

Crohn's disease respond with an improvement in symptoms within a few weeks. Once symptoms have improved, prednisone is reduced by 5–10 mg per week until a dose of 20 mg per day is reached. The dose then is reduced at a slower rate until the corticosteroid is discontinued. Gradually reducing corticosteroids not only minimizes the symptoms of adrenal insufficiency, it also reduces the chances of an abrupt recurrence of inflammation.

Many doctors use 5-ASA compounds and corticosteroids together. In patients who achieve remission with corticosteroids, 5-ASA compounds often are continued alone to maintain remission.

In patients whose symptoms return corticosteroids are slowly being reduced, the dose of corticosteroids is increased slightly to control the symptoms. Once the symptoms are under control, the reduction of corticosteroids can resume at a slower pace. Unfortunately, many patients who require corticosteroids to induce remissions become corticosteroid dependent. These patients consistently develop symptoms whenever the corticosteroid dose falls below a certain level. In such patients who are corticosteroid dependent as well as in patients who are unresponsive to corticosteroids and other anti-inflammatory medications, immuno-modulator medications or surgery must be considered. The management of patients who are corticosteroid dependent or patients with severe disease that responds poorly to medications is complex. Doctors who are experienced in treating ulcerative colitis and Crohn's disease and in using immuno-modulators should evaluate these patients.

Prevention of osteoporosis. Long-term use of corticosteroids can cause osteoporosis. Calcium is very important in the formation and maintenance of healthy bones. Corticosteroids decrease the absorption of calcium from the intestine and increase the loss of calcium from the kidneys. Increasing dietary calcium intake is important but alone cannot halt corticosteroid-induced osteoporosis. To prevent or minimize osteoporosis, management of patients on long-term corticosteroids should include:

Adequate intake of calcium (1000 mg daily in premenopausal women, 1,500 mg daily in postmenopausal women) and vitamin D (800 units daily).

Periodic review with the doctor of the need for continued corticosteroid treatment and use of the lowest effective dose if continued treatment is necessary.

For patients taking corticosteroids for more than three months, a bone density study may be helpful in determining the extent of bone loss and the need for more aggressive treatment.

Regular weight-bearing exercise and stopping smoking (cigarettes).

Discussion with the doctor regarding the use of alendronate (Fosamax), risedronate (Actonel), or etidronate (Didronel) to prevent or treat corticosteroid-induced osteoporosis.

Budesonide (Entocort EC). Budesonide (Entocort EC) is a new type of corticosteroid for treating Crohn's disease. Like other corticosteroids, budesonide is a potent anti-inflammatory medication. Unlike other corticosteroids, however, budesonide acts only via direct contact with the inflamed tissues (topically) and not systemically. As soon as budesonide is absorbed into the body, the liver converts it into inactive chemicals. Therefore, for effective treatment of Crohn's disease, budesonide, like topical 5-ASA, must be brought into direct contact with the inflamed intestinal tissue.

Budesonide capsules contain granules that allow a slow release of the drug into the ileum and the colon. In a double-blind multicenter study (published in 1998), 182 patients with Crohn's ileitis and/or Crohn's disease of the right colon were treated with either budesonide (9 mg daily) or Pentasa (2 grams twice daily). Budesonide was more effective than Pentasa in inducing remissions while the side effects were similar to Pentasa. In another study comparing the effectiveness of budesonide with corticosteroids, budesonide was not better than corticosteroids in treating Crohn's disease but had fewer side effects.

Because budesonide is broken down by the liver into inactive chemicals, it has fewer side effects than systemic corticosteroids. It also suppresses the adrenal glands less than systemic corticosteroids. Budesonide will be available as an enema for the treatment of proctitis.

Budesonide has not been shown to be effective in maintaining remission in patients with Crohn's disease. If used long-term, budesonide also may cause some of the same side effects as corticosteroids. Because of this, the use of budesonide should be limited to short-term treatment for inducing remission. Most budesonide is released in the terminal ileum, it will have its best results in Crohn's disease limited to the terminal ileum.

It is not known whether budesonide is effective in treating patients with ulcerative colitis, and it is currently not recommended for the treatment of ulcerative colitis.

Antibiotics for Crohn's disease. Antibiotics such as metronidazole and ciprofloxacin have been used for treating Crohn's colitis. Flagyl also has been useful in treating anal fistulae in patients with Crohn's disease. The mechanism of action of these antibiotics in Crohn's disease is not well understood.

Summary of antiinflammatory medications. Azulfidine, Asacol, Pentasa, Dipentum, Colazal and Rowasa all contain 5-ASA which is the active topical antiinflammatory ingredient. Azulfidine was the first 5-ASA medication used in treating ulcerative colitis and Crohn's disease, but the newer 5-ASA medications have fewer side effects.

Pentasa and Asacol have been found to be effective in treating patients with Crohn's ileitis and ileo-colitis. Rowasa enemas and Canasa suppositories are safe and effective for treating patients with proctitis. For mild to moderate Crohn's ileitis or ileo-colitis, doctors usually start with Pentasa or Asacol. If Pentasa or Asacol is ineffective, doctors may try antibiotics such as Cipro or Flagyl for prolonged periods (often months).

In patients with moderate to severe disease and in patients who fail to respond to 5-ASA compounds and/or antibiotics, systemic corticosteroids can be used. Systemic corticosteroids are potent and fast-acting anti-inflammatory agents for treating Crohn's enteritis and colitis as well as ulcerative colitis.

Systemic corticosteroids are not effective in maintaining remission in patients with Crohn's disease. Serious side effects can result from prolonged corticosteroid treatment.

To minimize side effects, corticosteroids should be gradually tapered as soon as a remission is achieved. In patients who become corticosteroid dependent or are unresponsive to corticosteroid treatment, surgery or immuno-modulator treatment is considered.

A new class of topical corticosteroids (budesonide) may have fewer side effects than systemic corticosteroids.

Immuno-modulator medications. Immuno-modulators are medications that affect the body's immune system. The immune system is composed of immune cells and the proteins that they produce. These cells and proteins serve to protect the body against harmful bacteria, viruses, fungi, and other foreign invaders. Activation of the immune system causes inflammation within the tissues where the activation occurs. (Inflammation is, in fact, an important mechanism used by the immune system to defend the body.) Normally, the immune system is activated only when the body is exposed to foreign invaders. In patients with Crohn's disease and ulcerative colitis, however, the immune system is abnormally and chronically activated in the absence of any known invader.

Immuno-modulators decrease tissue inflammation by reducing the population of immune cells and/or by interfering with their production of proteins. Decreasing the activity of the immune system with immuno-modulators increases the risk of infections; however, the benefits of controlling moderate to severe Crohn's disease usually outweigh the risks of infection due to weakened immunity. Examples of immuno-modulators are 6-mercaptopurine (6-MP), azathioprine (Imuran), methotrexate (Rheumatrex, Trexall), infliximab (Remicade), adalimumab (Humira).

Azathioprine (Imuran) and 6-mercaptopurine (6-MP, Purinethol). Azathioprine (Imuran) and 6-mercaptopurine (6-MP, Purinethol) are medications that weaken the body's immune system by reducing the population of a class of immune cells called lymphocytes. Azathioprine and 6-MP are related chemically. (Actually, azathioprine is converted into 6-MP within the body.) In high doses, these two drugs have been useful in preventing rejection of transplanted organs

and in treating leukemia. In low doses, they have been used for many years to treat patients with moderate to severe Crohn's disease and ulcerative colitis.

Azathioprine and 6-MP are increasingly recognized by doctors as valuable drugs in treating Crohn's disease and ulcerative colitis. Some 70% of patients with moderate to severe disease will benefit from these drugs. Azathioprine and 6-MP are used primarily in the following situations:

Severe Crohn's disease and ulcerative colitis not responding to corticosteroids.

The presence of undesirable corticosteroid-related side effects.

Corticosteroid dependency, a condition in which patients are unable to discontinue corticosteroids without developing relapses of their disease.

Maintenance of remission.

When azathioprine and 6-MP are added to corticosteroids in the treatment of Crohn's disease not responding to corticosteroids alone, there may be an improved response. Also, smaller doses and shorter courses of corticosteroids may be able to be used. Some patients can discontinue corticosteroids altogether without experiencing relapses of their disease. This corticosteroid-lowering effect has earned azathioprine and 6-MP their reputation as "steroid-sparing" medications.

In Crohn's disease patients with severe disease who suffer frequent relapses, 5-ASA may not be sufficient, and the more potent azathioprine and 6-MP will be necessary to maintain remissions. In the lower doses used to treat Crohn's disease, the long-term side effects of azathioprine or 6-MP are less serious than those of long-term corticosteroids or repeated courses of corticosteroids.

Patients with Crohn's disease may undergo surgery to remove a segment of the intestine that is obstructed or contains a fistula. After surgical removal of the diseased segments, the patients often will be free of disease and symptoms for a while, but many eventually will have their disease recur. During these recurrences, previously healthy intestine can become inflamed. Long-term 5-ASA (such as Pentasa) and 6-MP both are effective in reducing the chances of recurrence after surgery.

Anal fistulae can develop in some patients with Crohn's disease. Anal fistulae are abnormal tracts (tunnels) that form between the small intestine or colon and the skin around the anus. Drainage of fluid and mucous from the opening of the fistula is a troublesome problem. These fistulae are difficult to treat and do not heal readily. Metronidazole (Flagyl) has been used with some success in promoting healing of these fistulae. In difficult cases, azathioprine and 6-MP may be successful in promoting healing.

Side effects of azathioprine and 6-MP. Side effects of azathioprine and 6-MP include increased vulnerability to infections, inflammation of the liver (hepatitis) and the pancreas (pancreatitis), and bone marrow toxicity (interference with the formation of cells that circulate in the blood).

The goal of treatment with azathioprine and 6-MP is to lower the body's production of certain types of white blood cells (lymphocytes) in order to decrease the inflammation in the intestines; however, lowering the number of lymphocytes may increase vulnerability to infections. For example, in a group of patients with severe Crohn's disease unresponsive to standard doses of azathioprine, raising the dose of azathioprine helped to control the disease, but two patients developed cytomegalovirus (CMV) infection. (CMV typically infects individuals with weakened immune systems such as patients with AIDS and cancer patients receiving chemotherapy).

Azathioprine and 6-MP can induce inflammation of the liver (hepatitis) and pancreas (pancreatitis). Pancreatitis typically causes severe abdominal pain and sometimes vomiting. Pancreatitis due to azathioprine or 6-MP occurs in 3–5% of patients, usually during the first several weeks of treatment. Patients who develop pancreatitis should not receive either of these two medications again.

Azathioprine and 6-MP also suppress the bone marrow. The bone marrow is where the red blood cells, white blood cells, and platelets are made. Actually, a slight reduction in the white cell count during treatment is desirable since it suggests that the dose of azathioprine or 6-MP is high enough to have an effect; however, excessively low red or white blood cell counts indicates bone marrow toxicity. Therefore, patients on azathioprine or 6-MP should have periodic blood counts (usually every two weeks initially and then every three months during maintenance) to monitor the effect of the drugs on the bone marrow.

Patients on long-term, high dose azathioprine to prevent rejection of the kidney after kidney transplantation have an increased risk of developing lymphoma, a malignant disease of lymph cells. There is no evidence at present that long term use of azathioprine or 6-MP, in the lower doses used in Crohn's disease, increases the risk of lymphoma, leukemia or other malignancies.

The use of azathioprine and 6-MP in pregnant women must be carefully considered. There are reports suggesting that the use of azathioprine or 6-MP in pregnancy is safer than once thought. The risk of continuing azathioprine or 6-MP during conception and pregnancy must be weighed against the risk of worsening disease if they are stopped. On the other hand, worsening disease has been shown clearly to be a significant risk to the fetus.

Other issues with azathioprine and 6-MP. One problem with 6-MP and azathioprine is their slow onset of action. Typically, full benefit of these drugs is not realized for three months or longer. During this time, corticosteroids frequently have to be maintained at high levels to control inflammation.

The reason for this slow onset of action is partly due to the way doctors prescribe these drugs. For example, 6-MP is typically started at a dose of 50 mg daily. The blood count is then checked two weeks later. If the lymphocytes are not reduced, the dose of 6-MP is increased. This cautious, stepwise approach helps reduce bone marrow and liver toxicity but also delays benefit from the drug.

Studies have shown that giving higher doses of 6-MP early can hasten the benefit of 6-MP without increasing the toxicity in most patients, but some patients do develop severe bone marrow toxicity. Scientists now believe that an individual's vulnerability to 6-MP toxicity is genetically inherited. Blood tests can be performed to identify those individuals with increased vulnerability to 6-MP toxicity. Blood tests also can be performed to measure the levels of certain by-products of 6-MP. The levels of these by-products in the blood help doctors more quickly determine whether the dose of 6-MP is right for the patient.

TPMT genetics and safety of azathioprine and 6-MP. Azathioprine is converted into 6-MP in the body and 6-MP then is partially converted in the body into inactive and non-toxic chemicals by an enzyme called thiopurine methyltransferase (TPMT). These chemicals then are eliminated from the body. The activity of TPMT enzyme (the ability of the enzyme to convert 6-MP into inactive and non-toxic chemicals) is genetically determined, and approximately 10% of the population in the United States has a reduced or absent TPMT activity. In this 10% of patients, 6-MP accumulates and is converted into chemicals that are toxic to the bone marrow where blood cells are produced. Thus, when given normal doses of azathioprine or 6-MP, these patients with reduced or absent TPMT activities can develop seriously low white blood cell counts for prolonged periods of time, exposing them to serious life-threatening infections.

Doctors now can perform genetic testing for TPMT before starting azathioprine or 6-MP. Patients found to have genes associated with reduced or absent TPMT activity are treated with alternative medications or are prescribed substantially lower than normal doses of 6-MP or Azathioprine.

A word of caution is in order, however. Having normal TPMT genes is no guarantee against azathioprine or 6-MP toxicity. Rarely, a patient with normal TPMT genes can develop severe toxicity in the bone marrow and a low white blood cell count even with normal doses of 6-MP or azathioprine. Therefore, all patients taking 6-MP or azathioprine (regardless of TPMT

genetics) have to be closely monitored by a doctor who will order periodic blood counts for as long as the medication is taken.

Another cautionary note; allopurinol (Zyloprim), used in treating high blood uric acids levels, can induce bone marrow toxicity when used together with azathioprine or 6-MP. Zyloprim used together with azathioprine or 6-MP has similar effect as having reduced TPMT activity, causing increased accumulation of the 6-MP metabolite that is toxic to the bone marrow.

6-MP metabolite levels. In addition to monitoring blood cell counts and liver tests, doctors also may measure blood levels of the chemicals that are formed from 6-MP (6-MP metabolites), which can be helpful in several situations such as:

If a patient's disease is not responding to standard doses of 6-MP or azathioprine and his/her 6-MP blood metabolite levels are low, doctors may increase the 6-MP or azathioprine dose.

If a patient's disease is not responding to treatment and his/her 6-MP blood metabolite levels are zero, he/she is not taking his/her medication. The lack of response in this case is due to patient non-compliance.

Duration of treatment with azathioprine and 6-MP. Patients have been maintained on 6-MP or azathioprine for years without important long-term side effects. Patients on long-term azathioprine or 6-MP, however, should be closely monitored by their doctors. There are data suggesting that patients on long-term maintenance fare better than those who stop these medications. Thus, those who stop azathioprine or 6-MP are more likely to experience recurrence of their disease and are more likely to need corticosteroids or undergo surgery.

Infliximab (Remicade). Infliximab (Remicade) is an antibody that attaches to a protein called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is one of the proteins produced by immune cells during activation of the immune system. TNF-alpha, in turn, stimulates other cells of the immune system to produce and release other proteins that promote inflammation. In Crohn's disease, there is continued production of TNF-alpha as part of the immune activation. Infliximab, by attaching to TNF-alpha, blocks its activity and in so doing decreases the inflammation.

Infliximab, an antibody to TNF-alpha, is produced by the immune system of mice after the mice are injected with human TNF-alpha. The mouse antibody then is modified to make it look more like a human antibody, and this modified antibody is infliximab. Such modifications are necessary to decrease the likelihood of allergic reactions when the antibody is administered to humans. Infliximab is given by intravenous infusion over two hours. Patients are monitored throughout the infusion for adverse reactions.

Infliximab is an effective and fast-acting drug for the treatment of active Crohn's disease. In a study involving patients with moderate to severe Crohn's disease who were not responding to corticosteroids or immuno-modulators, 65% experienced improvement in their disease after one infusion of infliximab. Some patients noticed improvement in symptoms within days of the infusion. Most patients experienced improvement within two weeks.

In patients who respond to infliximab, the improvements in symptoms can be dramatic. Moreover, there can be impressively rapid healing of the ulcers and the inflammation in the intestines after just one infusion.

The anal fistulae of Crohn's disease are troublesome and often difficult to treat. Infliximab has been found to be effective for treating fistulae.

The majority of the patients who responded to a first infusion of infliximab developed recurrence of their disease within three months. However, studies have shown that repeated infusions of infliximab every eight weeks are safe and effective in maintaining remission in many patients over a one to two year period. Response to infliximab after repeated infusions sometimes is lost if the patient starts to develop antibodies to the infliximab (which attach to the infliximab and prevent it from working). Studies are now being done to determine the long-term safety and effectiveness of repeated infusions of infliximab.

One potential use of infliximab is to quickly control active and severe disease. The use of infliximab then may be followed by maintenance treatment with azathioprine, 6-MP or 5-ASA compounds. Azathioprine or 6-MP also may be helpful in preventing the development of antibodies against infliximab.

Infliximab generally is well-tolerated. There have been rare reports of side effects during infusions, including chest pain, shortness of breath, and nausea. These effects usually resolve spontaneously within minutes if the infusion is stopped. Other commonly-reported side effects include headache and upper respiratory tract infection.

TNF-alpha is an important protein for defending the body against infections. Infliximab, like immuno-modulators, increases the risk for infection. One case of salmonella colitis and several cases of pneumonia have been reported with the use of infliximab. There also have been cases of tuberculosis (TB) reported after the use of infliximab.

Because infliximab is partly a mouse protein, it may induce an immune reaction when given to humans, especially with repeated infusions. In addition to the side effects that occur while the infusion is being given, patients also may develop a "delayed allergic reaction" that occurs 7–10 days after receiving the infliximab. This type of reaction may cause flu-like symptoms with fever, joint pain and swelling, and a worsening of Crohn's disease symptoms. It can be serious, and if it occurs, a physician should be contacted. Paradoxically, those patients who have more frequent infusions of infliximab are less likely to develop this type of delayed reaction compared to those patients who receive infusions separated by long intervals (6–12 months). Although infliximab is only FDA approved for a single infusion at this time, patients should be aware that they are likely to require repeated infusions once Remicade therapy has been initiated.

Rare cases of nerve inflammation such as optic neuritis (inflammation of the nerve of the eye) and mother neuropathy has been reported with the use of infliximab.

Infliximab can aggravate and cause the spread of an existing infection. Therefore, it should not be given to patients with pneumonia, urinary tract infection or abscess (localized collection of pus). It now is recommended that patients be tested for TB prior to receiving infliximab. Patients who previously had TB should inform their physician of this before they receive infliximab infliximab can cause the spread of cancer cells; therefore, it should not be given to patients with cancer.

Infliximab can promote intestinal scarring (part of the process of healing) and, therefore, can worsen strictures (narrowed areas of the intestine caused by inflammation and subsequent scaring) and lead to intestinal obstruction. It also can cause partial healing (partial closure) of anal fistulae. Partial closure of fistulae impedes drainage of fluid through the fistulae, and may result in collections of fluid in which bacteria multiply, which can result in abscesses.

The effects infliximab on the fetus are not known.

Because infliximab is partly a mouse protein, some patients can develop antibodies against infliximab with repeated infusions. Such antibodies can decrease the effectiveness of the drug. The chance of developing such antibodies can be decreased by the concomitant use of 6-MP and corticosteroids. There are some reports of worsening heart disease in patients who have received Remicade. The precise mechanism and role of infliximab in the development of this side effect is unclear. As a precaution, individuals with heart disease should inform their physician of this condition before receiving infliximab.

While infliximab represents an exciting new class of medications in the fight against Crohn's disease, caution is warranted in its use. The long-term safety and effectiveness is not yet known.

Adalimumab (Humira). Adalimumab is an anti-TNF agent similar to infliximab and decreases inflammation by blocking tumor necrosis factor (TNF-alpha). In contrast to infliximab, adalimumab is a fully humanized anti-TNF antibody (no mouse protein). Adalimumab is administered subcutaneously (under the skin) instead of intravenously as in the case of infliximab.

Rheumatologists have been using adalimumab for treating inflammation of the joints in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Four recent

clinical trials (involving almost 1,500 patients) comparing adalimumab to placebo, have demonstrated that adalimumab is also effective in treating inflammation in the intestines of patients with Crohn's disease and in reducing signs and symptoms of Crohn's disease.

Adalimumab is comparable to infliximab in effectiveness and safety for inducing and maintaining remission in patients suffering from Crohn's disease. Adalimumab is also effective in healing Crohn's anal fistulas. Adalimumab has been shown to be effective for patients who either failed or cannot tolerate infliximab.

The Food and Drug Administration in February 2007, approved Humira (adalimumab) to treat adult patients with moderately to severely active Crohn's disease. Adalimumab (Humira) is administered subcutaneously every two weeks.

Adalimumab generally is well-tolerated. The most common side effect is skin reactions at the site of injection with swelling, itching, or redness. Other common side effects include upper respiratory infections, sinusitis, and nausea.

TNF-alpha is an important protein for defending the body against infections. Adalimumab, like infliximab, increases the risk of infection. There have been cases of tuberculosis (TB) reported after the use of infliximab and adalimumab. It now is recommended that patients be tested for TB prior to receiving these agents. Patients who previously had TB should inform their physician of this before they receive these agents. Adalimumab, like infliximab, can aggravate and cause the spread of an existing infection. Therefore, it should not be given to patients with pneumonia, urinary tract infection or abscess (localized collection of pus).

Rare cases of lymphoma (cancer of the lymphatic system) have been reported with the use of adalimumab. Rare cases of nervous system inflammation have been reported with the use of adalimumab. The symptoms may include numbness and tingling, vision disturbances, weakness in legs. Some patients receiving adalimumab may rarely develop symptoms that mimic systemic lupus; these symptoms include skin rash, arthritis, chest pain, or shortness of breath. These lupus-like symptoms resolve after stopping the drug.

There are some reports of worsening heart disease such as heart failure in patients who have received infliximab or adalimumab. The precise mechanism and role of these agents in the development of this side effect is unclear. As a precaution, individuals with heart disease should inform their physician of this condition before receiving infliximab or adalimumab.

Severe allergic reactions with rash, difficulty breathing, and severe low blood pressure or shock are rare, but serious allergic reactions can occur either after the first injection or after many injections. Patients experiencing symptoms of serious allergic reactions should seek emergency care are immediately.

Methotrexate (Rheumatrex, Trexall). Methotrexate (Rheumatrex, Trexall) is both an immuno-modulator and antiinflammatory medication. Methotrexate has been used for many years in the treatment of severe rheumatoid arthritis and psoriasis. It has been helpful in treating patients with moderate to severe Crohn's disease who are either not responding to azathioprine and 6-MP or are intolerant of them. Methotrexate also may be effective in patients with moderate to severe ulcerative colitis who are not responding to corticosteroids, azathioprine, or 6-MP. It can be given orally or by weekly injections under the skin or into the muscles, but it is more reliably absorbed with the injections.

One major complication of methotrexate is the development of liver cirrhosis when the medication is given over a prolonged period of time (years). The risk of liver damage is higher in patients who also abuse alcohol or are severely obese. Although it has been recommended that a liver biopsy should be obtained in patients who have received a cumulative (total) methotrexate dose of 1.5 grams or higher, the need for such biopsies is controversial.

Other side effects of methotrexate include low white blood cell counts and inflammation of the lungs.

Methotrexate should not be used in pregnant women because of toxic effects on the fetus.

Surgery in Crohn's disease

Indications for surgery.

Absolute:

- Free perforation.
- Massive hemorrhage.
- Cancer or dysplasia.
- Chronic high grade obstruction.

Relative:

- Intractability.
- Complex fistula & abscesses.
- Perianal complications.
- Growth retardation.

Types of operations

1. Removal of a diseased segment of the small intestine that is causing obstruction with primary anastomosis (*Fig. 5.21*).

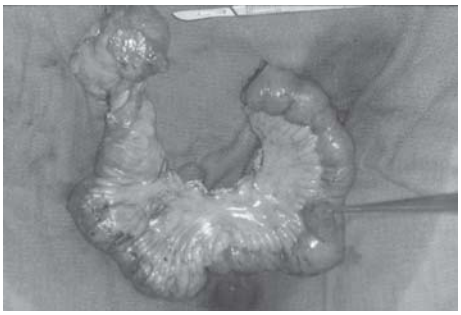


Figure 5.21. *Crohn's disease: segment of the small intestine, which is resected*

2. Drainage of pus from abdominal and peri-rectal abscesses.

3. Treatment of severe anal fistulae that do not respond to drugs.

4. Resection of internal fistulae (such as a fistula between the colon and bladder) that are causing infections.

5. Stricturoplasty in patients at risk of developing short bowel syndrome at obstruction (*Fig. 5.22*).

6. Bypass obstruction, e.g. duodenum.

7. Extensive colonic involvement may require proctocolectomy.

8. There is a 30–50% recurrence rate mostly at the neoterminal ileum; however, patients are still palliated well and not all require reoperation. Surgical procedures should be covered with corticosteroids.

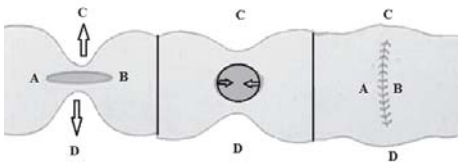


Figure 5.22. *Crohn's disease: enteroplasty on Heineke-Mikulicz (short stricture)*

Usually, after the diseased portions of the intestines are removed surgically, patients can be free of disease and symptoms for some time, often years. Surgery, when successfully performed, can lead to a marked improvement in a patient's quality of life. In many patients, however, Crohn's disease eventually returns, affecting previously healthy intestines. The recurrent disease usually is located at or near the previous site of surgery. In fact, 50% of patients can expect to have a recurrence of

symptoms within four years of surgery. Drugs such as Pentasa or 6-MP have been useful in some patients to reduce the chances of relapse of Crohn's disease after surgery.

General measures

General measures which may help control Crohn's disease include dietary changes and supplementation. Since fiber is poorly digestible, it can worsen the symptoms of intestinal obstruction. Hence, a low fiber diet may be recommended, especially in those patients with small intestinal disease. A liquid diet may be of benefit when symptoms are more severe. Intravenous nutrition or TPN (total peripheral nutrition) may be utilized when it is felt that the intestine needs to "rest." Supplementation of calcium, folate and vitamin B_{12} is helpful when malabsorption of these nutrients is apparent. The use of anti-diarrheal agents [diphenoxylate and atropine (Lomotil), loperamide (Imodium)] and anti-spasmotics also can help relieve symptoms of cramps and diarrhea.

Prognosis

• Most patients have a chronic intermittent disease course, while 13% have an unremitting disease course and 10% have a prolonged remission.

• Less than half require corticosteroids at any point.

• During any given year, approximately 10% are treated with corticosteroids and 30% are treated with 5-aminosalicylates.

• Up to 57% of patients require at least one surgical resection.

• About one tenth of patients have prolonged remission.

• Nearly 75% of patients have a chronic intermittent course, and about one eighth have an unremitting course.

• If the patient has both small and large bowel disease then about 70% will require surgical intervention.

• The atypical form of Crohn's is an acute ileitis. This, unlike other forms of Crohn's, does not recur and may represent a completely different disease.

• The excess mortality in patients with Crohn's disease is approximately double that of the general population. This is due to the complications of active disease.

5.4.2. Non-specific ulcerative colitis

Ulcerative colitis is a chronic disease of unknown aetiology in which a part or the whole of the mucosa of the large bowel becomes diffusely inflamed and may ulcerate, as a result of which the patient suffers from diarrhoea which may be bloody.

It is characterised by exacerbations and remissions.

The highest incidence of this disease is in adulthood, although it may occur in childhood. The cause of ulcerative colitis is unknown but genetic, immunological, dietary, and psychological factors have all been implicated.

Epidemiology

This condition may occur at any time from early childhood to late adulthood.

There is an annual incidence of 5–8/100,000 in most communities of Celtic and Anglo-Saxon origin in north-western Europe, North America and New Zealand.

The prevalence of symptomatic disease in north-western Europe is 70–150/100,000. This disease is very uncommon in Asia and Africa. As in Crohn's disease, familial clustering may be seen.

Pathological features

1. Ulcerative colitis primarily affects the mucosa and the submucosa, with inflammatory cell infiltrates, crypt abscess and ulcer formation. Goblet cells are few in number and frequently depleted of mucus.

2. Redundant mucosa between ulcers forms pseudopolyps, and the mucosa is friable and bleeding easily on contact.

3. There are no skip lesions.

4. The rectosigmoid is most commonly involved with 50% of patients having total colonic involvement.

5. Chronic disease causes shortening and thickening of the bowel wall with haustral loss.

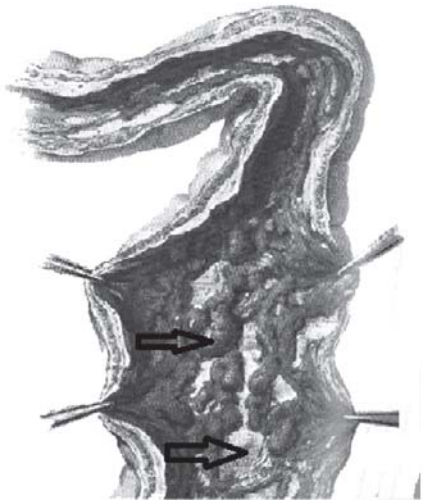


Figure 5.23. *Advenced colitis with ulceration and pseudopolyps (arrows)*

Clinical features

Ulcerative colitis may be fulminant, chronic, or relapsing (*Fig. 5.23*). The patient may present dehydrated and/or toxic.

Symptoms include:

• number of stools may vary from 1 or 2 to 20 or 30 per day;

• diarrhoea, sometimes bloody; mild abdominal pain in the left iliac fossa; fever; weight loss;

• if this condition occurs in infancy or childhood, then the presentation may be of failure to thrive or failure to progress normally into puberty;

• in fulminating disease the presentation may be of abdominal distension, catastrophic diarrhoea, fever and collapse.

Signs may be as follows: pallor, dehydration, mouth ulcers, abdominal tenderness.

Associated conditions include:

• erythema nodosum;
• pyoderma gangrenosum;
• uveitis;
• arthritis.

Severity

The severity of ulcerative colitis can be assessed on the basis of:

1. Bowel frequency – less than four motions per day is considered mild, more than six is severe.

2. Rectal bleeding.

3. Temperature patients with mild disease are apyrexial, those with severe disease may be higher than 37.8 C.

4. Haemoglobin of less than 10.5 is considered severe, greater than 11 is mild.

5. ESR of less than 30 mm per hour is mild, greater than this is severe.

6. Tachycardia is related to severity.

7. Low albumin – below 30g per litre implies severe disease.

Differential diagnosis

The differential diagnosis is influenced by the presentation, a principal factor being the age.

1. Crohn's disease.

2. Infective colitis is often a cause of one episode of colitis which is mislabeled as ulcerative colitis e.g. salmonellosis, shigellosis, campylobacter, amoebiasis. In the immunosuppressed patient then one must consider opportunistic infections e.g. cytomegalovirus, herpes virus, cryptosporidium, mycobacterium avium intracellular.

3. Colonic carcinoma, adenoma – diagnosed on endoscopy, particularly important in the elderly.

4. Diverticulitis not in childhood.

5. Irritable bowel disease, which would tend to occur in the young, and has early morning explosiveness, not tending to be bothered at night.

6. Ischaemic colitis – these patients may have a history of vascular disease with sudden onset of pain, and thumb printing on plain abdominal radiography or barium enema. It does not occur in childhood.

7. Post-radiation colitis, the diagnosis of which is based on the history.

Investigations

1. FBC – anemia due to blood loss; leukocytosis.

2. ESR – increased; correlates with active disease.

3. CRP – raised; but less so than in Crohn's disease.

4. Biochemistry – in active disease, biochemical abnormalities may include hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, and hypoalbuminemia. Abnormal LFTs due to associated chronic active hepatitis – increased ALT – or sclerosing cholangitis – increased alkaline phosphatase.

ANCA – found in HLA-DR2 associated form of ulcerative colitis.

Diagnosis

1. Plain abdominal X-ray – excludes toxic dilatation, which is more than 5.5 cm in diameter in adults.

2. Barium enema:

- diagnosis of extent and severity of the disease;
- procedure is contraindicated in those patients at risk of a toxic dilatation.

3. Rectal biopsy – taken at sigmoidoscopy (*Fig. 5.24*).

4. Colonoscopy – this is contraindicated in those patients at risk of toxic dilatation. Allows multiple biopsies to be taken throughout the colon and delineation of the extent and activity of the disease (*Fig. 5.25*).

5. White cell scan – allows imaging in severe disease.

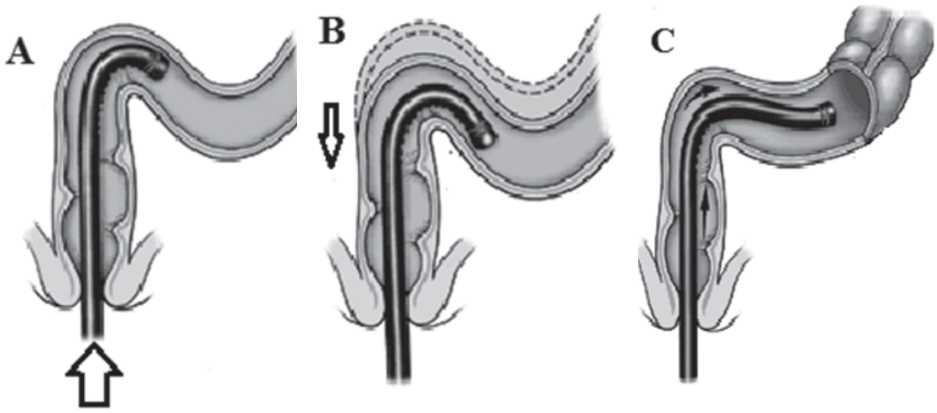


Figure 5.24. *Hooking and straightening technique used to pass through a tortuous sigmoid colon. (A) The scope is inserted to the angled sigmoid. (B) The scope tip is turned to a sharp angle, and the sigmoid is hooked as the scope is withdrawn. (C) The sigmoid is straightened as the scope is withdrawn. The scope can then be inserted through to the descending colon*

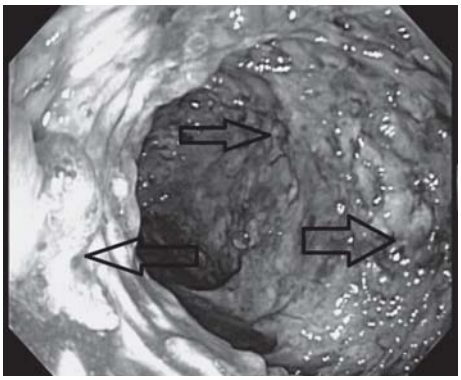


Figure 5.25. *Colonoscopy: ulcerative colitis (arrows)*

6. Molecular biology – a high intensity of CD44v6 and v3 epitope expression on crypt epithelial cells in patients with UC has been noted. This observation may have diagnostic potential in distinguishing UC from Crohn's.

Careful history and examination is, of course, very important for the diagnosis of ulcerative colitis. The hallmark is bloody diarrhoea with mucus, usually of gradual onset, but it can be abrupt.

The diagnosis of ulcerative colitis is based on:

• exclusion of other causes of diarrhea like bacillary or amoebic dysentery;
• colonoscopy and biopsy histological characteristics, and endoscopic features;
• differentiation from Crohn's disease this may be very difficult:
• ANCA positivity associated with forms of ulcerative colitis;
• increased expression of CD44v6 and CD44v3 variants in the colonic mucosa of patients with ulcerative colitis has been described and may have diagnostic potential in differentiating ulcerative colitis and Crohn's disease. There is absence of CD44v6 expression from normal colonic mucosa, but CD44v6 and CD44v3 have been identified in colorectal tumors.

Management

There have been massive improvements in the management of ulcerative colitis in the past 40 or 50 years, as evidenced by the death rates in severe attacks:

• before 1952, 45%;
• now, 1 to 2 %

The management has been improved by:

1. Corticosteroids.
2. Better understanding of fluid balance and electrolytes in severely ill patients.
3. Better understanding of indicators of severity of the disease.

Surgical management

1. Surgery is required in 20% of patients with ulcerative colitis.
2. The quality of life after surgery is excellent and a colectomy eliminates the need for continuous medical therapy and the need for cancer surveillance.
3. Most extraintestinal symptoms of UC will resolve after a colectomy. The exceptions to this are sclerosing cholangitis and arthritis. Note also that growth retardation is reversed if a colectomy is performed before puberty.

Indications

With ulcerative colitis, emergency surgery is indicated for:

- Hemorrhage.
- Perforation
- Toxic megacolon.
- Severe flares which have failed course of high dose steroids, complete bowel rest and intravenous feeding.
- Development of colonic carcinoma.

Elective surgery is indicated for:

- intractable symptoms;
- long-standing active disease which increases the risk of carcinoma.

Principles of surgery

Removal of the entire large bowel, by definition, is curative in ulcerative colitis.

Alternatives include a panproctocolectomy and terminal ileostomy, and total colectomy and ileo-rectal anastomosis.

Panproctocolectomy and terminal ileostomy:

- the whole colon is removed from the caecum to the anus;
- this procedure necessitates the construction of a permanent ileostomy.

Total colectomy and ileo-rectal anastomosis:

- in this procedure the colon is removed but the rectal stump is left in situ;
- the terminal ileum may be re-anastomosed to it, either at the initial operation or as a secondary procedure;
- it is possible to fashion the terminal ileum into a pouch – Park's pouch – to form a reservoir above the rectal stump. There is a risk recurrence of disease in the rectal stump. Thus the rectal mucosa is first stripped and the pouch anastomosed to the dentate line.

Cancer surveillance in Ulcerative Colitis

There is an increased risk of developing colorectal carcinoma in patients with UC. The risk of development of cancer is dependent on the duration and the extent of the disease.

If the patient has a pancolitis then:

- after 10 years risk is 1%;
- after 20 years risk is 13%;
- after 30 years risk is 34%.

It is conjectured that neoplasms are preceded by initially mild and later severe dysplasia of the colonic epithelium. Surveillance in the form of colonoscopy with multiple biopsies every 18–24 months is designed to identify such premalignant changes.

Complications

Local complications of ulcerative colitis include:

1. Hemorrhage.
2. Malnutrition.
3. Electrolyte imbalance.
4. Toxic megacolon.
5. Stricture formation – rare.
6. Fistula formation – rare.
7. Perforation.
8. Increased risk of malignancy – lymphoma, carcinoma.

General:

1. Weight loss.
2. Anemia.
3. Hypoproteinaemia.
4. Arthropathy – tends to affect large weight-bearing joints.
5. Liver associations: primary sclerosing cholangitis; fatty liver; non-specific hepatitis; pericholangitis; chronic active hepatitis; bile duct carcinoma.
6. Sacro-iliitis and ankylosing spondylitis.
7. Pyoderma gangrenosum.
8. Erythema nodosum.
9. Anterior uveitis.
10. Episcleritis.
11. Carcinoma of the bile ducts – rare.

Note that gallstones are associated with Crohn's disease but not ulcerative colitis.

Prognosis

• A colectomy is curative.

•70% of patients with untreated UC relapse annually.

• There is a 1% risk of the development of colonic cancer if someone has the disease for 10 years; in most UK centers, patients with extensive UC of 10 years' duration are offered colonoscopy every 1–2 years in an effort to prevent colonic cancer by taking multiple biopsies to look for mucosal dysplasia and to offer colectomy if appropriate, or to detect cancer at a curable stage.

• There is a substantial variation in severity, extent and responsiveness, together with extra-intestinal and multiple intestinal manifestations.

• Life-expectancy is similar to that of the general population.

• Patients with well-controlled distal UC can be followed up routinely in primary care (will require a blood count and liver function test every 6–12 months, and referral for colonoscopy at 8–10 years to reassess disease extent).

5.5. POLYPS AND POLYPOSIS OF THE LARGE INTESTINE

1. A polyp is a benign (non-cancerous) growth of the lining of the colon (large bowel).

2. It can be anything from 2 mm up to 5 cm or more in diameter.

3. Commonly, the abnormal cells form a small ball (about the size of a pea) on the end of a stalk of normal cells.

4. The type of cell that forms the polyp varies and is important in determining its potential for developing into a cancer.

A polyp is a growth of tissue from the intestinal or rectal wall that protrudes into the intestine or rectum and may be noncancerous (benign) or cancerous (malignant). Polyps vary considerably in size, and the bigger the polyp, the greater the risk that it is cancerous or precancerous. Polyps may grow with or without a stalk. Those without a stalk are more likely to be cancerous than those with a stalk. Adenomatous polyps, which consist primarily of glandular cells that line the inside of the large intestine, are likely to become cancerous (that is, they are precancerous). Serrated adenomas are a particularly aggressive form of adenoma.

Types of polyp

Metaplastic polyps versus adenomatous polyps

The most common sort of polyp is a metaplastic polyp (in which cells change from one normal type to another). These usually do not grow much more than 5 mm in diameter and have almost no risk of becoming malignant (cancerous). These polyps can be very similar in appearance to adenomatous polyps, the next most common type, which do have the potential to become malignant.

About 50 per cent of people aged 60 will have at least one adenomatous polyp of 1cm diameter or greater. Familial polyposis coli (familial adenomatous polyposis or FAP) involve multiple adenomatous polyps, often in their hundreds. This condition carries a very high risk of colon cancer.

Other rarer types of polyps include:

• **Juvenile polyps:** these are usually solitary polyps called hamartomas that affect 1 to 2 per cent of older children or adolescents. A single polyp carries no significant cancer risk but when these polyps are inherited and usually multiple (about one third of patients), the colon cancer risk is about 10 per cent. In this case, regular surveillance after excision (cutting out) of all polyps is required.

• **Peutz–Jeghers polyps:** found in Peutz–Jeghers syndrome, in association with freckling of the lips, are also of the hamartomatous type. These usually present in early adult life and carry a low but definite risk of malignancy, probably around five per cent per polyp, so they need excision. The number of polyps per individual is very variable and ranges, from as few as one or two to as many as 20 or more. Peutz–Jeghers polyps can also occur in the small intestine and can then be difficult to diagnose because they are beyond the reach of conventional fibre-optic endoscopes (internal telescope instruments). Such polyps tend to present with symptoms of obstruction (bowel blockage) or abdominal pain. Diagnosis is usually made with barium X-rays (taken after the patient swallows barium liquid to show up the inside of the intestine). Treatment will usually be an operation that opens up the abdomen.

• **Inflammatory pseudopolyps:** can occur as a complication of ulcerative colitis or Crohn's disease of the colon. They are completely harmless and carry no risk of cancer but they can be confused with adenomatous polyps on examination.

• **Cronkhite–Canada syndrome:** an exceptionally rare condition, involves multiple colon polyps, hyperpigmentation (darkening of the skin) and nail atrophy (wasting away). The syndrome is not inherited and affects middle-aged or older individuals. It is linked with malabsorption and has been reported to respond to vitamin E therapy.

Etiology and pathogenesis

Most polyps, with the exception of the inflammatory pseudopolyps, result from some form of genetic (DNA) mutation in one of the colon lining cells. Fortunately, several, probably at least five, mutations are needed in the same cell before cancer occurs and most benign polyps probably only have one gene mutated. DNA damage occurs surprisingly often.

Even in a healthy adult's colon, about 10 per cent of the lining cells, on average, contain major abnormalities of the chromosomes (packages of DNA that contain many genes). Fortunately, almost all these cells seem to undergo a form of programmed death called apoptosis, and then fall off harmlessly into the bowel lumen (cavity).

Adenomatous polyps, even those from individuals who do not have familial polyposis, commonly contain mutations that stop the gene working in both copies of the adenomatous polyposis coli (APC) gene, the gene that is mutated in familial polyposis coli.

Symptoms and diagnosis

Most polyps do not cause symptoms. When they do, the most common symptom is bleeding from the rectum. A large polyp may cause cramps, abdominal pain, or obstruction. Large polyps with tiny, fingerlike projections (villous adenomas) may excrete water and salts, causing profuse watery diarrhea that may result in low levels of potassium in the blood (hypokalemia). Rarely, a rectal polyp on a long stalk drops down and dangles through the anus.

A doctor may be able to feel polyps by inserting a gloved finger into the rectum, but usually polyps are discovered during flexible sigmoidoscopy (examination of the lower portion of the large intestine with a viewing tube). If flexible sigmoidoscopy reveals a polyp, colonoscopy is performed to examine the entire large intestine. This more complete and reliable examination is performed because more than one polyp is usually present and any may be cancerous. Colonoscopy also allows a doctor to perform a biopsy (removal of a tissue sample for examination under a microscope) of any area that appears cancerous.

Treatment

Doctors generally recommend removing all polyps from the large intestine and rectum because of their potential to become cancerous. Polyps are removed during a colonoscopy procedure using a cutting instrument or an electrified wire loop. If a polyp has no stalk or cannot be removed during colonoscopy, abdominal surgery may be needed.

If a polyp is found to be cancerous, treatment depends on whether the cancer is likely to have spread. The risk of spread is determined by microscopic examination of the polyp. If the risk is low, no further treatment is necessary. If the risk is high, particularly if the cancer has invaded the polyp's stalk, the affected segment of the large intestine is removed surgically, and the cut ends of the intestine are rejoined.

When a person has a polyp removed, the entire large intestine and rectum are examined by colonoscopy a year later and then at intervals determined by the doctor. If such an examination is impossible because of a narrowing of the large intestine, a barium enema may be used to view the large intestine on X-ray.

For people with familial adenomatous polyposis, complete removal of the large intestine and rectum eliminates the risk of cancer. Alternatively, the large intestine is removed and the rectum is joined to the small intestine; this procedure sometimes eliminates the rectal polyps and thus is preferred by many experts. The remaining part of the rectum is inspected by sigmoidoscopy every 3 to 6 months, so that new polyps can be removed. If new polyps appear too rapidly, however, the rectum must also be removed. If the rectum is removed, a surgical opening is created through the abdominal wall from the small intestine (ileostomy). Bodily wastes are eliminated through the ileostomy into a disposable bag.

Some nonsteroidal anti-inflammatory drugs (NSAIDs) are being studied for their ability to reverse the growth of polyps in people with familial adenomatous polyposis. Their effects are temporary, however, and once these drugs are discontinued, the polyps begin to grow again.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP) is an inherited condition in which numerous polyps form mainly in the epithelium of the large intestine. While these polyps start out benign, malignant transformation into colon cancer occurs when not treated.

Signs and symptoms

From early adolescence and onwards, patients with this condition develop hundreds to thousands of polyps. These may bleed, leading to blood in the stool. If the blood is not visible, it is still possible for the patient to develop anemia due to gradually developing iron deficiency. If malignancy develops, this may present with weight loss, altered bowel habit, or even metastasis to the liver or elsewhere.

The genetic determinant in familial polyposis may also predispose carriers to other malignancies, e.g., of the duodenum and stomach. Other signs that may point to FAP are pigmented lesions of the retina ("CHRPE – congenital hypertrophy of the retinal pigment epithelium"), jaw cysts, sebaceous cysts, and osteomata (benign bone tumors). The combination of polyposis, osteomas, fibromas and sebaceous cysts is termed *Gardner's syndrome* (with or without abnormal scarring).

Diagnosis and treatment

Making the diagnosis of FAP before the development of colon cancer is important not just for the individual, but also for the sake of other family members who may be affected. Colonoscopy is considered the diagnostic test of choice as it can provide not only a quantification of polyps throughout the colon but also a

histologic diagnosis. Barium enema and virtual colonoscopy can suggest the diagnosis of FAP.

Once the diagnosis of FAP is made, close colonoscopic surveillance with polypectomy is required. Prophylactic colectomy is indicated if more than a hundred polyps are present, if there are severely dysplastic polyps, or if multiple polyps larger than 1 cm are present. When a partial colectomy is performed, colonoscopic surveillance of the remaining colon is necessary as the individual still carries significant risk of developing colon cancer.

Ultrasound of the abdomen and blood tests evaluating liver function are often performed to rule out metastasis to the liver.

Genetic testing provides the ultimate diagnosis in 95% of cases; genetic counseling is usually needed in families where FAP has been diagnosed. Testing may also aid in the diagnosis of borderline cases in families that are otherwise known to p34.3 and p32.1 (1p34.3-p32.1).

APC is a tumor suppressor gene, acting as a "gatekeeper" to prevent development of tumors. Mutation of *APC* also occurs commonly in incident cases of colorectal carcinoma, emphasizing its importance in this form of cancer.

Although the polyps are inherently benign, the first step of the two-hit hypothesis has already taken place: the inherited APC mutation. Often, the remaining "normal" allele is mutated or deleted, accelerating generation of polyps. Further mutations (e.g. in p53 or *kRAS*) to APC-mutated cells are much more likely to lead to cancer than they would in non-mutated epithelial cells.

The normal function of the *APC* gene product is still being investigated; it is present both the cell nucleus and the membrane. The canonical tumor-suppressor function of Apc is suppression of the oncogenic protein beta-catenin. However, other tumor-suppressor functions of APC may be related to cell adherence and cytoskeleton organization.

MUTYH encodes DNA repair enzyme MYH glycosylase. During normal cellular activities, guanine sometimes becomes altered by oxygen, which causes it to pair with adenine instead of cytosine. MYH glycosylase fixes these mistakes by base excision repair, such that mutations do not accumulate in the DNA and lead to tumor formation. When MYH glycosylase does not function correctly, DNA errors may accrue to initiate tumorigenesis with a clinical presentation similar to that in patients with Apc mutations.

Genetics

Familial adenomatous polyposis can have different inheritance patterns and different genetic causes. When this condition results from mutations in the APC gene, it is inherited in an autosomal dominant pattern, which means one copy of the altered gene is sufficient to cause the disorder. The incidence of malignancy in these cases approaches 100%. In most cases, an affected person has one parent with the condition.

Mutations in the *MUTYH* gene are inherited in an autosomal recessive pattern, which means two copies of the gene must be altered for a person to be affected by the disorder. Most often, the parents of a child with an autosomal recessive disorder are not affected but are carriers of one copy of the altered gene.

Prenatal testing is possible if a disease-causing mutation is identified in an affected family member; however, prenatal testing for typically adult-onset disorders is uncommon and requires careful genetic counseling.

Because of the genetic nature of FAP, polyposis registries have been developed around the world. The purpose of these registries is to increase knowledge about the transmissibility of FAP, but also to document, track, and notify family members of affected individuals. One study has shown that the use of a registry to notify family members (call-ups) significantly reduced mortality when compared with probands. The St. Mark's polyposis registry is the oldest in the world, started in 1924, and many other polyposis registries now exist.

Epidemiology

The incidence of the mutation is between 1 in 10,000 and 1 in 15,000 births. By age 35 years, 95% of individuals with FAP have polyps. Without colectomy, colon cancer is virtually inevitable. The mean age of colon cancer in untreated individuals is 39 years (range 34–43 years).

Treatment

Treatment for FAP depends on the genotype. Most individuals with the APC mutation will develop colon cancer by the age of 40. Therefore, prophylactic surgery is generally recommended before the age of 25. There are several surgical options that involve the removal of either the colon or both the colon and rectum. The decision to remove the rectum depends on the number of polyps in the rectum as well as the family history. If the rectum has few polyps, the colon is removed and the small bowel (ileum) is connected to the rectum (ileorectal anastomosis). If the rectum is involved then the colon and rectum are removed and a patient may require an ileostomy (permanent stoma where stool goes into a bag on the abdomen) or have an ileo-anal pouch reconstruction.

Various medications are being investigated for slowing malignant degeneration of polyps, most prominently the non-steroidal anti-inflammatory drugs (NSAIDs). The NSAIDS have been shown to significantly decrease the number of polyps but do not usually alter management since there are still too many polyps to be followed and treated endoscopically

PEUTZ–JEGHERS SYNDROME

Peutz–Jeghers syndrome (PJS) is a rare familial cancer syndrome that causes intestinal polyps, skin freckling, and an increased risk for cancer.

Peutz–Jeghers syndrome affects both males and females. The characteristic, or pathognomonic, features of PJS are unusual skin freckling and multiple polyps of the small intestine. The skin freckles, which are bluish to brown to black in color, can be found on the lips, inside the mouth, around the eyes, on the hands and feet, and on the genitals. The freckles are called benign hyperpigmented macules and do not become cancerous. The polyps in PJS are called hamartomatous polyps, and are found in the small intestine, small bowel, stomach, colon, and sometimes in the nose or bladder. Hamartomatous polyps are usually benign (not cancerous), but occasionally become malignant (cancerous). Dozens to thousands of hamartomatous

polyps may develop. A person with PJS with benign hamartomatous polyps can have abdominal pain, blood in the stool, or complications such as colon obstruction or intussusception (a condition in which one portion of the intestine telescopes into another). Surgery may be required to remove the affected part of the colon. A person with PJS is at increased risk for cancer of the colon, small intestine, stomach and pancreas. Women with PJS are also at increased risk for breast and cervical cancer, and a specific type of benign ovarian tumor called SCTAT (sex cord tumors with annular tubules). Men with PJS are also at increased risk for benign testicular tumors.

Diagnosis

The diagnosis of Peutz–Jehgers syndrome can be made clinically in a person with the characteristic freckles and at least two hamartomatous polyps. A pathologist needs to confirm that the polyps are hamartomatous instead of another type of polyp. If a person has a family history of PJS, the diagnosis can be made in a person who has either freckles or hamartomatous polyps. When someone is the first person in his/her family to be diagnosed with PJS, it is important for all first-degree relatives to be carefully examined for clinical signs of PJS. About half of all persons with PJS will have family members with symptoms of PJS. Symptoms can vary between families and between members of the same family. Some family members may just have freckling and others may have more serious medical problems such as bowel obstruction or cancer diagnosis. The freckles in PJS usually appear in childhood and fade as a person gets older, so it may be necessary to look at childhood photos in an adult who is being examined for signs of PJS.

Risks

Hamartomatous polyps may be diagnosed from early childhood to later in adulthood. On average, a person with PJS develops polyps by his or her early 20s. The lifetime risk for cancer is greatly increased over the general population, and cancer may occur at an earlier age. Early and regular screening is important to try to detect any cancers at an early stage. The benign ovarian tumors in women with PJS may cause early and irregular menstruation. The benign testicular tumors in men may cause earlier growth spurts and gynecomastia (development of the male breasts).

Causes

PJS is a genetic disease caused by a mutation of a tumor suppressor gene called LBK1 (or STK11) on chromosome 19. The exact function of LBK1 is unknown at this time. PJS is inherited as an autosomal dominant condition, which means that a person with PJS has a 50% chance of passing it on to each of his or her children. Screening and/or genetic testing of family members can help sort out who has PJS or who is at risk for developing PJS. Identification of a person with PJS in a family may result in other family members with more mild symptoms being diagnosed, and then receiving appropriate screening and medical care.

Genetic Testing

Fifty percent of people clinically diagnosed with PJS will have a mutation in the LBK1/STK11 gene detected in the lab. The other half will not have a detectable mutation at that time, but may have other PJS-causing genetic mutations discovered in the future.

In families where a mutation is known, family members can be tested for the same mutation. A person who tests positive for the family mutation will be diagnosed with PJS (even if he or she does not currently show signs of PJS), will need to have the recommended screening evaluations, and is able to pass on the mutation to his or her children. A person who tests negative for a known family mutation will be spared from screening, and his or her children will not be at risk for PJS. When the mutation cannot be found in a family, genetic testing is not useful, and all persons at risk for inheriting PJS will need to have screening for PJS throughout their life span.

Screening and Treatment

Regular medical examinations and special screening tests are needed in people with PJS. The age at which screening begins and the frequency of the tests is best determined by a physician familiar with PJS. Screening schedules depend on symptoms and family history. Colonoscopy, used to search for polyps in the colon, usually begins in adolescence. X-rays and/or upper gastrointestinal endoscopy are used to screen for polyps in the stomach and small intestine. The goal of screening is to remove polyps before they cause symptoms or become cancerous. Surgery may be necessary. Females with PJS need to have annual gynecologic examinations by age 18, and breast mammography starting between the ages of 25 and 35. Males with PJS need to have annual testicular examinations. If a person with PJS develops cancer, it is treated as it would be in the general population.

Prognosis

Metaplastic polyps have no significant potential to cause cancer and are very unlikely to lead to any significant problem even if not removed. The only exception is rare cases of multiple metaplastic polyps (50 or more), which probably increases the risk of colon cancer somewhat.

Adenomatous polyps can all potentially become cancerous but the actual risk per polyp is very small even if they are not removed. Some 50 per cent of people aged 60 or over have one or more adenomatous polyps yet only 6 per cent of people develop bowel cancer (*Fig. 5.26*). As long as the whole polyp is removed, there is no risk of recurrence or cancerous change of that polyp even when cancerous cells have invaded the stalk of the polyp. Further polyps can develop however. The risk of recurrence is greater if any of the initial polyps was over 1cm diameter, if the original polyps were multiple (four or more) or if any of the polyps show severe dysplastic (pre-cancerous) change under the microscope. In these cases, colonoscopic surveillance is usually recommended every five or six years.

Familial adenomatous polyposis is likely when 100 or more adenomatous polyps are found. This condition carries a high risk of cancer development unless treated, usually by colectomy (surgical removal of the whole colon).

Juvenile polyps that are single and have been completely excised carry no significant increased risk of malignancy. Multiple juvenile polyps can be a sign of the familial juvenile polyposis syndrome. This has a significant risk (approximately 10 per cent) of subsequent colon cancer and also a possible increased risk of cancers of the stomach and duodenum (first part of the small intestine). Further surveillance is

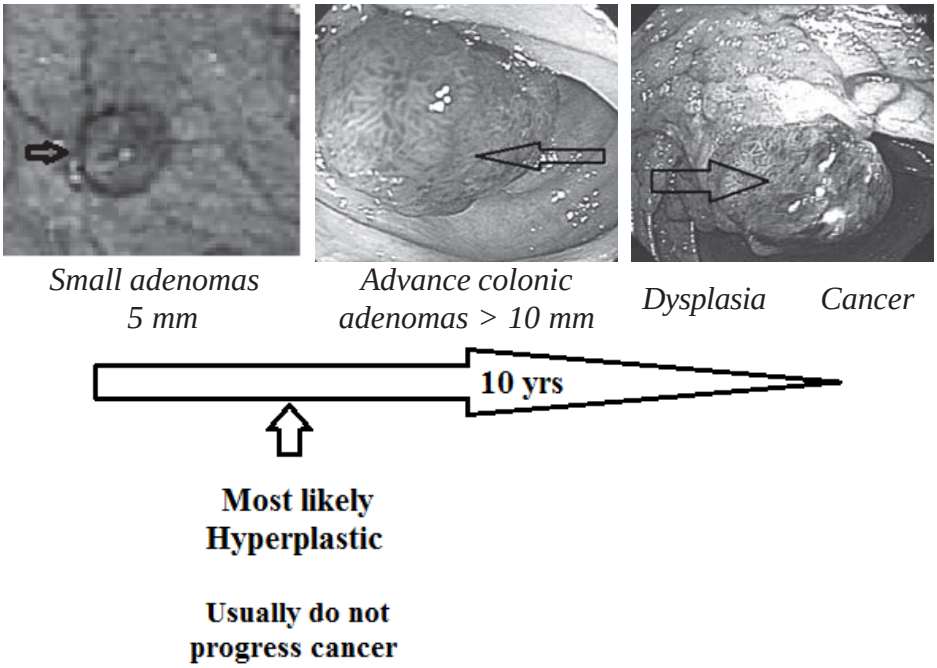


Figure 5.26. *Colonic adenoma progression*

then indicated, usually with both faeces testing for occult (non-visible) blood every year and flexible sigmoidoscopy every three to five years.

Peutz-Jeghers polyposis is associated with an increased risk of malignancy in the colon and small intestine. Reports differ over the size of this risk but it could be nearly 50 per cent of patients that develop cancer without careful surveillance. The modern surveillance using colonoscopy and other endoscopic techniques, much of this cancer risk should now be preventable.

5.6. CONGENITAL MEGACOLON (HIRSCHSPRUNG DISEASE)

Pathophysiology

Aganglionosis is caused by the arrested migration of cells caudad from the neural crest; these are the cells destined to develop as the intramural plexuses of the gut. In Hirschsprung disease, the aganglionic segment always extends from the internal anal sphincter for a variable distance proximally, but in most instances it remains *within the rectum and sigmoid colon*. The involvement of very short segments, affecting only the anal sphincters, has also been described. The aganglionic segment is permanently contracted, causing dilation proximally. Longer aganglionic segments occur in fewer than 20% of individuals; involvement of the entire colon is infrequent, and aganglionosis extending proximally into the small intestine is rare. Thus, the hallmark of diagnosis is the absence of ganglion cells from the myenteric and submucosal plexuses, as seen on a full-thickness or suction (mucosal-submucosal) biopsy specimen of the rectum. Proximal contents fail to enter the unrelaxed aganglionic segment.

Morphologically, ganglion cells are absent from the narrowed segment and for a short distance (usually 1–5 cm) into the dilated segment. In contrast, the nerve fibers are hypertrophic, with abundant, thickened bundles. Specific stains for acetylcholinesterase highlight the abnormal morphology. Adrenergic denervation of the dilated segment is another inconsistent finding, as is a decreased supply of peptidergic nerves (containing VIP, substance P, enkephalins, and other peptides).

The most characteristic functional abnormality of aganglionosis is a failure of the internal anal sphincters to relax following rectal distention. Transient distention of a balloon in the rectum causes the intralumenal pressure at the level of the internal anal sphincter to drop; the drop is often accompanied by a reflex contraction of the external sphincter. Up to 20% of normal children may have a falsely absent reflex, especially if they are premature or of low birth weight, but *a positive response is strong evidence against Hirschsprung disease*.

Clinical classification of congenital megacolon:

1. "Classical type".
2. Short segment.
3. Ultra short segment.
4. Total colonic aganglionosis, zonal loss of ganglia, and others variants.

Incidence and genetics

The defect occurs once in each 5000 live births and is in some cases familial, with an overall incidence of 3.6% among siblings of all index cases. Because the disease was highly lethal until the introduction of curative surgery in the 1950s, accurate assessment of the incidence in the offspring of successfully treated patients is incomplete. Consanguinity of parents is exceptional, and the condition is reported to be discordant in dizygotic twins and concordant in monozygotes.

The association of congenital aganglionosis of the colon with Down syndrome is ten times more frequent than would be expected by chance; approximately 2% of patients with congenital megacolon have Down syndrome. A number of other congenital anomalies have been reported: hydrocephalus, ventricular septal defect, cystic deformities and agenesis of the kidney, cryptorchidism, diverticulum of the urinary bladder, imperforate anus, Meckel diverticulum, hypoplastic uterus, polyposis of the colon, ependymoma of the fourth ventricle, the Laurence–Moon–Bardet–Biedl syndrome, and congenital central hypoventilation syndrome (Ondine curse).

Clinical features

Hirschsprung disease should be suspected shortly after birth when the infant passes little meconium and the abdomen are distended. Digital examination of the rectum, insertion of a rectal tube, or administration of a small enema causes retained fecal material to gush forth, with apparent relief of the symptoms. However, the respite is often short-lived; signs of partial intestinal obstruction return, with persistent vomiting and distention as the major features. In about 20% of patients, diarrhea persists; it is caused by pseudomembranous enterocolitis, which develops as a complication of the obstruction.

Later in life, the presentation is often less dramatic and may not mimic an acute intestinal obstruction. Severe constipation and recurrent fecal impactions are more common. Children occasionally show evidence of anemia, malnutrition, and even hypoproteinemia resulting from protein-losing enteropathy; their resistance to infection can also be impaired. Although difficulties develop in most children before the second month of life, very-short-segment aganglionosis may not cause severe symptoms until after infancy.

Variants of congenital megacolon

The spectrum of Hirschsprung disease has widened considerably. Patients with a compatible clinical picture may have an ultra short segment of aganglionosis, involving only the internal anal sphincter. Morphologic confirmation of the diagnosis may be difficult, and physiological testing becomes even more important. Patchy or zonal loss of ganglia (ladder pattern) and dysplastic neurons have also been described. Cases classified as acquired aganglionosis have been reported. In these, ganglia were seen in tissues removed at an initial operation, but when clinical failure led to further surgery, an aganglionic segment was clearly demonstrable. Rather than that these were cases of acquired disease, it seems more likely that a short aganglionic segment was missed on the initial evaluation. With greater awareness of the more subtle morphologic and physiological abnormalities, Hirschsprung disease is being detected more often in adults. The clinical, physiological, and morphologic features in adulthood are usually similar to those of the milder form of the disease when recognized earlier in life. Thus, congenital megacolon (Hirschsprung disease) can be subdivided into the classical form, short-segment types, ultras hort-segment types, and other variants.

Differential diagnosis

Hirschsprung disease must be distinguished in the neonate from other developmental causes of intestinal obstruction, such as atresias and imperforate anus. Later in life, acquired (secondary) megacolon is the other major consideration. The diagnosis of congenital megacolon is usually not difficult beyond the immediate neonatal period, and the better diagnostic methods now available allow a positive diagnosis in most cases. Obstipation, with infrequent spontaneous passage of stool, dates from infancy, and the rectal examination reveals an empty ampulla. Overflow incontinence is not a feature of Hirschsprung disease.

A barium enema X-ray film (*Fig. 5.27*) confirms the diagnosis if the characteristic transition from the narrowed, distal rectum or rectosigmoid to the dilated proximal colon is seen. However, when the aganglionic segment is very short, a narrowed segment is not seen radiologically. In patients with acquired megacolon, encopresis is common, dilation extends all the way to the anus, and a narrowed zone is not seen.

Proctosigmoidoscopy reveals a normal but empty rectum. The dilated proximal bowel, if within range of the scope, is easily traversed except for abundant feces in the lumen; occasionally, stercoral ulcers are noted. The key findings are the empty lower segment and the absence of evidence of organic obstruction.

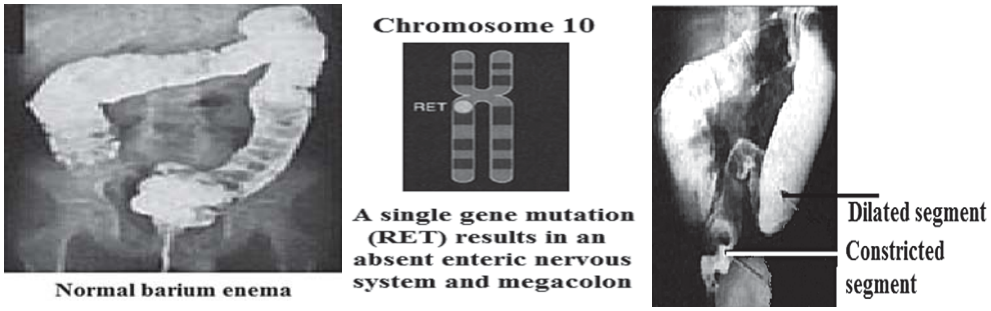


Figure 5.27. *Barium enema in a normal child contrasted with a study showing megacolon and a narrow segment affected with Hirschsprung disease. The genetic defect involves a mutation of the RET protooncogene on chromosome 10q11.2*

The diagnosis is best substantiated by a full-thickness biopsy of the rectum. The presence of normal numbers of ganglion cells excludes the diagnosis. Mucosal suction biopsy, satisfactory in many instances, is the initial procedure of choice because it is performed easily and requires no anesthesia. If the depth of the examination is sufficient to show the presence of ganglia in the Meissner (submucosal) plexus, the classical form of Hirschsprung disease is excluded. However, the absence of ganglion cells does not establish the diagnosis, and a full-thickness biopsy specimen should be obtained at least 3 cm proximal to the pectinate line. A diminution or absence of ganglion cells distal to this point is difficult to interpret. Careful histology proximal to the internal sphincter reveals that mesenteric ganglia may be absent from normal infants over a distance of 4 to 5 mm in this segment; ganglia may be absent from the deep and superficial submucosal layers for even longer distances. Immunohistochemical techniques can highlight the morphologic abnormalities, showing an abundance of hyperplastic axons but an absence of ganglion cells. Several approaches, in which antibodies to acetylcholinesterase, neuron-specific enolase, neurofilament, and neuropeptides are used, have been described.

Physiological tests complement the diagnosis in doubtful cases, and they may be crucial when the aganglionic segment is very short. Such cases are less easily detected on X-ray films and are also likely to be missed by biopsy. The most important pathophysiological test is the response of the anal sphincters to distention of the rectum. In contrast to the internal sphincter in normal individuals and in patients with acquired megacolon, the internal sphincter in patients with congenital aganglionosis fails to relax (or contracts even further) after the rectum is distended. The most common cause of a false-positive test result is a capacious rectum in constipation or megarectum; under these circumstances, distension of the rectal balloon does not stimulate the reflex. Therefore, an enlarged rectum should be excluded before Hirschsprung disease is diagnosed.

Treatment of megacolon

Preliminary decompression by colostomy is still sometimes necessary to relieve obstruction, or it may be necessary **in some infants** when it is decided to postpone

definitive surgery. However, the goal should be early diagnosis and a one-stage surgical approach.

The main goals are to establish regular and spontaneous defecation, to maintain normal continence, and not to interfere with sexual potency. The surgical procedure should cause essentially no mortality and minimal morbidity. A number of different operations have been used to remove successfully or to counterbalance the obstructing effect of the **aganglionic segment**. Long-term results are good in the great majority of patients.

In adults there are several surgical approaches to treat megacolon, such as a colectomy (removal of the entire colon) with ileorectal anastomosis (ligation of the remaining ileus and rectum segments), or a total proctocolectomy (removal of colon, sigmoid and rectum) followed by ileostomy or followed by ileoanal anastomosis.

REFERENCES

1. Ackland G, Grocott MP, Mythen MG. Understanding gastrointestinal perfusion in critical care: so near, and yet so far. Crit Care. 2000;4(5):269–81.

2. Acosta S, Nilsson TK, Bjorck M. Preliminary study of D-dimer as a possible marker of acute bowel ischaemia. Br J Surg. Mar 2001;88(3):385–8.

3. Albert JG, Martiny F, Krummenerl A, et al. Diagnosis of small bowel Crohn's disease: a prospective comparison of capsule endoscopy with magnetic resonance imaging and fluoroscopic enteroclysis. Gut 2005; 54(12): 1721–1727.

4. Altman DG. Some common problems in medical research. In: Altman DG, ed. Practical statistics for medical research. London, England: Chapman & Hall, 1991; 403–408.

5. Ambrosetti P, Chautems P, Soravia C, et al: Long-term outcome of mesocolic and pelvic diverticular abscesses of the left colon: a prospective study of 73 cases. Dis Colon Rectum. 2005, 48: 787–791.

6. Ambrosetti P, Jenny A, Becker C, et al: Acute left colonic diverticulitis-compared performance of computed tomography and water-soluble contrast enema: Prospective evaluation of 420 patients. Dis Colon Rectum. 2000, 43: 1363–1367.

7. Amos-Landgraf J, Kwong LN, Dove WF, et al. (2007). "A target-selected Apc-mutant rat kindred enhances the modeling of familial human colon cancer". PNAS 104 (10): 4036–41.

8. Armstrong PA. Visceral duplex scanning: evaluation before and after artery intervention for chronic mesenteric ischemia. Perspect Vasc Surg Endovasc Ther. Dec 2007;19(4):386–92; discussion 393–4.

9. Assar AN, Abilez DJ, Zarins CK. Outcome of open versus endovascular revascularization for chronic mesenteric ischemia: review of comparative studies. J Cardiovasc Surg (Torino). May 19 2009.

10. Aydin HN, Remzi FH, Tekkis PP, et al: Hartmann's reversal is associated with high postoperative adverse events. Dis Colon Rectum. 2005, 48: 2117–2126.

11. Bahadursingh AM, Virgo KS, Kaminski DL, et al: Spectrum of disease and outcome of complicated diverticular disease. Am J Surg. 2003, 186: 696–701.

12. Bernstein CN, Greenberg H, Boult I, Chubey S, Leblanc C, Ryner L. A prospective comparison study of MRI versus small bowel follow-through in recurrent Crohn's disease. Am J Gastroenterol 2005; 100(11): 2493–2502.

13. Bodily KD, Fletcher JG, Solem CA, et al. Crohn disease: mural attenuation and thickness at contrast-enhanced CT enterography-correlation with endoscopic and histologic findings of inflammation. Radiology 2006; 238(2): 505–516.

14. Booya F, Fletcher JG, Huprich JE, et al. Active Crohn disease: CT findings and interobserver agreement for enteric phase CT enterography. Radiology 2006; 241(3): 787–795.

15. Brandao D, Koullias GJ, Caparrelli DJ, Diethrich EB. Inferior mesenteric artery stenting: a solution for chronic mesenteric ischemia. Perspect Vasc Surg Endovasc Ther. Sep 2009;21(3):186–9.

16. Brenner DJ, Elliston CD. Estimated radiation risks potentially associated with full-body CT screening. Radiology 2004; 232(3): 735–738.

17. Cademartiri F, Palumbo A, Maffei E, et al. Noninvasive evaluation of the celiac trunk and superior mesenteric artery with multislice CT in patients with chronic mesenteric ischaemia. Radiol Med. Dec 2008;113(8):1135–42.

18. Cappell MS. Intestinal (mesenteric) vasculopathy. I. Acute superior mesenteric arteriopathy and venopathy. Gastroenterol Clin North Am. Dec 1998;27(4):783–825, vi.

19. Casella IB, Bosch MA, Sousa WO Jr. Isolated spontaneous dissection of the superior mesenteric artery treated by percutaneous stent placement: case report. J Vasc Surg. Jan 2008;47(1):197–200.

20. Chahid T, Alfidja AT, Biard M, et al. Endovascular treatment of chronic mesenteric ischemia: results in 14 patients. Cardiovasc Intervent Radiol. Nov-Dec 2004;27(6):637–42.

21. Chang JB, Stein TA. Mesenteric ischemia: acute and chronic. Ann Vasc Surg. May 2003;17(3):323–8.

22. Chapman J, Davies M, Wolff B, et al: Complicated diverticulitis: Is it time to rethink the rules?. Ann Surg. 2005, 242: 576–583.

23. Cokkinis AJ. Observations on the mesenteric circulation. J Anat. Jan 1930;64:200–205.

24. Colombel JF, Solem CA, Sandborn WJ, et al. Quantitative measurement and visual assessment of ileal Crohn's disease activity by computed tomography enterography: correlation with endoscopic severity and C reactive protein. Gut 2006; 55(11): 1561–1567.

25. Dwivedi A, Chahin F, Agrwal S, et al: Laparoscopic colectomy vs. open colectomy for sigmoid diverticular disease. Dis Colon Rectum. 2002, 45: 1309–1314.

26. Echenique-Elizondo M, Amondarain-Arratibel JA. Barium-induced peritonitis. An infrequent but persistent picture. Gastroenterol Hepatol. 2000, 23: 25–26.

27. English WP, Pearce JD, Craven TE, et al. Chronic visceral ischemia: symptom-free survival after open surgical repair. Vasc Endovascular Surg. Nov-Dec 2004;38(6):493–503.

28. Ersoy H. The role of noninvasive vascular imaging in splanchnic and mesenteric pathology. Clin Gastroenterol Hepatol. Mar 2009;7(3):270–8.

29. Fearnhead NS, Mortensen NJ. Clinical features and differential diagnosis of diverticular disease. Best Pract Res Clin Gastroenterol. 2002, 16: 577–593.

30. Florie J, Wasser MN, Arts-Cieslik K, Akkerman EM, Siersema PD, Stoker J. Dynamic contrast-enhanced MRI of the bowel wall for assessment of disease activity in Crohn's disease. AJR Am J Roentgenol 2006; 186(5): 1384–1392.

31. Ford MJ, Camilleri M, Wiste JA, Hanson RB. Differences in colonic tone and phasic response to a meal in the transverse and sigmoid human colon. Gut. 1995, 37: 264–269.

32. Furukawa A, Saotome T, Yamasaki M, et al. Cross-sectional imaging in Crohn disease. RadioGraphics 2004; 24(3): 689–702.

33. Gardner EJ (Jun 1951). "A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum". Am J Hum Genet 3 (2): 167–76.

34. Gourtsoyiannis N, Papanikolaou N, Grammatikakis J, Papamastorakis G, Prassopoulos P, Roussomoustakaki M. Assessment of Crohn's disease activity in the small bowel with MR and conventional enteroclysis: preliminary results. Eur Radiol 2004; 14(6): 1017–1024.

35. Guller U, Jain N, Harvey S, et al: Laparoscopic vs. open colectomy: Outcomes comparison based on large nationwide databases. Arch Surg. 2003, 138: 1179–1186.

36. Guzzo J, Hyman N. Diverticulitis in young patients: Is an aggressive approach really justified. Dis Colon Rectum. 2004, 47: 1187–1191.

37. Hara AK, Leighton JA, Heigh RI, et al. Crohn disease of the small bowel: preliminary comparison among CT enterography, capsule endoscopy, small-bowel follow-through, and ileoscopy. Radiology 2006; 238(1): 128–134.

38. Herbert GS, Steele SR. Acute and chronic mesenteric ischemia. Surg Clin North Am. Oct 2007;87(5):1115–34, ix.

39. Hladík P, Raupach J, Lojík M, Krajina A, Voboril Z, Jon B, et al. Treatment of acute mesenteric thrombosis/ischemia by transcatheter thromboaspiration. Surgery. Jan 2005;137(1):122-3.

40. Hong HS, Ha HK, Byun JH, Shin YM, Won HJ, Park SH. Optimization of low-density barium suspension in peroral small bowel follow-through examination [abstr]. In: Radiological Society of North America Scientific Assembly and Annual Meeting Program. Oak Brook, Ill: Radiological Society of North America, 2005; 185.

41. Horsthuis K, Lavini C, Stoker J. MRI in Crohn's disease. J Magn Reson Imaging 2005; 22(1): 1–12.

42. Indes JE, Giacovelli JK, Muhs BE, Sosa JA, Dardik A. Outcomes of endovascular and open treatment for chronic mesenteric ischemia. J Endovasc Ther. Oct 2009;16(5):624–30.

43. James AW, Rabl C, Westphalen AC, Fogarty PF, Posselt AM, Campos GM. Portomesenteric venous thrombosis after laparoscopic surgery: a systematic literature review. Arch Surg. Jun 2009;144(6):520–6.

44. Janes S, Meagher A, Frizelle A. Elective surgery after diverticulitis. Br J Surg. 2005, 92: 133–142.

45. Juillerat P, Mottet C, Froehlich F, et al. Extraintestinal manifestations of Crohn's disease. Digestion 2005; 71(1): 31–36.

46. Ko GJ, Han KJ, Han SG, Hwang SY, Choi CH, Gham CW, et al. [A case of spontaneous dissection of the superior mesenteric artery treated by percutaneous stent placement]. Korean J Gastroenterol. Feb 2006;47(2):168–72.

47. Koh DM, Miao Y, Chinn RJ, et al. MR imaging evaluation of the activity of Crohn's disease. AJR Am J Roentgenol 2001; 177(6): 1325–1332.

48. Kozuch PL, Brandt LJ. Review article: diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy. Aliment Pharmacol Ther. Feb 1 2005;21(3):201–15.

49. Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med. Dec 6 2001;345(23):1683–8.

50. Laghi A, Borrelli O, Paolantonio P, et al. Contrast enhanced magnetic resonance imaging of the terminal ileum in children with Crohn's disease. Gut 2003; 52(3): 393–397.

51. Laissy JP, Trillaud H, Douek P. MR angiography: noninvasive vascular imaging of the abdomen. Abdom Imaging. Sep-Oct 2002;27(5):488–506.

52. Lashner B. Clinical features, laboratory findings, and clinical course of Crohn's disease. In: Kirsner J, ed. Inflammatory bowel disease. 5th ed. Philadelphia, Pa: Saunders, 2000; 305–314.

53. Lauenstein TC, Ajaj W, Narin B, et al. MR imaging of apparent small-bowel perfusion for diagnosing mesenteric ischemia: feasibility study. Radiology. Feb 2005;234(2):569–75.

54. Lee SS, Ha HK, Yang SK, et al. CT of prominent pericolic or perienteric vasculature in patients with Crohn's disease: correlation with clinical disease activity and findings on barium studies. AJR Am J Roentgenol 2002; 179(4): 1029–1036.

55. Leung DA, Schneider E, Kubik-Huch R, Marincek B, Pfammatter T. Acute mesenteric ischemia caused by spontaneous isolated dissection of the superior mesenteric artery: treatment by percutaneous stent placement. Eur Radiol. 2000;10(12):1916–9.

56. Loffroy R, Steinmetz E, Guiu B, et al. Role for endovascular therapy in chronic mesenteric ischemia. Can J Gastroenterol. May 2009;23(5):365–73.

57. Low RN, Francis IR, Politoske D, Bennett M. Crohn's disease evaluation: comparison of contrast-enhanced MR imaging and single-phase helical CT scanning. J Magn Reson Imaging 2000; 11(2): 127–135.

58. Low RN, Sebrechts CP, Politoske DA, et al. Crohn disease with endoscopic correlation: single-shot fast spin-echo and gadolinium-enhanced fat-suppressed spoiled gradient-echo MR imaging. Radiology 2002; 222(3): 652–660.

59. Ludeman L, Warren BF, Shepherd NA. The pathology of diverticular disease. Best Pract Res Clin Gastroenterol. 2002, 16: 543–562.

60. Maccioni F, Bruni A, Viscido A, et al. MR imaging in patients with Crohn disease: value of T2-versus T1-weighted gadolinium-enhanced MR sequences with use of an oral superparamagnetic contrast agent. Radiology 2006; 238(2): 517–530.

61. Maglinte DD, Sandrasegaran K, Chiorean M, Dewitt J, McHenry L, Lappas JC. Radiologic investigations complement and add diagnostic information to capsule endoscopy of small-bowel diseases. AJR Am J Roentgenol 2007; 189(2): 306–312.

62. Maglinte DD, Sandrasegaran K, Lappas JC, Chiorean M. CT enteroclysis. Radiology 2007; 245(3): 661–671.

63. Mansour MA. Management of acute mesenteric ischemia. Arch Surg. Mar 1999;134(3):328-30; discussion 331.

64. Masselli G, Casciani E, Polettini E, Lanciotti S, Bertini L, Gualdi G. Assessment of Crohn's disease in the small bowel: prospective comparison of magnetic resonance enteroclysis with conventional enteroclysis. Eur Radiol 2006; 16(12): 2817–2827.

65. McKinsey JF, Gewertz BL. Acute mesenteric ischemia. Surg Clin North Am. Apr 1997;77(2):307–18.

66. Miyamoto N, Sakurai Y, Hirokami M, Takahashi K, Nishimori H, Tsuji K, et al. Endovascular stent placement for isolated spontaneous dissection of the superior mesenteric artery: report of a case. Radiat Med. Nov 2005;23(7):520–4.

67. Moawad J, Gewertz BL. Chronic mesenteric ischemia. Clinical presentation and diagnosis. Surg Clin North Am. Apr 1997;77(2):357–69.

68. Mueller MH, Glaetzer J, Kasparek MS, et al: Long-term outcome of conservative treatment in patients with diverticulitis of the sigmoid colon. Eur J Gastroenterol Hepatol. 2005, 17: 649–654.

69. Oderich GS, Bower TC, Sullivan TM, et al. Open versus endovascular revascularization for chronic mesenteric ischemia: risk-stratified outcomes. J Vasc Surg. Jun 2009;49(6):1472–9.e3.

70. Paterno F, Longo WE. The etiology and pathogenesis of vascular disorders of the intestine. Radiol Clin North Am. Sep 2008;46(5):877–85, v.

71. Penugonda N, Gardi D, Schreiber T. Percutaneous intervention of superior mesenteric artery stenosis in elderly patients. Clin Cardiol. May 2009;32(5):232–5.

72. Rafferty J, Shellito P, Hyman NH, et al: Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006, 49: 939–944.

73. Reittner P, Goritschnig T, Petritsch W, et al. Multiplanar spiral CT enterography in patients with Crohn's disease using a negative oral contrast material: initial results of a noninvasive imaging approach. Eur Radiol 2002; 12(9): 2253–2257.

74. Reyes Moreno J, Ginard Vicens D, Vanrell M, et al. (2007). "[Impact of a registry on the survival familial adenomatous polyposis.]" (in Spanish; Castilian). Medicina clínica 129 (2): 51–2.

75. Rhee RY, Gloviczki P. Mesenteric venous thrombosis. Surg Clin North Am. Apr 1997;77(2):327–38

76. Roberts P, Abel M, Rosen L, et al: Practice parameters for sigmoid diverticulitis. The Standards Task Force American Society of Colon and Rectal Surgeons. Dis Colon Rectum. 1995, 38: 125–132.

77. Salem L, Veenstra DL, Sullivan SD, et al: The timing of elective colectomy in diverticulitis: A decision analysis. J Am Coll Surg. 2004, 199: 904–912.

78. Schaefer PJ, Schaefer FK, Mueller-Huelsbeck S. Chronic mesenteric ischemia: stenting of mesenteric arteries. Abdom Imaging. Sep 6 2006.

79. Schoetz DJ Jr. Diverticular disease of the colon: A century-old problem. Dis Colon Rectum. 1999, 42: 703–709.

80. Schunk K, Kern A, Oberholzer K, et al. Hydro-MRI in Crohn's disease: appraisal of disease activity. Invest Radiol 2000; 35(7): 431–437.

81. Schwandener O, Farke S, Fischer F, et al: Laparoscopic colectomy for recurrent and complicated diverticulitis: A prospective study of 396 patients. Langenbecks Arch Surg. 2004, 389: 97–103.

82. Sempere GA, Martinez Sanjuan V, Medina Chulia E, et al. MRI evaluation of inflammatory activity in Crohn's disease. AJR Am J Roentgenol 2005; 184(6): 1829–1835.

83. Sharafuddin MJ, Olson CH, Sun S, et al. Endovascular treatment of celiac and mesenteric arteries stenoses: applications and results. J Vasc Surg. Oct 2003;38(4):692–8.

84. Silva JA, White CJ, Collins TJ. Endovascular therapy for chronic mesenteric ischemia. J Am Coll Cardiol. Mar 7 2006;47(5):944–50.

85. Sivamurthy N, Rhodes JM, Lee D. Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. J Am Coll Surg. Jun 2006;202(6):859–67.

86. Stollman N, Raskin JB. Diverticular disease of the colon. Lancet. 2004, 363: 631–639.

87. Stumpf M, Cao W, Klinge U, et al: Increased distribution of collagen type III and reduced expression of matrix metalloproteinase 1 in patients with diverticular disease. Int J Colorectal Dis. 2001, 16: 271–275.

88. Sullivan TM, Oderich GS, Malgor RD, Ricotta JJ 2nd. Open and endovascular revascularization for chronic mesenteric ischemia: tabular review of the literature. Ann Vasc Surg. Sep-Oct 2009;23(5):700–12.

89. Thaler K, Baig MK, Berho M, et al: Determinants of recurrence after sigmoid resection for uncomplicated diverticulitis. Dis Colon Rectum. 2003, 46: 385–388.

90. Thomson HJ, Busuttil A, Eastwood MA, et al: Submucosal collagen changes in the normal colon and in diverticular disease. Int J Colorectal Dis. 1987, 2: 208–213.

91. Travis SP, Stange EF, Lémann M, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. Gut 2006; 55(suppl 1): i16–i35.

92. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. Am J Gastroenterol 2006; 101(5): 954–964.

93. Umschaden HW, Szolar D, Gasser J, Umschaden M, Haselbach H. Small-bowel disease: comparison of MR enteroclysis images with conventional enteroclysis and surgical findings. Radiology 2000; 215(3): 717–725.

94. Wess L, Eastwood M, Busuttil A, et al: An association between maternal diet and colonic diverticulosis in an animal model. Gut. 1996, 39: 423–427.

95. Wess L, Eastwood MA, Wess TJ, et al: Cross linking of collagen is increased in colonic diverticulosis. Gut. 1995, 37: 91-94.

96. Wills JS, Lobis IF, Denstman FJ. Crohn disease: state of the art. Radiology 1997; 202(3): 597-610.

97. Wold PB, Fletcher JG, Johnson CD, Sandborn WJ. Assessment of small bowel Crohn disease: noninvasive peroral CT enterography compared with other imaging methods and endoscopy-feasibility study. Radiology 2003; 229(1): 275–281.

98. Wong WD, Wexner SD, Lowry A, et al: Practice parameters for the treatment of sigmoid diverticulitis-supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. Dis Colon Rectum. 2000, 43: 290–297.

Chapter 6

DISEASES OF THE RECTUM

6.1. ANATOMY

The rectum, along with the sigmoid colon, serves as a fecal reservoir. There is some controversy in the definition of the proximal and distal extent of the rectum. Some consider the rectosigmoid junction to be at the level of the sacral promontory, whereas others consider it to be at the point at which the teniae converge. Anatomists consider the dentate line the distal extent of the rectum, whereas surgeons typically view this union of columnar and squamous epithelium as existing within the anal canal and consider the end of the rectum to be the proximal border of the anal sphincter complex. The rectum is 12 to 15 cm in length and lacks teniae coli or appendices epiploicae. It occupies the curve of the sacrum in the true pelvis, and the posterior surface is almost completely extraperitoneal in that it is adherent to presacral soft tissues and thus is outside the peritoneal cavity. The anterior surface of the proximal third of the rectum is covered by visceral peritoneum. The peritoneal reflection is 7 to 9 cm from the anal verge in men and 5 to 7.5 cm in women. This anterior peritonealized space is called the pouch of Douglas or the pelvic cul-de-sac, and it may serve as the site of "drop" metastases from visceral tumors. These peritoneal metastases can form a mass in the cul-de-sac ("Bloomer's shelf") that can be detected by a digital rectal examination.

Pararectal fascia

The endopelvic fascia is a thick layer of parietal peritoneum that lines the walls and floor of the pelvis. The portion that is closely applied to the periosteum of the anterior sacrum is the presacral fascia. The fascia propria of the rectum is a thin condensation of the endopelvic fascia that forms an envelope around the mesorectum and continues distally to help form the lateral rectal stalks. The lateral rectal stalks or "ligaments" are actually anterolateral structures containing the middle rectal artery. The stalks reside in close proximity to the mixed autonomic nerves (containing both sympathetic and parasympathetic nerves), and division of these structures close to the pelvic sidewall may result in injury to these nerves, resulting in impotence and bladder dysfunction (*Fig. 6.1*).

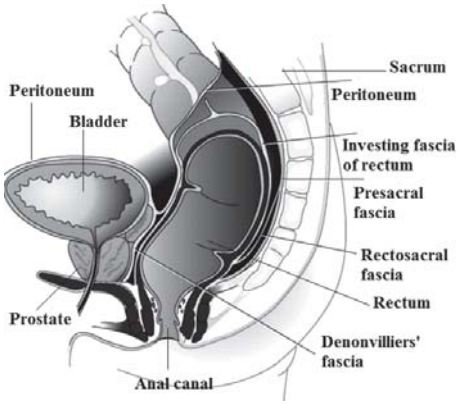


Figure 6.1. *Endopelvic fascia*

The rectosacral fascia, or Waldeyer's fascia, is a thick condensation of endopelvic fascia connecting the presacral fascia to the fascia propria at the level of S4 and extends to the anorectal ring. Waldeyer's fascia is an important surgical landmark, and its division during dissection from an abdominal approach provides

entry to the deep retrorectal pelvis. Dissection between the fascia propria and the presacral fascia follows the principles of surgical oncology and minimizes the risk of vascular or neural injuries. Disruption of the presacral fascia may lead to injury of the basivertebral venous plexus, resulting in massive hemorrhage. Disrupting the fascia propria during an operation for rectal cancer significantly increases the incidence of subsequent recurrence of cancer in the pelvis.

The Pelvic Floor

The muscles of the pelvic floor, like those of the anal sphincter mechanism, arise from the primitive cloaca. The pelvic floor or diaphragm consists of the pubococcygeus, iliococcygeus, and puborectalis, a group of muscles that together form the levator ani. The pelvic diaphragm resides between the sacrum, obturator fascia, ischial spines, and pubis. It forms a strong floor that supports the pelvic organs and, together with the external anal sphincter, regulates defecation. The "levator hiatus" is an opening between the decussating fibers of the pubococcygeus that allows egress of the anal canal, urethra, and dorsal vein in men and the anal canal, urethra, and vagina in women. The puborectalis is a strong U-shaped sling of striated muscle coursing around the rectum just above the level of the anal sphincters. Relaxation of the puborectalis straightens the anorectal angle and permits descent of feces; contraction produces the opposite effect. The puborectalis is in a state of continual contraction, a factor vital to the maintenance of continence. Puborectalis dysfunction is an important cause of defecation disorders. The pubococcygeus and iliococcygeus most likely participate in continence by applying lateral pressure to narrow the levator hiatus.

Arterial Supply and Venous and Lymphatic Drainage

The inferior mesenteric artery (IMA) originates from the aorta at the level of L2-3, approximately 3 cm above the aortic bifurcation.

The IMA terminates in the superior rectal (superior hemorrhoidal) artery that courses behind the rectum in the mesorectum, branching and then entering the rectal submucosa. Here, the capillaries form a submucosal plexus in the distal rectum at the level of the anal columns. The anal canal also receives arterial blood from the middle rectal (hemorrhoidal) and inferior rectal (hemorrhoidal) arteries. The middle rectal artery is a branch of the internal iliac artery. It is variable in size and enters the rectum anterolaterally, passing alongside and slightly anterior to the lateral rectal stalks. It has been reported to be absent in 40 to 80% of specimens studied. The inferior rectal artery is a branch of the pudendal artery that itself is a more distal branch of the internal iliac. From the obturator canal, it traverses the obturator fascia, ischiorectal fossa, and external anal sphincter to reach the anal canal. This vessel is encountered during the perineal dissection of an abdominoperineal resection.

The venous drainage of the colon and rectum mirrors the arterial blood supply. Venous drainage from the right and proximal transverse colon empties into the superior mesenteric vein, which coalesces with the splenic vein to become the portal vein. The distal transverse colon, descending colon, sigmoid, and most of the rectum drain into the inferior mesenteric vein, which empties into the splenic vein to the left of the aorta. The anal canal is drained by the middle and inferior rectal veins into the internal

iliac vein and subsequently the inferior vena cava. The bidirectional venous drainage of the anal canal accounts for differences in patterns of metastasis from tumors arising in this region.

Lymphatic drainage also follows the arterial anatomy. Lymph nodes are commonly grouped into "levels" depending on their location. Epicolic nodes are located along the bowel wall and in the epiploicae. Nodes adjacent to the marginal artery are paracolic. Intermediate nodes are located along the main branches of the large blood vessels; primary nodes are located on the SMA or IMA. Lymph node invasion by metastatic cancer is an important prognostic factor for patients with colorectal cancer. Accurate pathologic assessment of lymph nodes is essential for accurate staging, which serves as a determinant for treatment of patients with colorectal cancer.

Role in human defecation

The rectum intestinum acts as a temporary storage site for feces. As the rectal walls expand due to the materials filling it from within, stretch receptors from the nervous system located in the rectal walls stimulate the desire to defecate. If the urge is not acted upon, the material in the rectum is often returned to the colon where more water is absorbed. If defecation is delayed for a prolonged period, constipation and hardened feces results.

When the rectum becomes full, the increase in intrarectal pressure forces the walls of the anal canal apart, allowing the fecal matter to enter the canal. The rectum shortens as material is forced into the anal canal and peristaltic waves propel the feces out of the rectum. The internal and external sphincters allow the feces to be passed by muscles pulling the anus up over the exiting feces.

Anorectal examination

The anorectal examination is an important part of the gastrointestinal evaluation and not merely a means of obtaining stool for occult blood testing. It must be performed with particular care and thoroughness in anyone with anorectal complaints. The anorectal evaluation is usually reserved for the terminal portion of the examination after the patient-physician relationship has at least been partially established. Step-by-step explanation, reassurance, and gentle technique help to minimize patient embarrassment and discomfort. The patient should be placed in the left lateral decubitus position with the buttocks protruding just beyond the edge of the examining table. The hips may be slightly raised with a sandbag or a folded sheet. The prone jackknife position is ideal for examination of the anorectum, although it requires a specialized examining table and places the patient in a somewhat unfamiliar position. After the patient is adequately draped and the instruments are at hand but out of direct patient view, examination begins with inspection of the perineum. The buttocks, sacral region, and thighs are observed for signs of pilonidal disease, dermatologic conditions, and infections. The buttocks are then firmly retracted with both hands to permit inspection of the perianal region. Fistulous openings, fecal or mucus soiling, and excoriations or chronic skin changes give clues to underlying disease processes. Anal pathology such as tumors, skin tags, anal fissures, and prolapsing hemorrhoids are often best identified at this time. Lesions should be described with regard to their anatomic location.

Clock-face descriptions are confusing unless patient position and orientation are specified. Digital examination begins with palpation of the perianal area. Induration, tenderness, or the cord of a fistulous tract may be appreciated. The examining finger is well lubricated and slowly, gently inserted into the anus. Palpation begins away from the area of suspected pathology. Anesthetic lubricant may be necessary in those with painful lesions. Occasionally, adequate examination is impossible except under anesthesia. External hemorrhoids, thrombosed internal hemorrhoids, fissures, and fistulous tracts should be sought. Sphincter tone and the posterior puborectalis impression should be appreciated with the patient at rest, during squeeze, and when bearing down. The presacral area, the prostate, and even the cul-de-sac region may be palpated. Anteriorly, the impression of the cervix or an indwelling tampon should not be confused with pathology. During the examination of the rectal mucosa, the presence of polyps, tumors, feces, and foreign bodies is ascertained.

Anoscopy is the best means of examining the anal canal. It should be performed only if the patient has specific anal complaints. Fistulous openings and anal canal lesions are noted. Internal hemorrhoids may be seen arising just above the dentate line. Their true magnitude is best appreciated if the patient bears down and the hemorrhoids are seen to bulge into the lumen. Fissures and perianal lesions may be appreciated as the instrument is withdrawn to below the dentate line. Rigid proctosigmoidoscopy is performed for full evaluation of the distal colon and rectum. The rigid instrument is particularly useful for preoperative documentation of the position of a rectal cancer, large-bite rectal biopsy specimens for diagnosis of Hirschsprung disease, removal of foreign bodies, and evaluation of the mucosa if fiberoptic or video equipment is unavailable. For most other indications, the flexible instrument is preferred.

6.2. HEMORRHOIDS

Hemorrhoids it's result of dilation of the superior and inferior hemorrhoidal veins with disturbances in cavernous tissue of the rectum. These veins form a hemorrhoidal plexus, or cushion, in the submucosal layer of the lower rectum. Because the hemorrhoidal cushion is a normal anatomic structure, all adults are candidates for the development of symptomatic hemorrhoids. In the United States, estimates of prevalence range from 4.4% to as high as 50% of the adult population. Although it is widely believed that constipation is an important risk factor for hemorrhoids, recent studies suggest that diarrheal disorders are more frequently associated with hemorrhoidal disease.

Anatomic considerations

Hemorrhoids may be either external or internal, and often both types are present in the same individual. Internal hemorrhoids arise from the superior hemorrhoidal cushion above the mucocutaneous junction of the anorectum, or dentate line. Internal hemorrhoids are lined with rectal mucosa and occur in three primary locations: right anterior, right posterior, and left lateral, although anatomic variability is common. The end branches of the superior and middle hemorrhoidal arteries terminate in the

submucosa above the dentate line with an anterior and posterior branch on the right and a single lateral branch on the left, corresponding to the three primary hemorrhoid locations. The right posterior and left branches give off two end branches to potentially form secondary hemorrhoids. External hemorrhoids arise from the inferior hemorrhoidal venous plexus below the mucocutaneous junction and are lined by perianal squamous epithelium. The perianal squamous epithelium of the anus contains numerous pain receptors, so that thrombosis of external hemorrhoids causes significant pain. Internal and external hemorrhoidal plexuses freely communicate to drain the lower rectum and anus. Internal and external hemorrhoids drain into the inferior vena cava through the internal pudendal veins (*Fig. 6.2*).

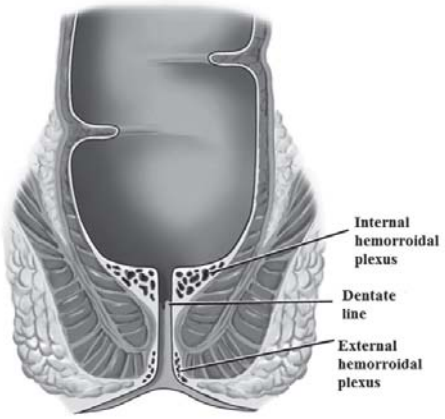


Figure 6.2. *Rectum*

Pathogenesis

Elegant histological studies have shown that hemorrhoids are normal features of the human anatomy. They have three important parts: the lining (rectal mucosa or anoderm), the stroma (blood vessels, smooth muscle, supporting connecting tissue), and the anchoring connective tissue (which secures the hemorrhoids to the sphincter mechanism). Hemorrhoidal tissue has anatomic similarities to erectile tissue such as the corpora cavernosa. With age or other aggravating factors, the anchoring and supporting connective tissue deteriorates, causing the hemorrhoids to bulge and descend, leading eventually to symptoms. This theory is supported by the increased incidence of hemorrhoids in patients with chronic constipation, diarrhea, pregnancy, or pelvic tumors-conditions that increase pelvic venous pressure. In certain individuals, the internal sphincter becomes hypertrophic and the anal outlet becomes functionally narrowed. At straining, the fecal bolus acts as an obturator forcing the hemorrhoidal cushions to descend through the hypertrophic sphincter, enlarge, and become symptomatic.

Definitions

External skin tags are redundant folds of skin that arise from the anal verge. External hemorrhoids arise from the inferior hemorrhoidal plexus below the dentate line and are covered by anal squamous epithelium. Internal hemorrhoids arise from the superior hemorrhoidal plexus above the dentate line and are covered by columnar epithelium of the rectum. They may be classified according to their degree of protrusion or prolapse. First-degree hemorrhoids bulge into the lumen of the anorectal canal on anoscopy but do not protrude out of the anus. Second-degree hemorrhoids prolapse out of the anus with defecation or straining but reduce to a normal anatomic position spontaneously. Third-degree hemorrhoids prolapse out of the anus with defecation or straining and require digital reduction. Fourth-degree hemorrhoids are irreducible and are at risk for strangulation. The clinical presentation and recommended therapy

for the various degrees of hemorrhoids are different and are discussed later. Anorectal varices are not hemorrhoids; they occur as a consequence of portal hypertension and are discussed separately.

External skin tags

After thrombosis of an external hemorrhoid, the overlying skin becomes redundant, and this excess skin remains long after the underlying clot resolves. External skin tags may also arise after formal hemorrhoidectomy or de novo in cases of inflammatory bowel disease. Primary symptoms, if present, are complaints of a palpable growth near the anus and difficulty with anal hygiene. Skin tags are relatively easy to distinguish from more serious pathology such as anal cancer or condyloma acuminata by their gross appearance as normal skin and their soft, fleshy texture on palpation. Treatment is conservative whenever possible, and surgical excision is only necessary in cases of poor hygiene or patient anxiety.

External hemorrhoids

Thrombosis of an external hemorrhoid can be an extremely painful event. Distention of overlying perianal skin and inflammation associated with the process of thrombosis may cause severe patient discomfort (*Fig. 6.3*). Bleeding usually occurs late in the course of thrombosed external hemorrhoids after the overlying perianal skin ulcerates and the resolving, liquefied hematoma necessitates. External hemorrhoids should be distinguished from strangulated internal hemorrhoids and anorectal varices. Strangulated internal hemorrhoids tend to be larger and more circumferential, encompassing the entire anus. Anorectal varices should be considered in any patient with a history of cirrhosis or portal hypertension.

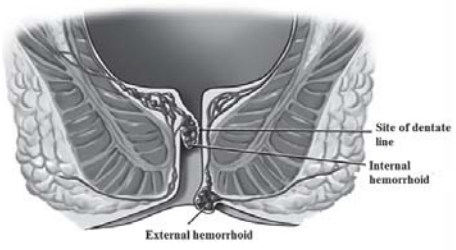


Figure 6.3. *Anatomy of hemorrhoids*

Many thrombosed external hemorrhoids can be treated with warm sitz baths two to three times per day. Stool softening agents such as psyllium seed preparations, synthetic mucilloids, and the sodium or calcium salts of dioctyl sulfosuccinate can minimize straining at stool and prevent aggravation of the pain and thrombosis. Topical therapy with anesthetic ointments and witch hazel-impregnated pads may provide additional relief. One must temper the attribution of clinical improvements to medical therapy with the knowledge that the natural history of thrombosed external hemorrhoids is resolution after 48 to 72 hours.

If the pain is severe and the patient is seen within 48 hours of symptom onset, surgical evacuation or excision of the thrombosed external hemorrhoid should be performed. After the thrombus has organized, it cannot be evacuated. This can usually be done in the clinic setting and provides prompt relief.

Internal hemorrhoids

Internal hemorrhoids (*Fig. 6.4*) may be asymptomatic or associated with discomfort, pruritus ani, fecal soiling, or prolapse. Bleeding, however, is the typical

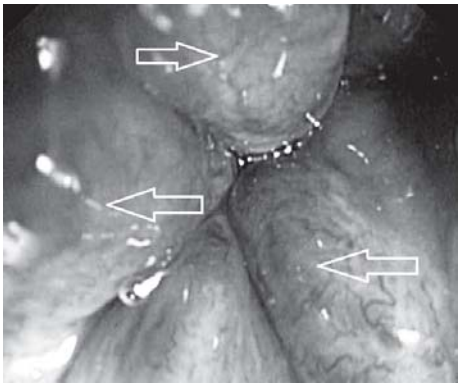


Figure 6.4. *Internal hemorrhoids (arrows)*

complaint that brings the patient to the physician and hemorrhoids are the most common cause of rectal bleeding. Such bleeding is described as bright red spotting on the toilet tissue or dripping into the toilet bowl. It most often occurs at the end of defecation and is separate from the stool. It does not usually occur apart from defecation. Rarely, acute severe bleeding requires transfusion and, occasionally, ongoing chronic losses cause iron-deficiency anemia. However, hemorrhoids should not be considered the source of hematochezia until other potential bleeding sources in the colon and rectum have been investigated. With the possible exception of a young patient with a bleeding pattern typical of hemorrhoids, a flexible sigmoidoscopy or, if clinically appropriate, a full colonoscopy should be performed. Occult bleeding should not be attributed to hemorrhoids. Occult blood in the stool deserves a complete evaluation regardless of the presence of hemorrhoids.

Prolapse of the hemorrhoidal tissue is another common complaint (*Figs. 6.5, 6.6*). Prolapse may manifest itself anywhere along a continuum of symptoms from difficulty with anal hygiene to painful strangulation. Prolapsed tissue may also be a presenting symptom of rectal prolapse, rectal polyps, or rectal cancer. Sigmoidoscopic evaluation with biopsy of suspicious lesions should be carried out if appropriate. Anal condyloma and anal cancer are easily differentiated from prolapsing hemorrhoids, and thrombosed external hemorrhoids tend to cause pain as a presenting symptom.

All degrees of internal hemorrhoids may be associated with mild discomfort, but only strangulated hemorrhoids cause significant pain. Strangulated hemorrhoids usually possess an external and internal component and occur secondary to prolapse with subsequent lack of blood supply. Progression to gangrene with resultant infection is life threatening and will occur if immediate surgical therapy is not instituted. In contrast to complete rectal prolapse, strangulated hemorrhoids lack concentric mucosal folds and are irreducible.

CLASSIFICATION

Hemorrhoids are divided into **two forms**: acute and chronic.

Acute hemorrhoids:

• 1st Degree: characterized by thrombosis of external and internal hemorrhoids without inflammatory process.

• 2nd Degree: the inflammation of the hemorrhoids is peculiar: more pronounced edema, hyperemia is observed.

• 3rd Degree: against the background of thrombosis and inflammation of the hemorrhoids develop inflammation of the subcutaneous tissue and perianal skin.

Chronic Hemorrhoids:

• 1st Degree: bleeding occurs, but do not prolapse outside the anal canal.

• 2nd Degree: prolapse outside the anal canal upon defecation, but retract spontaneously.

• 3rd Degree: require manual reduction after prolapsed (*Fig. 6.5*).

• 4th Degree: cannot be reduced, because of strangulation (*Fig. 6.6*).

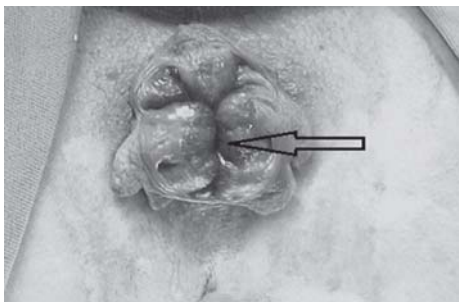


Figure 6.5. *3rd Degree prolapse (arrow)*

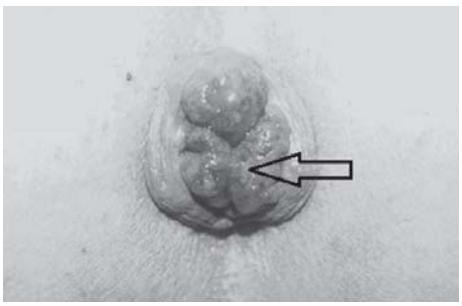


Figure 6.6. *4rd Degree prolapse (arrow)*

Risk factors

1. Past history of hemorrhoid symptoms or anal fissure.
2. Age 30–65.
3. Heavy lifting, prolonged sitting.
4. Constipation/Diarrhea.
5. Pregnancy.
6. Failure to eat breakfast.
7. Diet-Spicy food, fats, alcohol, smoking, low water intake.
8. Obesity.
9. Spinal cord injuries.
10. Increased sphincter tone.

Hemorrhoid prevention

1. Add fiber to prevent constipation and diarrhea.
2. Drink lots of water.
3. Do not ignore the urge to go.
4. Do not strain.
5. Limit time on commode to two minutes.
6. Remove the library from the bathroom.
7. Avoid obesity.

Complications

Hemorrhoids can produce several uncomfortable, but non-serious problems.

Thrombosis and pain (*Fig. 6.7*). A blood clot in the hemorrhoid may cause severe pain and usually demands immediate medical attention.

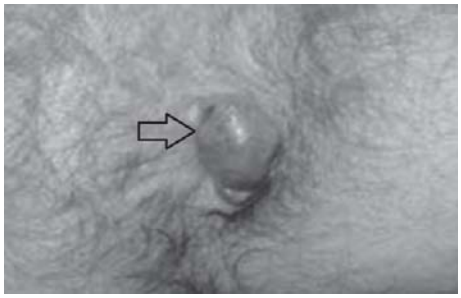


Figure 6.7. *Thrombosed external hemorrhoid (arrow)*

Bleeding. Hemorrhoids can ooze fresh red blood, whether located externally or

internally. External hemorrhoids often cause dripping of blood from the anus while sitting on the toilet. The blood might also be seen as soiling of the underwear. Internal hemorrhoids that bleed may produce fresh blood in the stool.

Itching and irritation. External hemorrhoids can be itchy, especially if the area is moist and irritated.

TREATMENT

Conservative therapy. Dietary counseling, behavior adjustment, and topical agents are effective for most first-and second-degree hemorrhoids. A high-fiber diet and adequate fluid intake should be prescribed to promote passage of soft, bulky stools to prevent straining. Some patients may require the addition of hydrophilic bulk-forming agents such as psyllium extracts or mucilloids. Excessive and prolonged defecatory straining should be discouraged. Many patients benefit from warm sitz baths twice daily and attention to proper anal hygiene. A number of proprietary agents such as suppositories, ointments, and medicated pads (witch hazel and glycerin) may provide topical astringent relief. Hydrocortisone or anesthetic-containing preparations (benzocaine, lidocaine, pramoxine, dibucaine) offer short-term relief of pruritus, burning, and soreness, although firm efficacy data are lacking.

If conservative therapy does not suffice, a definitive procedure is necessary. The available treatment modalities can be broadly classified into one of two categories: those that involve loss of redundant mucosa and those that do not. In general, first- and second-degree hemorrhoids can be treated without removal of redundant hemorrhoidal tissue. Third- and fourth-degree hemorrhoids usually require a form of therapy that results in both thrombosis of the hemorrhoid and removal of redundant tissue.

And other types of treatment

Rubber band ligation

Barron first described a rapid, simple, effective device for the treatment of internal hemorrhoids in the office or outpatient setting. Band ligation is associated with both thrombosis of the hemorrhoid and removal of redundant mucosal tissue. By inducing submucosal scarring, development of new hemorrhoidal tissue is prevented. Rubber band ligation is a good treatment for refractory first-degree hemorrhoids as well as all second- and selected third-degree hemorrhoids. Fourth-degree hemorrhoids are not well treated by this method.

Because it is an outpatient procedure, no special preparation is needed for the majority of patients. After anorectal evaluation is performed, the anoscope is inserted and a hemorrhoidal cushion is selected for band application. No anesthetic is required if care is taken to place the band at least 0.5 cm above the dentate line. Some authors recommend banding of only one column per session to minimize tissue necrosis, but up to four ligations has been performed with acceptable morbidity. Rubber band ligation allows a controlled removal of tissue rivaled only by formal hemorrhoidectomy.

Complications are rare but serious. Migration of the band onto the anoderm is associated with excruciating pain requiring immediate removal of the band. Persistent

severe pain, fever, urinary retention, or foul-smelling rectal drainage may herald the presence of a rectal infection. A number of case reports of necrotizing infection and death as a result of band ligation have appeared in the literature. Significant discomfort lasting for days occurs in some patients and mucosal slough with potential for bleeding occurs 5 to 7 days after band application.

Results of rubber band ligation are generally excellent. Long-term patient satisfaction is about 90%. No requirement for anesthesia and the ability to perform band ligation in the clinic setting continue to make this a popular treatment option for patients with hemorrhoids. Novel methods to perform banding have also been employed. A band ligator cap device attached to the tip of a flexible endoscope allows excellent visualization of band placement. Inexpensive plastic single-handed ligators have been developed that employ suction to capture the hemorrhoidal tissue for band placement.

Injection sclerotherapy

The use of a sclerosant solution such as sodium morrhuate or 5% phenol is an accepted treatment for first- and second-degree hemorrhoids. The sclerosant is injected with a special hemorrhoidal needle into the submucosa around, but not into, symptomatic hemorrhoids. An intense inflammatory reaction results in fixation of the mucosa to the underlying muscle thus obliterating the submucosal layer where hemorrhoids form. Injection of sclerosants is a less controlled and therefore less popular technique than rubber band ligation. Known complications are mucosal slough, prostatic infection, contact hypersensitivity, and rectal infection. A refinement of injection sclerotherapy for hemorrhoids uses a flexible endoscope to inject 23.4% saline through a sclerotherapy needle into the hemorrhoidal cushion.

Cryosurgery

Special cryoprobes activated by liquid nitrogen, carbon dioxide, or nitrous oxide have been developed. Local tissue destruction is caused by freezing and subsequent necrosis. All symptomatic hemorrhoids are treated in one session. If deep freezing of the submucosal hemorrhoidal cushions does not occur, symptoms persist. Tissue damage is uncontrolled, and wound healing is accompanied by prolonged anal drainage, late bleeding, and pain. Compared with rubber band ligation, patient satisfaction is less and local complications more frequent with the cryosurgical technique.

Electrocoagulation

Electrosurgical units have been adapted for use in the outpatient therapy of internal hemorrhoids. Application of direct electrical current is less precise than with band ligation or formal hemorrhoidectomy and requires several minutes of contact time. Excess electrical current is grounded through the patient's body, and occasionally discharges occur that cause injury at sites distant from the area of intended tissue destruction. Bipolar electrocoagulation is as efficacious as the direct current technique and is performed more rapidly. It may be easier to perform and less painful than rubber band ligation.

Photocoagulation

Both infrared light and lasers have been used to treat symptomatic hemorrhoids. Photocoagulation stimulates fibrosis of the submucosal layer by first causing tissue coagulation and necrosis. Advocates of photocoagulation point to the lack of electrical contact with the patient's body and a more controlled application of destructive force compared with electrofulgeration. Infrared devices are hand-held and much less expensive than laser devices. Equipment for both forms of photocoagulation is more expensive than equipment for rubber band ligation or injection sclerotherapy. The incidence of discomfort and complications compare favorably with those of rubber band ligation and injection sclerotherapy. Rubber band ligation therapy produces more posttreatment pain than injection sclerotherapy or infrared photocoagulation, but fewer patients are likely to need re-treatment because of symptomatic recurrences. Laser photocoagulation is an additional, albeit expensive, alternative. Using a carbon dioxide laser, 1816 consecutive patients were treated with success rates approaching those of more established therapies.

Hemorrhoidectomy

Fewer than 10% of symptomatic hemorrhoids require surgical hemorrhoidectomy. It is the treatment of choice for most third-degree hemorrhoids, all fourth-degree hemorrhoids, strangulated hemorrhoids, and hemorrhoids that have persisted despite other forms of therapy. Advantages of the surgical approach include precise removal of all internal and external hemorrhoids, control of bleeding, and rapid wound healing. Disadvantages include the need for regional anesthesia, postoperative pain, risk of postoperative urinary retention, and expenses incurred from both hospitalization and lost time from work.

The most common operation is aimed at excising three hemorrhoids. In 1927, E. Milligan and S. Morgan described the operation, focusing on ligation of the vascular legs of the hemorrhoidal nodes on the 3rd, 7th and 11th hours. Hemorrhoidal nodes excised from the outside inward, stitched and cut off. Three wound surfaces remain open, and they heal by secondary tension (*Fig. 6.8*). Therefore, the operation is also called "open hemorrhoidectomy".

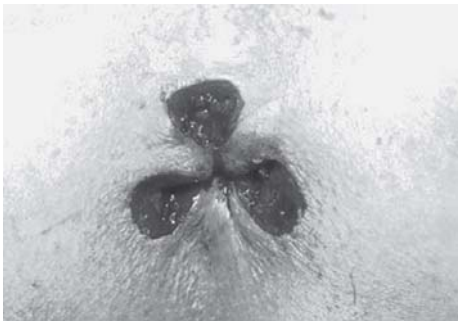


Figure 6.8. *Hemorrhoidectomy on Milligan-Morgan's*

Currently, its varieties are most often used. The first is a closed hemorrhoidectomy with restoration of the mucous membrane of the anal canal with nodular or continuous catgut sutures (Ferguson-Chiton's operation). This kind of surgical intervention is more often treated with hemorrhoids of the third and fourth stage in the absence of clear boundaries between the external and internal hemorrhoids. The second type is submucosal hemorrhoidectomy, which is performed on the basis of a plastic type. It was first proposed by A. Pares in 1956. The advantage lies in the fact that the mucous membrane of the anal canal is not excised together with the

hemorrhoidal node, but it is dissected by arcuate incisions, after which a haemorrhoidal node is isolated from the submucosal layer, bandaged leg, knot is cut off, leaving the stump of the removed node in the submucosa layer. This technique allows to completely restoring the mucous membrane of the anal canal without deformation and cover it with the stump of the node.

New methods for treating hemorrhoids include stapler hemorrhoidopexy (Longo's operation, 1998) and desarterization under the control of Doppler – a procedure in which a special anoscope with an integrated Doppler sensor is used, with which arterial vessels feeding the hemorrhoidal nodes are found and ligated.

Ablation of the internal sphincter

Two strategies have been employed to decrease the abnormally high resting anal pressure found in some patients with hemorrhoids. Lord advocated forceful anal dilation under general anesthesia, but the procedure causes variable and uncontrolled damage to the anal sphincters with resulting fecal incontinence. Good results occur in 80% of patients, but some of the efficacy of this procedure may reflect submucosal hemorrhage and subsequent scar formation. A more controlled disruption of the internal sphincter is achieved with lateral internal sphincterotomy.

A meta-analysis of randomized controlled trials assessing at least two treatment modalities for symptomatic hemorrhoids found that rubber band ligation was superior to sclerotherapy and patients undergoing ligation were less likely to require future therapy than those treated with sclerotherapy or infrared coagulation. Hemorrhoidectomy resulted in a better response than rubber band ligation, but the surgical group had significantly more pain and a higher incidence of complications. Based on these findings, it seems reasonable to suggest band ligation or a similar treatment as first-line therapy for grades 1 to 3 hemorrhoids, reserving hemorrhoidectomy for large grade 3 and grade 4 hemorrhoids and for those failing other techniques.

Anorectal varices

Meticulous histological study has shown that anorectal varices and hemorrhoids are unrelated. Hemorrhoids are vascular cushions of ectatic venular-arteriolar connections of the hemorrhoidal plexus and they have no direct connection to the portal system. They occur independently of anorectal varices and the presence or degree of portal hypertension. Alternatively, rectal varices represent enlarged portal-systemic collaterals which correlate with the presence of portal hypertension. They develop as a result of hepatofugal portal venous flow through the inferior mesenteric vein to the superior hemorrhoidal veins. The varices represent the communication between these superior hemorrhoidal veins (portal circulation) and the middle and inferior hemorrhoidal veins (systemic circulation) which, in turn, flow into the femoral vein and then to the inferior vena cava. The distinction of anorectal varices from external hemorrhoids may be difficult. Often patients with anorectal varices have other known manifestations of portal hypertension such as esophageal varices and ascites. Anorectal varices are usually discrete, serpentine, submucosal veins. In contrast to external hemorrhoids, varices are compressible and refill rapidly. They extend from the squamous portion of the anal canal across the dentate line and into the

rectum proper. Nearly 45% of patients with cirrhosis will be found to have anorectal varices by careful endoscopic examination and the prevalence increases to 75% using rectal endosonography, 5% of patients with bleeding as a manifestation of portal hypertension bled from anorectal varices. Bleeding may occur from either the anal or rectal portion of the varix and can be massive and life threatening.

The optimal management of anorectal varices is not known. Injection sclerotherapy, cryotherapy, rubber band ligation, and hemorrhoidectomy have all been associated with torrential, occasionally fatal bleeding. Treatment by underrunning the variceal columns with absorbable suture achieves primary control in a majority of cases and has a very low rate of morbidity. Rubber band ligation has also been advocated but must be done in a controlled environment with full resuscitation capabilities. Inferior mesenteric vein embolization or ligation has been reported. Ultimately, surgical or transjugular intrahepatic portosystemic shunting may be required.

6.3. ANORECTAL ABSCESS AND FISTULA

Suppurative anorectal infection can be divided into two categories-anorectal abscess and anorectal fistula. Anorectal abscess may be defined as an undrained collection of perianal pus. Anorectal fistula is an abnormal communication between the anorectal canal and the perianal skin. Abscess is the acute manifestation and fistula the chronic manifestation of suppurative anorectal infection. In most cases, the underlying pathophysiology is thought to be the same and the treatment for each is essentially surgical.

Epidemiology and Etiology

In a series of 1023 patients treated for anorectal abscess or fistula, the male-to-female ratio was 2:1. The age distribution was from 10 to 82 years, with the majority in the third and fourth decades of life. The most common associated medical diseases were hypertension, diabetes, heart disease, and inflammatory bowel disease. The incidence of perirectal infection in patients with acute leukemia is approximately 8%.

Current evidence suggests that infection of the anal glands is the most common cause of anorectal abscess and anorectal fistula. The most common bacterial isolates are *Escherichia coli, Enterococcus species,* and *Bacteroides fragilis*. Histological specimens from patients with anorectal fistula revealed infected anal glands 70% to 90% of the time. Anal glands arise from the anal canal at the level of the crypts of Morgagni. At least half of the glands are observed to penetrate into the intersphincteric space. Obstruction of the anal glands may occur in the presence of trauma, anal eroticism, diarrhea, hard stools, or foreign bodies, with resultant stasis and secondary infection. This cryptoglandular origin of anorectal abscess and fistula is further supported by the fact that the primary internal orifice is found at the level of the dentate line.

6.3.1. ANORECTAL ABSCESS

Anorectal abscess (also known as an anal/rectal abscess, perianal/perirectal abscess) is an abscess (a large pocket of infection) adjacent to the anus. It arises from an infection at one of the anal crypts of Morgagni which leads to inflammation and abscess formation.

Anorectal abscesses may be classified by anatomic site of origin and potential pathways of extension. Abscesses that are inferior to the puborectalis and levator ani muscles are classified as low intermuscular abscesses, and those that extend above these muscles are classified as high intermuscular abscesses. Low intermuscular abscesses are subclassified as perianal, submucosal, intersphincteric, or ischiorectal. High intermuscular abscesses are described as pelvirectal, retrorectal, or rectovesical. Proper surgical management is guided by correct anatomic identification of the type of anorectal abscess.

Classification

There are four types of anorectal abscesses:

- Perianal.
- Ischiorectal.
- Intersphincteric.
- Supralevator (*Fig. 6.9*).

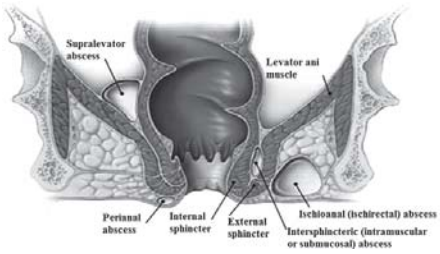


Figure 6.9. *Anatomic classification of perirectal abscess*

Signs and symptoms

Pain in the perianal area is the most common symptom of an anorectal abscess. The pain may be dull, aching, or throbbing. It is worst when the person sits down and right before a bowel movement. After the individual has a bowel movement, the pain usually lessens. Other signs and symptoms of anorectal abscess include constipation, drainage from the rectum, fever and chills, or a palpable mass near the anus. The condition invariably becomes extremely painful, and usually worsens over the course of just a few days. The pain may be limited and sporadic at first, but invariably worsens to a constant pain which can become very severe when body position is changed (e.g., when standing up, rolling over, and so forth). Depending upon the exact location of the abscess, there can also be excruciating pain during bowel movements, though this is not always the case. This condition may occur in isolation, but is frequently indicative of another underlying disorder, such as Crohn's disease.

Differential diagnosis

Specific diseases may cause anorectal abscess and anorectal fistula in the absence of primary cryptoglandular infection. These include Crohn's disease, anorectal malignancy, tuberculosis, actinomycosis, lymphogranuloma venereum, radiation-induced proctitis, leukemia, and lymphoma. Other disease states that may cause a similar clinical picture and should be included in the differential diagnosis of suppurative anorectal conditions are infected presacral epidermal inclusion cysts, hidradenitis suppurativa, diverticulitis, pilonidal disease, and Bartholin abscesses.

This condition is often misdiagnosed initially by the patient as a bad case of hemorrhoids, since this is almost always the cause of any sudden anal discomfort. The presence of the abscess, however, is to be suspected when the pain quickly

worsens over one or two days and the usual hemorrhoid treatments are ineffective in bringing relief. Furthermore, any serious abscess will eventually begin to cause signs and symptoms of general infection, including fever and nighttime chills.

A physician can rule out a hemorrhoid with a simple visual inspection, and usually appreciate an abscess by touch.

Diagnostic approach

Diagnosis of anorectal abscess begins with a medical history and physical exam. Imaging studies which can help determine the diagnosis in cases of a deep non-palpable perirectal abscess include pelvic CT scan, MRI or trans-rectal ultrasound. These studies are not necessary, though, in cases which the diagnosis can be made upon physical exam.

Treatment

Anal abscesses, unfortunately, cannot be treated by a simple course of antibiotics or other medications. Even small abscesses will need the attention of a surgeon immediately. Treatment is possible in an emergency room under local anesthesia, but it is highly preferred to be formally admitted to a hospital and to have the surgery performed in an operating room under general anesthesia.

Generally speaking, a fairly small but deep incision is performed close to the root of the abscess. The surgeon will allow the abscess to drain its exudate and attempt to discover any other related lesions in the area. This is one of the most basic types of surgery, and is usually performed in less than thirty minutes by the anal surgical team. Generally, a portion of the exudate is sent for microbiological analysis to determine the type of infecting bacteria. The incision is not closed (stitched), as the damaged tissues must heal from the inside toward the skin over a period of time.

The patient is often sent home within twenty-four hours of the surgery, and is instructed to perform several "sitz baths" per day, whereby a small basin (which usually fits over a toilet) is filled with warm water (and possibly, salts) and the affected area is soaked for a period of time. During the week following the surgery, many patients will have some form of antibiotic therapy, along with some form of pain management therapy, consistent with the nature of the abscess.

The patient usually experiences an almost complete relief of the severe pain associated to his/her abscess upon waking from anesthesia; the pain associated with the opening and draining incision during the post-operative period is often mild in comparison. In many cases, the patient is completely healed with no discomfort whatsoever within just one or two weeks of the surgery.

Complications

If left untreated, an anal fistula will almost certainly form, connecting the rectum to the skin. This requires more intensive surgery. Furthermore, any untreated abscess may (and most likely will) continue to expand, eventually becoming a serious systemic infection.

6.3.2. ANORECTAL FISTULA

Anorectal fistula is described based on pathogenesis of the disease (e.g., Crohn's disease, hidradenitis suppurativa) and classified according to the normal

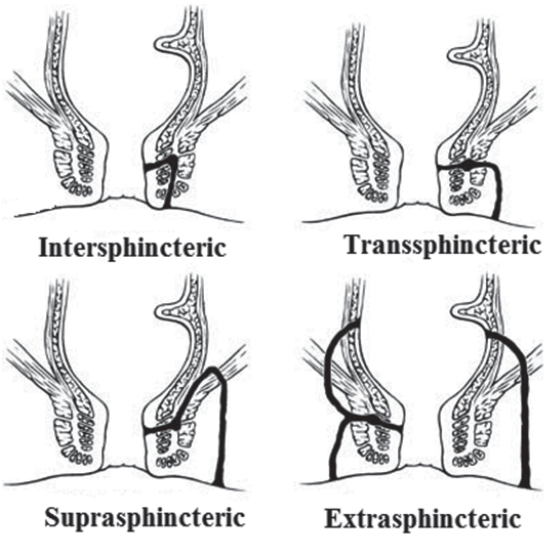


Figure 6.10. *Anatomic classification of anorectal fistula*

muscular anatomy of the pelvic floor. All anorectal fistulas are anatomically divided into one of four groups (*Fig. 6.10*). The most common type of anorectal fistula is the intersphincteric fistula, in which the fistula ramifies only in the areolar tissue between the internal and external anal sphincters. Transsphincteric fistula passes from the intersphincteric plane through the external sphincter and into the ischiorectal fossa. Suprasphincteric fistula passes upward in the intersphincteric plane, over the puborectalis muscle, and into the ischiorectal fossa. Extrasphincteric fistula passes from the perianal skin through the ischiorectal fat and levator muscles into the rectum. Division of the entire tract of either suprasphincteric or extrasphincteric fistula results in total division of the muscles of continence.

Clinical manifestations

Acute pain and swelling are the most common complaints in the patient with anorectal abscess. Pain may occur in the absence of swelling, especially with small intersphincteric or pelvirectal abscesses. Sitting, movement, and defecation exacerbate pain. Antecedent history may reveal a bout of constipation, diarrhea, or minor trauma. Constitutional symptoms include malaise and fever. The presence of foul-smelling drainage means that the abscess has necessitated, or is discharging through the primary anal orifice. Inspection of the perineum of a patient with perirectal abscess reveals the cardinal signs of inflammation: redness, heat, swelling, and tenderness. Drainage may be observed from the infected crypt orifice. An intersphincteric abscess may manifest only as localized tenderness. Rectal examination is often difficult because of pain, so evaluation under anesthesia is indicated if a complete examination is otherwise impossible. Delay in making the diagnosis of anorectal abscess leads to extension of the infection into previously uninfected spaces and also increases the subsequent risk of overwhelming sepsis.

Chronic, purulent drainage is the chief complaint of patients with anorectal fistula. A history of prior anorectal abscess is frequently elicited. Discomfort or pain often occurs with defecation but is not as severe as that associated with anal fissure or anorectal abscess. The perianal skin may be pruritic or excoriated. Bleeding is usually minor and caused by granulation tissue at the orifice of the primary or secondary anal orifice. Anorectal fistula can usually be diagnosed by the presence of a red, granular papule from which pus is expressed. The primary orifice is the fistulous

opening at the level of the dentate line, which is thought to be the original site of the infected anal gland. The secondary orifice is the fistulous opening anywhere else on the perineum. Multiple secondary openings should alert one to the possibility of either Crohn's disease or hidradenitis suppurativa. It is often possible to palpate a fistulous tract as a firm cord just beneath the perianal skin. Attempts to pass metal probes are best made in the operating room. Anoscopy and sigmoidoscopy are performed to identify the primary orifice and to determine the presence of proctocolitis.

Patients who are neutropenic as a result of hematologic malignancy are particularly susceptible to serious anorectal infection. Mortality rates from anorectal infection in patients with acute leukemia, if untreated, may be more than 45%. Early diagnosis and aggressive surgical drainage may be life-saving in these individuals, with improvement in mortality rates to below 10%. Point tenderness and poorly demarcated induration are the most frequent findings. Frequent reexamination may allow detection of an abscess if initial findings are equivocal. Because of the profound granulocytopenia, fluctuant masses are not usually seen. Necrosis and tissue breakdown may proceed quite rapidly, with extension into the genitalia and pelvis. If spontaneous drainage has already occurred, pain rapidly subsides and further surgical drainage may be postponed. *Pseudomonas aeruginosa* is a common wound isolate, and appropriate perioperative intravenous antibiotics should be administered if it is found.

Treatment

Because of the risk of extension of pus into adjacent spaces and the potential for the development of necrotizing anorectal infection, the treatment of anorectal abscess is a surgical emergency. In one series, the time interval from onset of primary anorectal abscess to necrotizing anorectal infection was from 0.5 to 5 days, with a mortality in excess of 50%. If one chooses to temporize waiting for an abscess to point or become ripe, it must be with the realization that the risks of necrotizing infection and extension into previously uninfected spaces rise dramatically.

In healthy patients with superficial abscesses in the perineal or ischiorectal location, drainage can be performed in the outpatient setting with local anesthesia. All other abscesses should be drained in the operating room with adequate anesthesia, lighting, and surgical instrumentation. If a primary fistula tract is identified and is not thought to encompass a large proportion of the sphincter mechanism, fistulotomy may be done in selected cases. In general, the patient should be counseled as to the possibility of persistent drainage from a retained or unidentified fistula which may require a second operation. An abscess may also recur if the underlying fistula has not been definitively treated.

Antibiotics are usually not necessary, and they may temporarily mask the underlying suppurative infection and delay surgical therapy. Only in occasional cases does a perianal cellulitis resolve with antibiotic therapy alone. In otherwise healthy individuals with minimal infection of the surrounding tissues, incision and drainage of the abscess is all that is required. Patients with significant underlying disease, such as diabetes, acute leukemia, valvular heart disease, or extensive soft tissue infection,

benefit from perioperative antibiotics. The choice of antibiotics should be directed by the clinical situation and culture results but, in general, both gram-negative aerobic and anaerobic bacteria should be covered. Ticarcillin/clavulanate, piperacillin/tazobactam, or a broad-spectrum cephalosporin are recommended for empiric coverage, but a particular clinical situation may mandate antibiotics with specific anaerobic, enterococcal, or pseudomonal coverage. The most common wound isolates are polymicrobial with *Escherichia coli*, *Proteus vulgaris*, *Bacteroides species*, streptococci, and staphylococci predominating. A high proportion of necrotizing anorectal infections contains *Clostridium species*. Immunosuppressed patients often demonstrate *Pseudomonas aeruginosa*.

Postoperative management consists of frequent wound inspection, warm sitz baths, attention to stool consistency, and judicious analgesia. The wound should be observed to heal from the base up so that skin bridges do not form, allowing the abscess to recur. If persistent drainage occurs, a second operation for fistulotomy is necessary. Warm baths improve hygiene and offer some symptomatic relief. Narcotic analgetics and perirectal pain both predispose to constipation, so a high-fiber diet, bulk-forming agents, or laxatives should be prescribed.

The presence of an anorectal fistula is an indication for operation. The operative approach depends on the location of the fistulous tract in relation to the sphincteric mechanism. Anorectal manometry has been used to improve the clinical and functional results of surgery for fistula-in-ano. The basic prerequisites for successful therapy of a fistula include removal of the primary orifice, identification and opening of the entire extent of the fistula, and conservation of as much external sphincter as possible. Postoperative care is similar to that for anorectal abscess. In a series of 624 patients undergoing anal fistula surgery the fistula recurred in 8%, and 45% complained of some degree of postoperative incontinence. A novel fibrin sealant has been touted as a less invasive method to heal fistula. Further refinement is needed to improve the healing rates and lessen the chance of recurrences.

Anorectal disease as a manifestation of Crohn's disease requires special consideration. In addition to standard therapy with 5-aminosalicylate derivatives and immunosuppressives, the use of metronidazole or ciprofloxacin is modestly beneficial in the healing of perineal Crohn's disease. Unfortunately, the required long-term therapy with metronidazole is associated with several side effects, most notably paresthesias. Also, discontinuation of therapy is often associated with flaring of disease. Conservative surgical techniques are usually adequate to drain abscesses, reduce inflammation, and provide relief of symptoms. In one study, proctectomy-once widely practiced-was necessary in only 12% of patients with complicated perianal Crohn's disease. Surgical diversion of the fecal stream, usually in conjunction with resection of diseased intestine or a local anorectal procedure, may be necessary for perianal disease. Infliximab, a chimeric monoclonal antibody to tumor necrosis factor, has emerged as an agent with impressive effectiveness for persistent Crohn's perianal fistulous disease. A controlled trial using 5 mg/kg at 0, 2, and 6 weeks improved (68%) and healed (55%) of patients compared to those receiving placebo (26 and 13%, respectively).

6.4. RECTAL PROLAPSE

Rectal prolapse is simply protrusion of the rectum through the anal orifice (*Fig. 6.11*). Complete rectal prolapse, or procidentia, is the classic situation in which all layers of the rectum visibly descend through the anus. Occult rectal prolapse refers to internal intussusception of rectal tissue without visible protrusion at the anus. Mucosal prolapse is a common condition in which only distal rectal tissues and not the entire rectal circumference protrude through the anus.

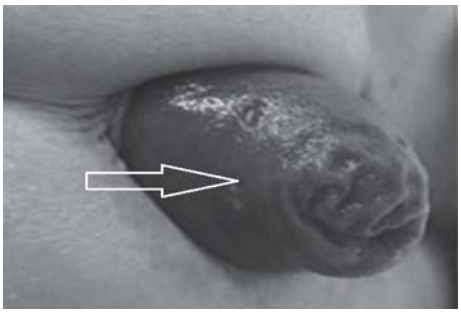


Figure 6.11.*Complete rectal prolapse-procidentia*

Rectal prolapse in children is an uncommon problem usually seen in infancy. It may be idiopathic, associated with congenital defects, such as spina bifida or myelomeningocele, or associated with cystic fibrosis. Prolapse occurs with defecation and usually reduces spontaneously. Treatment is conservative, and the condition is often self-limited. Rectal prolapse in adults occurs at least 3 to 10 times more often in women than men and is not associated with multiparity. Men may develop prolapse at any age, but in women, the peak incidence is in the sixth and seventh decades. It is associated with poor tone of the pelvic musculature, chronic straining at stool, fecal incontinence, and, sometimes, neurological disease or traumatic damage to the pelvis.

Pathogenesis

Anatomic defects that have been described with rectal prolapse include a weakened endopelvic fascia and diastasis of the levator ani, loss of the normal horizontal rectal position in the sacrum, an abnormally deep pouch of Douglas, a redundant rectosigmoid colon, and a weak anal sphincter. Most authors support the view that prolapse is caused by the intussuscepting rectum and that most of the anatomic defects described occur secondarily. Weakening of the fascial attachments of the rectum to the presacral fascia allows lengthening of the rectosigmoid and its mesentery. The normal positioning of the rectum in the sacral hollow is lost. The subsequent vertical orientation of the rectum enhances the ability of the rectum to intussuscept. Chronic straining in a misguided attempt to evacuate the internally prolapsing rectal tissue only serves to exacerbate the problem. Signs of pelvic neuropathy and anal sphincter dysfunction are common in patients with rectal prolapse. Many patients complain of partial or major fecal incontinence. On manometric evaluation, incontinent patients have low basal and voluntary contraction pressures. Denervation of striated musculature on electromyogram, perineal descent, and absence of the anocutaneous reflex are also common findings. The presence of disturbed sphincter function and pelvic denervation may explain the disappointingly high incidence of persistent incontinence after surgical correction of the prolapse. Manometric findings associated with a higher risk of postoperative fecal incontinence include a resting anal pressure of less than 10 mm Hg and a maximal voluntary contraction pressure of less than 50 mm Hg.

Classification

There are three stages of prolapse: I stage – prolapse of the rectum only during defecation; II stage – with physical activity; III stage – when walking and moving the body in a vertical position.

Rectal prolapse is categorized into 3 types, depending upon how much rectum has protruded out of the anus. Following are the sub types given below:

Complete Rectal Prolapse: This is the most severe form of rectal prolapse in which the entire rectal wall is seen protruding through the anal activity.

Mucosal or Partial Rectal Prolapse: Here only the rectal mucosa (mucus-secreting membrane lining of the rectum) freely hangs from the anus.

Internal Prolapse: This is the early stage of rectum prolapse, in which only the tissue of rectum is lightly displaced, but does not come out of the anus.

Clinical manifestations

Patients complain of prolapse of tissue with defecation. As the condition progresses, rectal prolapse may occur with straining or even upright posture alone. Common accompanying symptoms include straining at stool, the sensation of incomplete evacuation, tenesmus, and fecal incontinence. Protrusion of the rectum through the anus is a striking clinical sign. Complete rectal prolapse is signaled by the presence of red concentric mucosal folds with a palpable double thickness to the rectal wall tissue. The protruding rectum may extend many centimeters, and usually the lumen tip points slightly posteriorly. The patient is asked to sit and strain to produce prolapse if it is not immediately obvious. Endoscopic or barium examination is performed on all patients with rectal prolapse to exclude tumors and mucosal lesions. Sigmoidoscopy may reveal changes consistent with solitary rectal ulcer. A voiding defecogram is the best way to identify occult prolapse (internal intussusception).

Complete rectal prolapse must be differentiated from mucosal prolapse, prolapsing internal hemorrhoids, anorectal varices, anal polyps, benign and malignant anorectal tumors, and hypertrophic anal papillae. Mucosal prolapse is characterized by a short segment of mucosa with disordered or radially arranged (not concentric) mucosal folds. Internal hemorrhoids usually have a varicose appearance and are separated into discrete cushions.

Every attempt should be made to manually reduce a persistently prolapsed rectum to avoid potential complications such as strangulation, ulceration, bleeding, and perforation. Some form of intravenous sedation may facilitate manual reduction. Placing granulated sugar on the prolapsed mucosa often eliminates edema and allows reduction. Gangrene of the anterior rectal wall, a surgical emergency, is occasionally associated with evisceration of small bowel onto the perineum.

Treatment

Mucosal prolapse may be treated with procedures designed to remove redundant tissue and induce local fibrosis (see previous discussion of treatment of internal hemorrhoids). There is controversy over the appropriate treatment for occult rectal prolapse. To oversimplify, occult prolapse may be best treated surgically if fecal incontinence or chronic solitary rectal ulcer is present and conservatively if defecation difficulties or lesser symptoms predominate. One study suggests that sclerotherapy is successful if there is only a small associated rectocele and short

perineal descent but that transanal excision of prolapsing mucosa is necessary if the rectocele and perineal descent are more prominent.

To avoid complications and ongoing damage to the pelvic floor and sphincter muscles, complete rectal prolapse should be surgically corrected. Perineal muscle exercises and buttock strapping offer palliation in the patient who refuses or is unable to undergo surgery. There are many surgical options advocated for the treatment of rectal prolapse, but they can be simply summarized as follows. Management in healthy patients involves replacement of the rectum into the sacral hollow with or without resection of redundant rectosigmoid colon. The two intra-abdominal operations that have been popularized in the United States are the anterior sling rectopexy (Ripstein procedure) and abdominal proctopexy with or without sigmoid resection.

Ripstein operation involves mobilization of the rectum to the tip of the coccyx and attachment of the rectum to the presacral fascia by means of a band of nonabsorbable plastic such as Teflon or Marlex mesh. Abdominal proctopexy as a sole procedure can be performed with very acceptable recurrence rates and function. Constipation is common in patients who are continent, and continence is not assured in others. Internal anal sphincter pressures and continence usually improve after rectopexy but not to normal values. A laparoscopic approach has been used to further decrease operative morbidity.

Abdominal proctopexy and sigmoid resection as a combined procedure eliminates two of the theorized causes of rectal prolapse by fixing the rectum directly to the sacral hollow by means of nonabsorbable sutures and removing the redundant sigmoid colon. Prosthetic materials, such as Marlex, are generally not placed in the peritoneal cavity if sigmoid resection is performed because of the risk of contamination of the mesh and resultant sepsis. In a series of 102 patients with abdominal proctopexy and sigmoid resection, 80% had well to excellent results, no mortality, and improved morbidity, compared with those treated with the Ripstein procedure. Abdominal proctopexy and sigmoid resection is physiologically the most demanding procedure and should be used only in patients in good general physical condition. These procedures have continued fecal incontinence as the major postoperative complaint. Patients who continue to have incontinence 6 to 12 months after definitive correction of the rectal prolapse often benefit from a Parks postanal repair or a plication sphincteroplasty. A systematic review suggested that residual fecal incontinence was less common after abdominal (vs. perineal) approaches and that division (vs. preservation) of the lateral ligaments during rectopexy was associated with less recurrent prolapse but at the price of more constipation.

In the elderly or debilitated patient, a perineal or extra-abdominal approach is associated with acceptable morbidity and mortality rates. A diverting colostomy may be also be an appropriate alternative for this group of high-risk patients.

6.5. ANAL FISSURE

Anal fissure is a painful linear ulcer in the anal canal. Primary anal fissures are usually found in young and middle-aged adults and occur equally in males and females.

Primary fissures are located in the posterior midline more than 90% of the time. The remainder is found in the anterior midline. Fissures may occur secondary to an underlying disease such as inflammatory bowel disease (especially Crohn's disease), proctitis, leukemia, carcinoma, and, rarely, syphilis or tuberculosis. These lesions, in contrast to primary fissures, are usually found in a more lateral position.

Etiology

The elliptical arrangement of the anal sphincter fibers offers less muscular support to the anal canal posteriorly. This deficient support predisposes the posterior anal canal to traumatic tears during passage of a large, hard stool. Fissures may become chronic because of high resting anal sphincter tone and repeated trauma during passage of fecal boluses. Rectal distention normally causes a transient internal anal sphincter relaxation. Patients with anal fissure have an abnormal overshoot contraction following the normal relaxation. The overshoot contraction may explain the reflex spasm and pain seen after defecation. This phenomenon disappears after successful treatment of the fissure.

Preoperative maximal resting pressure and maximal contraction pressure are also elevated in patients with fissure. A histopathological study documented the presence of fibrosis throughout the anal sphincter in patients with anal fissure. Recent studies have emphasized the potential role for ischemia in fissure disease. Vascular perfusion of the anoderm is lower in the posterior midline than in other locations and measurements performed are particularly low in patients with anal fissure. Measurements before and after lateral sphincterotomy in patients with chronic anal fissure demonstrated the inverse relationship between anal sphincter pressures and posterior anoderm perfusion pressures.

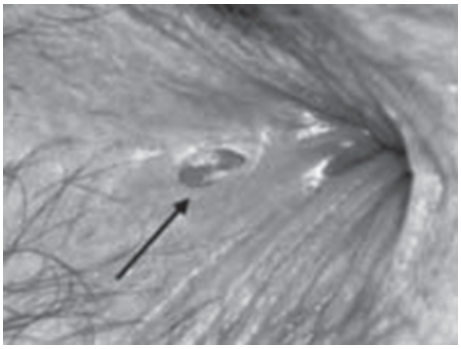


Figure 6.12. *Anal fissure (arrow)*

Clinical manifestations

Severe pain associated with scant, bright red rectal bleeding is the hallmark of anal fissure (*Fig. 6.12*).

The pain occurs during and after defecation ("like passing a piece of glass") and usually seems out of proportion to the clinical findings. Severe pain may make anoscopy impossible, and even digital examination is difficult without topical anesthesia. The fissure is best identified by simple inspection after spreading the buttocks. Acute fissures are small, linear tears oriented perpendicular to the dentate line in the posterior midline. Fissures located in a lateral position should prompt a search for a secondary etiology. If an acute anal fissure does not heal promptly, certain characteristic secondary features develop. The classic triad of chronic anal fissure includes the fissure, a proximal hypertrophic papilla, and a sentinel pile or fibrotic nubbin of skin found at the anal verge (*Fig. 6.13*).

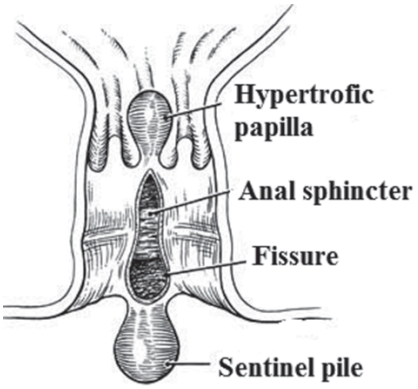


Figure 6.13. *The classic triad of chronic anal fissure: hypertrophic papilla, anal fissure, and sentinel pile*

Treatment

Prescribing a high-fiber diet and adequate fluid intake should soften stools. Hydrophilic bulk agents or salts of dioctyl sulfosuccinate are important aspects of therapy because many fissures are precipitated by the traumatic passage of hard, dry stools. The temporary use of topical anesthetic preparations containing agents such as benzocaine or pramoxine hydrochloride provides symptomatic relief. The use of these medications, in addition to warm sitz baths two to three times daily, acts to decrease sphincter spasm to provide additional relief. A combination of bran supplements and sitz baths was shown to be superior to a topical anesthetic or hydrocortisone cream with respect to symptoms and healing. With such a conservative regimen, most acute fissures heal in 4 to 6 weeks. Occasionally, patient anxiety, severe pain, or other considerations may rule out such a prolonged trial of conservative therapy.

Chronic fissure usually requires some form of surgical therapy to reduce internal sphincter tone. Reduced sphincter tone permits easier passage of the fecal bolus through the anal canal. Repetitive injury is avoided so that the traumatic tear may finally heal. The beneficial effects of sphincterotomy on internal sphincter spasm and healing of anal fissure have been well documented, and surgical cure rates on the order of 95% can be expected. Midline sphincterotomy with fissurectomy also offers definitive therapy for chronic anal fissure. However, in a retrospective study of 300 patients, a higher rate of postoperative complications was seen compared with the lateral sphincterotomy. Also, an unfortunate complication of posterior midline sphincterotomy and fissurectomy is development of a residual keyhole deformity of the anus, which predisposes to long-term leakage of feces and mucus. Another approach to treating sphincter spasm is manual dilation. The anus is dilated to six fingers under regional anesthesia. A metaanalysis of operative techniques concluded that internal anal sphincterotomy was superior to manual dilation for both fissure healing and the occurrence of incontinence to flatus.

Chemical methods may also be used to lower sphincter pressures to allow healing. Topically applied nitroglycerin heals fissures by reducing maximum resting pressure and by increasing anodermal blood flow. Several open and controlled trials have demonstrated the efficacy of 0.2% nitroglycerin ointment although a large, controlled trial failed to confirm this. Headaches are a frequent adverse effect of even a pea-sized application of nitroglycerin. For this reason, other topical smooth muscle relaxa nts have been investigated. A controlled trial of nearly 300 patients found that nifedipine gel healed 90% of fissures at 3 weeks and more recently, diltiazem ointment healed 75% of patients after 2 to 3 months of therapy. Headaches were not

seen. Botulinum toxin injected into the sphincter muscles directly through the perianal skin heals the majority of fissures (>80%), a finding confirmed in a controlled trial (73 vs. 13% healing at 2 months). Temporary mild fecal incontinence appears to be rare. In a direct comparison, botulinum toxin healed 96% of fissures versus 60% using 0.2% nitroglycerin ointment. A randomized trial found surgical sphincterotomy to be more effective than nitroglycerin. However, sphincterotomy may cause fecal incontinence in approximately 8% of patients. A reasonable, but not yet evaluated, strategy to treat chronic anal fissure disease is to use a topical muscle relaxant or botulinum toxin initially and reserve surgical sphincterotomy for those who fail to respond.

6.6. RECTOCELE

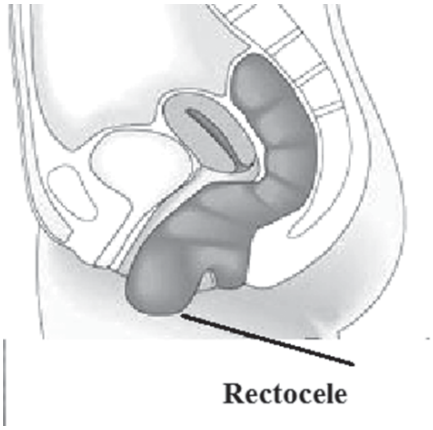


Figure 6.14. *Rectocele*

A rectocele (*Fig. 6.14*) results from a tear in the rectovaginal septum (which is normally a tough, fibrous, sheet-like divider between the rectum and vagina). Rectal tissue bulges through this tear and into the vagina as a hernia. There are two main causes of this tear: childbirth, and hysterectomy.

Symptoms

Mild cases may simply produce a sense of pressure or protrusion within the vagina, and the occasional feeling that the rectum has not been completely emptied after a bowel movement. Moderate cases may involve difficulty passing stool (because the attempt to evacuate pushes the stool into the rectocele instead of out through the anus), discomfort or pain during evacuation or intercourse, constipation, and a general sensation that something is "falling down" or "falling out" within the pelvis. Severe cases may cause vaginal bleeding, intermittent fecal incontinence, or even the prolapse of the bulge through the mouth of the vagina, or rectal prolapse through the anus. Digital evacuation, or, manual pushing, on the posterior wall of the vagina helps to aid in bowel movement in a majority of cases of rectocele.

Causes

It can be caused by many factors, but the most common is childbirth, especially with babies over nine pounds in weight, or rapid births. The use of forceps is more likely a marker for the vaginal injury, than a direct cause of the tear. Episiotomy or lower vaginal tears play little role in the formation of a cystocele, but may in rectoceles. The risk increases with the number of vaginal births, although it can also happen in women who have never borne a child.

A hysterectomy or other pelvic surgery can be a cause,[1] as can chronic constipation and straining to pass bowel movements. It is more common in older women than in younger ones; estrogen which helps to keep the pelvic tissues elastic

decreases after menopause. Another cause which is sometimes overlooked in younger women is sexual abuse during childhood.

Treatment

Treatment depends on the severity of the problem, and may include changes in diet (increase in fiber and water intake), pelvic floor exercises such as Kegel exercises, use of stool softeners, hormone replacement therapy for post-menopausal women, insertion of a pessary into the vagina, and various forms of surgery (usually posterior colporrhaphy – the suturing of vaginal tissue). More recent developments in surgery are directed at repairs to the rectovaginal septum, than simple excision or plication of vaginal skin, which provides no support (*Fig. 6.15*). Both gynecologists and colorectal surgeons can address this problem.

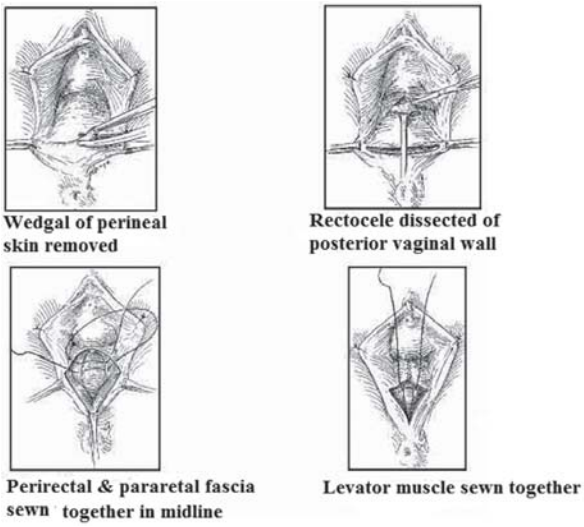


Figure 6.15. *Surgical repair of rectocele*

6.7. RECTOVAGINAL FISTULA

A rectovaginal fistula is a medical condition where there is a fistula or abnormal connection between the rectum and the vagina (*Fig. 6.16*).

Rectovaginal fistula may be extremely debilitating. If the opening between the rectum and vagina is wide it will allow both flatulence and feces to escape through the vagina, leading to fecal incontinence. There is an association with recurrent urinary and vaginal infections. This type of fistula can cause pediatricians to misdiagnose imperforate anus.

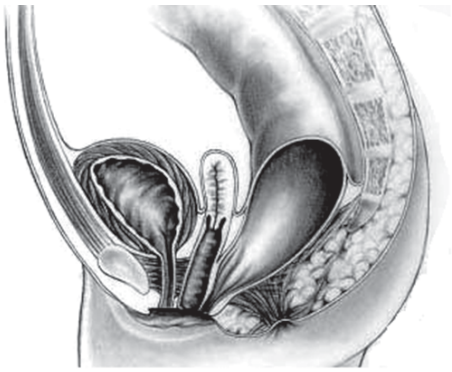


Figure 6.16. *Rectovaginal fistula*

Causes

Rectovaginal fistula is often the result of trauma during childbirth (in which case it is known as obstetric fistula) in situations where there is inadequate health care, such as in some developing countries. Rates in Eritrea are estimated as high as 350 per 100,000 vaginal births. Fistulas can also develop in women and children who are raped; women with rectovaginal fistula are often stigmatized in third world countries, and become outcasts.

Rectovaginal fistula can also be a symptom of various diseases, including infection by Lymphogranuloma venereum, or the unintended result of surgery, such

as episiotomy or sexual reassignment surgery. They may present as a complication of vaginal surgery, including vaginal hysterectomy. They are a recognized presentation of rectal carcinoma or rarely diverticular disease of the bowel or Crohn's disease. They are seen rarely after radiotherapy treatment for cervical cancer.

Symptoms

Signs and symptoms of a rectovaginal fistula may include:

1. Passage of gas, stool or pus from your vagina.
2. A foul-smelling vaginal discharge.
3. Recurrent vaginal or urinary tract infections.
4. Irritation or pain in the vulva, vagina and the area between your vagina and anus (perineum).
5. Pain during sexual activity.

Causes

A rectovaginal fistula may form as a result of:

Injuries in childbirth. Obstetric injuries are the most common cause of rectovaginal fistulas. Such injuries include tears in the perineum that extend to the bowel or an infection or tear of an episiotomy – a surgical incision to enlarge the perineum during vaginal delivery. These may happen following a long, difficult labor. Fistulas arising from childbirth may also involve injury to your anal sphincter, the rings of muscle at the end of the rectum that help you hold in stool.

Crohn's disease. The second most common cause of rectovaginal fistulas, Crohn's disease is a type of inflammatory bowel disease in which the lining of your digestive tract becomes inflamed. Most women with Crohn's disease never develop a rectovaginal fistula, but having Crohn's disease does increase your risk of the condition.

Surgery involving your vagina, perineum, rectum or anus. Prior surgery in your lower pelvic region, such as removal of your uterus (hysterectomy), in rare cases can lead to development of a fistula.

Cancer or radiation treatment in your pelvic area. A cancerous tumor in your rectum, cervix, vagina, uterus or anal canal can lead to development of a rectovaginal fistula. Radiation therapy for cancers in these areas can also put you at risk of developing a fistula. A fistula caused by radiation usually forms within two years following the treatment. Before the fistula forms, you may experience pain in your anus or rectum, bloody diarrhea, or bright red blood in your stool. If you spot these warning signs, your doctor will first rule out a return of cancer as the cause.

Other causes. Less commonly, a rectovaginal fistula may be caused by infections in your anus or rectum; infections of small, bulging pouches in your digestive tract (diverticulitis); or vaginal trauma.

Tests and diagnosis

Physical examination

To figure out the cause of a rectovaginal fistula, your doctor will perform a physical examination to try to locate the fistula and check for a possible tumor mass, infection or abscess. The exam includes a visual inspection of your vagina, anus and the area between them.

Tests for identifying fistulas

Often a fistula isn't found during the physical exam. A variety of other tests may be used to locate and evaluate a rectovaginal fistula. These tests also help your medical team in planning for surgery.

Water and blue dye tests

Filling the vagina with water and the rectum with air can help locate the fistula. Air passing from the rectum through the fistula forms bubbles on the vaginal side of the passage. Another test involves placing a tampon into your vagina, then injecting blue dye into your rectum. Blue staining on the tampon shows the presence of a fistula.

Contrast tests

A vaginogram or a barium enema can help identify a fistula located in the upper rectum. These tests use a contrast material to show either the vagina or the bowel on an X-ray image.

Computerized tomography (CT)

A CT scan is a special X-ray technique that provides more detail than a standard X-ray does. A CT scan of your abdomen and pelvis can help locate a fistula and determine its cause.

Magnetic resonance imaging (MRI)

This test uses a magnetic field and radio waves to create images of soft tissues in your body. MRI can show the location of a fistula as well as involvement of pelvic organs or the presence of a tumor.

Anorectal ultrasound

This procedure uses sound waves to produce a video image of your anus and rectum. Your doctor inserts a narrow, wand-like instrument into your anus and rectum. Anorectal ultrasound can evaluate the structure of your anal sphincter and may show defects caused by obstetric injury.

Anorectal manometry

In this test, a narrow, flexible tube is inserted into your anus and rectum and a small balloon at the tip of the tube is expanded. The test measures the sensitivity and function of your rectum and can provide useful information when a fistula is due to Crohn's disease or radiation. This test does not locate fistulas but can help with planning repair.

Other tests: colonoscopy; biopsy.

Complications

Physical complications of rectovaginal fistula may include incontinence, problems with hygiene, and irritation or inflammation of your vagina, perineum or the skin around your anus. In some cases, a fistula may become infected and form an abscess, a problem that can become life-threatening if not treated. Among women with Crohn's disease who develop a fistula, the chance of another fistula forming later is high.

Treatments and drugs

Treatment for a rectovaginal fistula depends on its cause, size, location and effect on surrounding tissues. Sometimes fistulas heal on their own, but most people

need surgery to close or repair the abnormal connection. Before an operation can be done, the skin and other tissue around the fistula must be healthy, with no signs of infection or inflammation.

Medications

If the area around your fistula is infected, you'll take a course of antibiotics before surgery. Antibiotics may also be recommended for women with Crohn's disease who develop a fistula. Another medication that may help heal a fistula in women with Crohn's disease is infliximab (Remicade). This drug blocks the action of an immune system protein called tumor necrosis factor-alpha (TNF-alpha), which causes inflammation. Side effects may include chest pain, chills, fever, flushing, hives, itching and troubled breathing.

Surgery

Rectovaginal fistula must be divided into two groups. The first group consists of those that occur secondary to obstetric or gynecologic surgery for benign disease. The second group consists of those that are associated with radiation therapy for pelvic malignancy. Rarely is a diverting colostomy needed for fistula from benign disease. A transverse colostomy is always needed, however, for pelvic cancer patients who have rectovaginal fistula secondary to irradiation. An outside blood supply, such as a muscular flap, is not required for the repair of small rectovaginal fistula secondary to obstetric or gynecologic surgery, unless there is excessive scarring or repeated attempts at closure have been unsuccessful. Patients with rectovaginal fistula associated with pelvic irradiation, however, require a vascular flap to improve blood supply to the irradiated tissues.

The bulbocavernosus muscle is the most convenient source of blood supply, but other sources include the omentum, gracilis muscle, and myocutaneous flaps.

The cardinal principles of repair of rectovaginal fistula are 1) delay of repair until all inflammation has cleared at the fistula site, even if a preoperative perineotomy is required; 2) excision of all fibrotic and scar tissue surrounding the fistulous tract; 3) complete mobility of the rectum and colon to eliminate any tension on the rectal mucosa after excision of the scarred tissue; 4) use of delicate surgical technique to preserve as much vascularity as possible; 5) broad surface-to-surface closure; 6) improved vascularity using an outside blood supply; and 7) diverting colostomy, in cases of irradiation, until 3–4 months after the fistula has been confirmed closed by repeated examination.

Physiologic changes. The rectovaginal fistula is closed, and normal defecation per anus is resumed.

The bulbocavernosus flap used to cover the rectovaginal fistula suture line improves vascularity and gives an additional layer to the closure, thus improving the chances of permanent fistula repair.

Points of caution. The margins of the rectal mucosa must lie adjacent to each other without tension. Tension on the rectal mucosa suture line wills invariable result in separation of the wound. Hemostasis is a vital factor. The hemorrhoidal plexus of veins can be difficult to control, but meticulous technique in clamping, tying, and/or electrocoagulating each of these vessels is imperative to fistula closure.

Dilatation of the anus at operation produces temporary rectal paralysis of the sphincter muscle and, thereby, temporary rectal incontinence, preventing the buildup of flatus and stool in the terminal rectum and avoiding tension on the suture line.

6.8. CRYPTITIS AND PAPILLITIS

Cryptitis is a localized infection of one of the anal glands. This unusual condition is identified anoscopically as a pearl of pus beading up from the crypt at the level of the dentate line. Treatment is obliteration of the gland which necessarily involves as internal sphincterotomy. Fistula and abscesses can develop with untreated prolonged infection.

Inflammation to anal papillae is called papilitis. Papillae may become painful and reddened. Inflammation of papillae is frequently associated with fissure, fistula, Crohn's disease, pruritus ani, and/or internal haemorrhoids. Inflammation of papillae may result from trauma or chemical irritation, such as the passage of hard stool or of irritating liquid stools, etc .

6.9. PROCTALGIA

Proctalgia fugax (or levator syndrome) is a severe, episodic, rectal and sacrococcygeal pain. It can be caused by cramp of the pubococcygeus or levator ani muscles.

It most often occurs in the middle of the night and lasts less than 20 minutes, an indicator for the differential diagnosis of levator ani syndrome, which presents as pain and aching lasting twenty minutes or longer. In a study published in 2007 involving 1809 patients, the attacks occurred in the daytime, (33 percent) as well as at night (33 percent) and the average number of attacks was 13. Onset can be in childhood, however, in multiple studies the average age of onset was 45. Many studies showed that women are affected more commonly than men. The pain is sometimes described as an "anal charlie horse," an anal cramp, an anal spasm, a Dani spasm, or repeated spasms of the anus.

During an episode, the patient feels spasm-like, sometimes excruciating, pain in the anus, often misinterpreted as a need to defecate. Simultaneous stimulation of the local autonomic system can cause erection in males. Because of the high incident of internal anal sphincter thickening with the disorder, it is thought to be a disorder of the internal anal sphincter or that it is neuralgia of pudendal nerves. It is recurrent and there is also no known cure. However, some studies show effective use of botulinum toxin, pudendal nerve block, and calicum channel blockers. It is not known to be linked to any disease process and data on the number of people afflicted varies, but is more prevalent than usually thought.

Like all ordinary muscle cramps, it is a severe, deep rooted pain.

Episodes happen almost always with an empty colon. Defecation of any feces present can worsen the spasm, but may relieve it, or provide a measure of comfort. The pain might subside by itself as the spasm disappears on its own, or may persist or reoccur during the same night.

Treatment

Traditional remedies have ranged from warm baths (if the pain lasts long enough to draw a bath), warm to hot enemas,[5] relaxation techniques, and various medications including medical marijuana.

One method of quickly alleviating the pain is to stretch the area by touching one's toes or apply any other pressure/dilatation to the area by any means , followed by taking the anti-inflammatory ibuprofen (e.g. Advil) with a glass of water. Alternatively, it has been suggested that one takes acetaminophen / paracetamol (e.g. Tylenol) with a hot drink (or simply a glass of water). A rolled up washcloth soaked in very warm water placed between the buttocks and applied pressure allows the muscles to relax. In patients who suffer frequent, severe, prolonged attacks, inhaled salbutamol has been shown in some studies to reduce their duration. The use of botulinum toxin has been proposed, as has diazepam.

REFERENCES

1. Gordon PH, Nivatnongs S. Principles and practice of surgery for the colon, rectum and anus, 2nd ed. St. Louis, MO: Quality Medical Publishing, Inc., 1999.

2. Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation. Gastroenterol 1990;98:380.

3. Johanson JF, Sonnenberg A. Constipation is not a risk factor for hemorrhoids: a case-control study of potential etiological agents. Am J Gastroenterol 1994;89:1981.

4. Johanson JF. Association of hemorrhoidal disease with diarrheal disorders: potential pathogenic relationship? Dis Colon Rectum 1997;40:215.

5. Thomson WH. The nature of hemorrhoids. Br J Surg 1975;62:542.

6. Haas PA, Fox TA, Haas G. The pathogenesis of hemorrhoids. Dis Colon Rectum 1984;27:442.

7. Kluiber RM, Wolff BG. Evaluation of anemia caused by hemorrhoidal bleeding. Dis Colon Rectum 1994;37:1006.

8. Barron J. Office ligation treatment of hemorrhoids. Dis Colon Rectum 1963;6:109.

9. Bleday R, Pena JP, Rothenberger DA, et al. Symptomatic hemorrhoids: current incidence and complications of operative therapy. Dis Colon Rectum 1992;35:477.

10. Khubchandani IT. A randomized comparison of single and multiple rubber band ligations. Dis Colon Rectum 1983;26:705. P.2008

11. Lee HH, Spencer RJ, Beart RW, Jr. Multiple hemorrhoidal bandings in a single session. Dis Colon Rectum 1994;37:37.

12. Bat L, Melzer E, Koler M, et. al. Complications of rubber band ligation of symptomatic internal hemorrhoids. Dis Colon Rectum 1993;36:287.

13. O'Hara VS. Fatal clostridial infection following hemorrhoidal banding. Dis Colon Rectum 1980;23:570.

14. Russell TR, Donohue JH. Hemorrhoidal banding: a warning. Dis Colon Rectum 1985;28:291.

15. Komborozos VA, Skrekas GJ, Pissiotis CA. Rubber band ligation of symptomatic internal hemorrhoids: results of 500 cases. Dig Surg 2000;17:71.

16. Trowers E, Ganga U, Rizk R, et. al. Endoscopic hemorrhoidal ligation: preliminary clinical experience. Gastrointest Endosc 1998;48:49.

17. O'Regan PJ. Disposable device and a minimally invasive technique for rubber band ligation of hemorrhoids. Dis Colon Rectum 1999;42:1509.

18. Dickey W. Hemorrhoid banding using videoendoscopic anoscopy and a single-handed ligator: an effective, inexpensive alternative to endoscopic band ligation. Am J Gastroenterol 2000;95:1714.

19. Ponsky JL, Mellinger JD, Simon IB. Endoscopic retrograde hemorrhoidal sclerotherapy using 23.4% saline: a preliminary report. Gastrointest Endosc 1991;37:155.

20. Buls JG, Goldberg SM. Modern management of hemorrhoids. Surg Clin North Am 1978;58:469.

21. Goligher JC. Cryosurgery for hemorrhoids. Dis Colon Rectum 1976;19:213.

22. Keighley MRB, Buchmann P, Minervini S, et al. Prospective trials of minor surgical procedures and high-fibre diet for hemorrhoids. Br Med J 1979;2:967.

23. Norman DA, Newton R, Nicholas GV. Direct current electrotherapy of internal hemorrhoids: an effective, safe, and painless outpatient approach. Am J Gastroenterol 1989;84:482.

24. Yang R, Migikovsky B, Peicher J, et al. Randomized, prospective trial of direct current versus bipolar electrocoagulation for bleeding internal hemorrhoids. Am J Gastroenterol 1993;39:766.

25. Randall GM, Jensen DM, Machicado GA, et al. Prospective randomized comparative study of bipolar versus direct current electrocoagulation for treatment of bleeding internal hemorrhoids. Gastrointest Endosc 1994;40:403.

26. Griffith CDM, Morris DL, Wherry D, et al. Outpatient treatment of hemorrhoids: a randomized trial comparing contact bipolar diathermy with rubber band ligation. Coloproctology 1987;6:322.

27. Leicester RJ, Mitchells RJ, Mann CV. Infrared coagulation: a new treatment for hemorrhoids. Dis Colon Rectum 1981;24:602.

28. O'Connor JJ. Infrared coagulation of hemorrhoids. Practical Gastroenterol 1986;10:8.

29. Johanson JF, Rimm A. Optimal nonsurgical treatment of hemorrhoids: a comparative analysis of infrared coagulation, rubber band ligation, and injection sclerotherapy. Am J Gastroenterol 1992;87:1601.

30. Iwagaki H, Higuchi Y, Fuchimoto S, et al. The laser treatment of hemorrhoids: results of a study on 1816 patients. Jpn J Surg 1989;19:658.

31. Ferguson JA, Mazier WP, Ganchrow MI, et al. The closed technique of hemorrhoidectomy. Surgery 1971;70:480.

32. Ho Y, Seow-Choen F, Tan M, et al. Randomized controlled trial of open and closed haemorrhoidectomy. Br J Surg 1997;84:1729.

33. Bonardi RA, Rosin JD, Stonesifer GL, et al. Bacteremias associated with routine hemorrhoidectomies. Dis Colon Rectum 1976;19:233.

34. Lord PH. A day-case procedure for the cure of third-degree haemorrhoids. Br J Surg 1969;56:747.

35. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatments: a meta-analysis. Can J Surg 1997;40:14.

36. Hoskins SW, Smart HL, Johnson AG, et al. Anorectal varices, haemorrhoids, and portal hypertension. Lancet 1989;1:349.

37. Wang TF, Lee FY, Tsai YT, et al. Relationship of portal pressure, anorectal varices and hemorrhoids in cirrhotic patients. J Hepatol 1992;15:170.

38. Dhiman RK, Saraswat VA, Choudhuri G, et al. Endosonographic, endoscopic, and histologic evaluation of alterations in the rectal venous system in patients with portal hypertension. Gastrointest Endosc 1999;49(2):218.

39. Hosking SW, Johnson AG. Bleeding anorectal varices: a misunderstood condition. Surgery 1988;104:70.

40. Hsieh JS, Huang CJ, Huang TJ. Demonstration of rectal varices by transhepatic inferior mesenteric venography. Dis Colon Rectum 1986;29:459.

41. Keane RM, Britton DL. Massive bleeding from rectal varices following repeated injection sclerotherapy of esophageal varices. Br J Surg 1986;73:120.

Chapter 7

THE DISEASES OF THE SOFT TISSUES OF THE PERITONEUM

7.1. SOFT TISSUE INFECTIONS

Definitions and Etiologies

Soft tissue infections were first defined slightly more than a century ago. In 1883, Fournier described a gangrenous infection of the scrotum that continues to be associated with his name. In 1924, Meleney documented the pathogenic role of streptococci in soft tissue infection. Shortly thereafter, Brewer and Meleney described progressive polymicrobial postoperative infection of the muscular fascia with necrosis (the term necrotizing fasciitis was not introduced until the 1950's). The association between toxic-shock syndrome and streptococcal soft tissue infection was delineated as this disease reemerged in the 1980s.

• Diverse group of diseases that involve the skin and underlying subcutaneous tissue, fascia, or muscle.

• May be localized to a small area or may involve a large portion of the body.

• May affect any part of the body, though the lower extremities, the perineum, and the abdominal wall are the most common sites of involvement.

• Some are relatively harmless if treated promptly and adequately; others can be life-threatening even when appropriately treated.

• Simple vs. complex.

• Primary vs. secondary vs. tertiary.

• Cellulitis vs. abscess.

• Superficial vs. deep.

• Necrotizing vs. non-necrotizing.

• Traumatic vs. non-traumatic.

• Dermatitis, fasciitis, myositis (combinations).

• Single vs. multiple pathogens.

• Classic syndromes: rapidly progressive infections; toxic shock syndromes; specific etiologies or pathogens.

Symptoms and signs

• Pain (localized tenderness) → loss of sensation.

• Erythema, edema / induration.

• Blisters, crusted plaques.

• Epidermal erosion and necrosis.

• Fluctuation, crepitus.

• Systemic signs of SIRS/Sepsis: fever, tachycardia, hypotension, organ dysfunction.

7.2. PYODERMA GANGRENOSUM

Pyoderma gangrenosum is an unusual debilitating skin condition that complicates about 2% of cases of inflammatory bowel disease (IBD). The ulcers typically occur

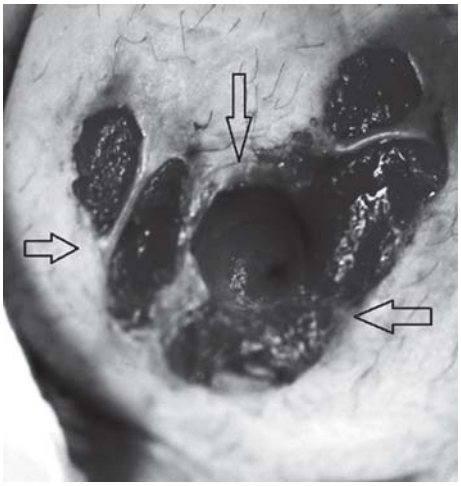


Figure 7.1. *Typical peristomal pyoderma gangrenosum Crohn diseases (arrows)*

on the lower extremities of patients with ulcerative colitis (UC). Although the histopathology of pyoderma gangrenosum is well described, the diagnosis is a clinical one. Skin lesions begin as pustules, break down, and rapidly coalesce to form superficial ulcers with necrotic undermined borders. The ulcers have a characteristic violaceous appearance (*Fig. 7.1*) and severe pain is a consistent feature. First described in 1984 by McGarity et al, peristomal pyoderma gangrenosum (PPG) is much less common than lower-extremity pyoderma gangrenosum; to our knowledge, only 25 cases have been reported in the world literature. Whereas lower-extremity pyoderma gangrenosum usually occurs in patients with UC, PPG is usually seen in patients with Crohn disease (CD). It is difficult to determine the true incidence of PPG, as it is usually not recognized and infrequently reported. In the peristomal position, the ulcers may be confused with local trauma, infection, or a cutaneous manifestation of some other systemic disease. Usually, ulcers of these types respond to conservative therapy and local wound management. Because of the rarity of the condition, PPG ulcers are usually present for quite some time before they are properly diagnosed and treated. After failure of conservative measures, the treatment is usually medical and the response is variable. No single therapy has been demonstrated to be efficacious in all cases.

The misdiagnosis of pyoderma gangrenosum can have serious consequences. Cutaneous ulcerations in patients with suspected pyoderma gangrenosum often prove, on further workup, to have a different cause. Moreover, treatment directed at pyoderma gangrenosum – high-dose prednisone or other immunosuppressive medications may be contraindicated in patients with any of several diseases that may produce ulceration resembling that of pyoderma gangrenosum, such as infectious or malignant processes.

7.3. PERIANAL DERMATITIS

Perianal dermatitis

Perianal dermatitis is one of the most common proctological disorders. The anatomy of the anal region provides suitable conditions for the development of dermatitis. In the diagnostic work-up and the management of patients with perianal dermatitis, three types need to be distinguished: irritant contact dermatitis, atopic dermatitis, and allergic contact dermatitis. Each type has its etiological and pathogenetic factors, which will provide clues to the diagnosis and subsequent management of the condition.

Perianal streptococcal dermatitis

Perianal streptococcal dermatitis is an infectious condition of the skin around the anus in children. It is caused by group A beta-haemolytic streptococcus bacteria (*Fig. 7.2*).

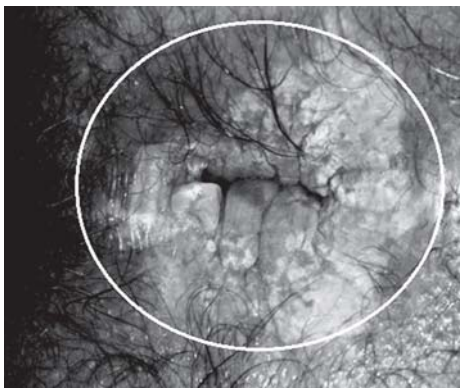


Figure 7.2. *Perianal streptococcal dermatitis*

Symptoms

Perianal streptococcal dermatitis presents with sharply demarcated redness, local swelling and itch of the area around the anus. It may be accompanied by inflammation of the vulva and vagina in girls (or end of the penis in boys), pain on passing a bowel motion, constipation, cracks in the anus and discharge of pus and/or blood from the rectum.

Causes

Perianal streptococcal dermatitis is caused by streptococcal bacteria of the group A beta-hemolytic type.

The same bacterium may be carried in the throat. The bacteria may be passed to other children. However, some children carry the bacteria in the anal and genital area without it causing disease.

Investigations

A swab for bacterial culture will confirm the diagnosis. A rapid streptococcal test may provide a quicker result.

Management

Oral or parenteral antibiotics for 10–14 days are usually prescribed.

7.4. CODYLOMATOSIS OF PERINEUM

The genital Condylomatosis or genital infection by Human Papillomavirus (H.P.V.) was known since the time of ancient Greeks and Romans and had always been considered as a disease undergoing sexual transmission, so that for long time, until its viral etiology was proved, it was considered to be a clinical manifestation of the syphilis (*Fig. 7.3*) .

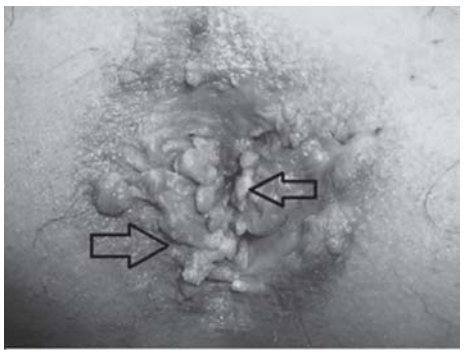


Figure 7.3. *Codylomatosis of perineum (arrows)*

Certainly the most common way of contraction of the disease is through sexual exposure, although the presence of the H.P.V. on vehicle materials such as underwear, speculem, biopsy forceps, and towels has been extensively demonstrated. Moreover, it has been documented a vertical transmission to the fetus at parturition via the maternal birth channel. In infants born naturally from mothers affected by vulvo-vaginalis exophytic Condylomatosis, the risk of contraction of laryngeal papillomatosis

is increased of about 30 times. The condyloma appears as a benign neoplasia, raised up from the underlying epithelium via a single implantation basis, sessile or pedunculate, displaying a roundish or rough surface. The first manifestations appear generally on the fourchette as well as on the posterior part of the vulvar vestibulum, both areas undergoing mostly a traumatic stress during sexual intercourses. The Condylomas can develop in groups on the external organs as well as around the urethral meatus and in the clitoral area; they often expand in the first third inferior of the vagina, extending sometimes throughout its length, with a clinical involvement also of the cervix.

The disease can develop in the anterior area of the vulva up to the mons Veneris, as well as more posterior toward the perineum and perianus, so that around 25 % of roundish women display concomitant anal warts, not necessarily indicatives of their sexual habits. The Condylomatosis of the anal channel is more frequent than people may think, and when this remained not diagnosed or properly treated it could give rise to recurrent lesions of the vulva. Symptoms can be accented and may include itching, burning and pain.

Up to date, the natural history of H.P.V. infection has not been understood yet. An estimation of the real prevalence of the pathology in the general population has been made difficult by the lack of a unified organization in the specialized clinical services. The incidence of the disease, which has been estimated of around 0,5–1 ,2 % between the age of 18 and 25', is continuously increasing both in the developing countries as well as in the Western world. In the United Kingdom for example, such increase seems to be of about 10% every year and American studies document around one million of new infections per year.

During the last decade, the scientific interest toward the virus has exploded because of its relation with the pre-cancerous and cancerous degeneration of the genital tract. However, the intimate mechanism underlying the integration of the viral genome with that of the host cell is not known yet. Such integration is a condition unique and necessary for initiating the pre-neoplastic process.

The H.P.V. belongs to the family of the PA.PO.VA. (Papilloma, Polyoma, Vacuolation), and is an epitheliotrophic virus, species-specific, not reproducible in vitro, with a diameter of about 50–55 μm. This virus replicates in vivo onto the squamous epithelium, starting from the basal layer that can be reached via microtrauma-induced passages.

Up to date, a specific presidium against H.P.V. virus is not available. What are available are miscellanea of different and debated approaches which always require a tight follow up, or eventually a change in the therapeutic strategy in the presence of the always feared relapse and\or of an unfortunate iatrogenic outcome. Specular features can be described in the partner, who has a 45–60 % probability to contract the disease.

The actual therapeutic approaches are trying to treat the identifiable lesions, to reduce signs and symptoms, to prevent the consequences, to restore the morphological physiology of the tissues, to prevent the transmission. All of the above, considering

that the H.P.V. infection, as known, can interest a much larger area than the one identifiable by the clinical lesions; up to date there are no clinical studies that can document a reduction of the incidence of such infection by the deletion of its lesions; such strategy indeed results more from the common sense than from controlled scientific observations. The above rationale let us understand how aleatory the prevention of relapse or transmission. Moreover, all the therapeutic strategies available at the moment do not help restoring the morphological physiology of the tissue.

The surgical presidia applied against the H.P.V. include Laser-surgery CO_2, Radio-frequency (Leep), Cryotherapy, Electro-surgery, CoId-blade bistouries. In terms of healing these methods lead to equivalent result, in percentage values that fluctuate between 70 and 90% following the first application. The first mentioned technique is the most expensive due to the high costs of the equipment as well as of the operator long training required. The medical presidia applied against the H.P.V. include the cytotoxic therapy, which consists in the administration of Podophyillin and Podophyllotoxin, Trichloracetic Acid, 5-Fluorouracil, and the immunomodulating therapy via the use of interferon (alpha, beta, gamma), retinoids, cytokine inducers, Imiquinod, and Vaccines (tetravalent or bivalent) certainly very expensive and just partially covering the risk of infection.

None of the mentioned treatments is able to eradicate the virus. To the scope, the vaccine, although very futuristic, represents a hope. During the third national congress ESIDOG-O9 the need of a combined approach has clearly emerged, which include the synergistic usage of different presidia in combination with the destructive or excisional surgical therapy. Regardless the therapeutic choice, between the 10% and 15% of the patients relapse for several years.

7.5. PERIANAL PAGET'S DISEASE

The first case of perianal Paget's was reported in 1893, by Darier and Coulillaud, 19 years after Sir James Paget first described the characteristic breast lesion in 1874. Unlike Paget's disease of the nipple, which invariably is associated with an underlying ductal carcinoma, a subjacent or visceral malignancy, usually of the apocrine gland type, is found in 20% of patients who present with perianal Paget's disease. So far, fewer than 120 cases of perianal Paget's disease have been described in the literature. The majority of the reported cases have appeared as case reports, so it is not easy to estimate the frequency with which it manifests. Treatment is usually regarded as surgical, although most authors describe local recurrences even after extensive local resections. Local recurrence and morbidity from surgery, especially in the elderly can be high. Radiation therapy, as the primary treatment modality, is seldom used in this condition and the few reports that do include radiation poorly describe treatment selection, radiation dose, field size, treatment technique, beam energy or the outcome of treatment. A case of perianal Paget's disease is reported here in a patient successfully treated with radiation after four unsuccessful surgical resections.

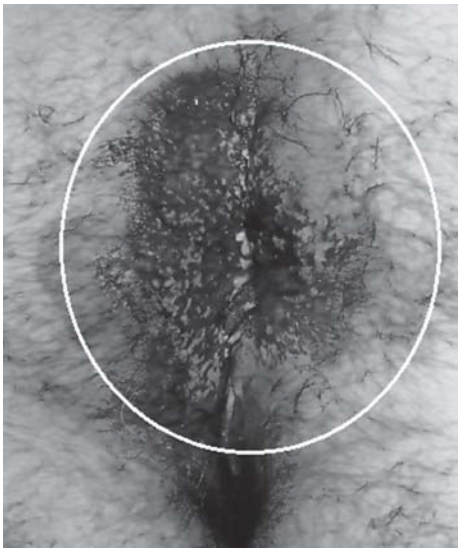


Figure 7.4. *Extensive perianal Paget's disease in the perineum*

Perianal Pagel's disease is a rare condition (*Fig.7.4*). It occurs more commonly in women than in men and usually starts in ihe fifth decade or thereafter. Unlike Paget's disease of the nipple, which is always associated with a subjacent breast adenocarcinoma, a primary carcinoma of other organs, principally rectum, cervix uteri or urethra and also more distant organs such as breast, is found in only 20% cases of perianal Paget's disease. Clinical features of perianal Paget's disease include erythematous, crusted or scaly areas which may weep clear serous fluid. These areas may resemble atopic eczema or contact dermatitis. The margins of the lesions are usually well demarcated, slightly raised and erythematous. Lichenified, leukokeralolic or leukoplakia-like patches may also develop in some patients. The duration of symptoms can be very long as in the case presented here and there is usually a history of multiple unsuccessful attempts at dermatological treatment. Any rash in the ano-genital area that is not responsive to 6–8 weeks of topical therapy should be biopsied.

Histologically, perianal Paget's disease is identical to Paget's disease of the breast. Paget's cells appear lo be uniquely epidermolropic. They spread laterally within the epidermis, and the deepest eels hug the basal lamina without showing tendency to breach it, although extension of inlraepidermal Paget's disease to produce an underlying carcinoma has been documented. The cells slain positively for acid as well as neutral mucopolysaccharides and may contain melanin granules. Expression of c-ErbB-2 oncoprotein may play a role in promoting intraepithelial spread of adenocarcinoma cells.

Most authors recommend surgery as the treatment of choice. Extended surgical excision for non-invasive lesions and excision of rectum or abdominoperineal excision for invasive disease or lesions associated with an adnexal carcinoma is recommended.

Most authors recommend surgery as the treatment of choice. Extended surgical excision for non-invasive lesions and excision of rectum or abdominoperineal excision for invasive disease or lesions associated with an adnexal carcinoma is recommended.

Butler et al recommend that radiotherapy has no place in treatment because of high recurrence rale after its use. On the contrary this case report demonstrates that even extensive lesions can be salvaged with radiation therapy after surgical failure.

Besa el al make a strong case for the use of primary radiotherapy for patients not considered suitable for surgery, and for the use of postoperative radiotherapy following resection. They observed a 36–66% rate of positive margins after surgical excision alone in their series of 65 patients with exlramammary Paget's disease of the

perianal skin. The ability of surgery adequately to control a multicentric widespread process is limited and likely to be associated with considerable morbidity or functional impairment. In such cases, radiation therapy may be a reasonable alternative or adjunctive treatment in selected cases. When radiotherapy is used as primary treatment, photon or electron field directed to localized region of the perineum have achieved local control. The advantage of using an electron beam is lo spare deeper structures since only superficial structures are at risk. For lack of electron facility in the department, the present case was treated on a kilo volt age unit using 300 kV photons. Perianal Paget's disease is probably best regarded as an intraepithelial adenocarcinoma, so the dose and fractionation used in this case was as for treatment of skin malignancies. Use of radiotherapy for treatment of perianal Paget's disease has been limited and the few reports that include radiation poorly describe treatment selection, radiation dose, field size, treatment technique, beam energy or the outcome of treatment. Recurrences following radiation therapy occurred mainly in patients receiving less than 50 Gy, so Besa et al recommend doses greater than 50 Gy. The treatment was delivered with minimal morbidity although their follow-up was short and the numbers small. The case described here had acute discomfort from delayed healing of the radiation reaction but follow-up at 10 years showed acceptable late radiation sequelae, with no loss of anal sphincter function, which frequently follows wide excision in this region.

Paget's Disease of Vulva

This curious and rare lesion of the vulva, and sometimes the perianal region, is similar in its skin manifestations to Paget disease of the breast.

1. As a vulvar neoplasm, it manifests as a pruritic red, crusted, sharply demarcated, map like area, occurring usually on the labia majora. It may be accompanied by a palpable submucosal thickening or tumor.

2. The diagnostic microscopic feature of this lesion is the presence of Paget cells, large tumor cells lying singly or in small clusters within the epidermis and its appendages. These cells are distinguished by a clear separation ("halo") from the surrounding epithelial cells and a finely granular cytoplasm containing periodic acid-Schiff stain-, Alcian blue-, or mucicarmine-positive mucopolysaccharide.

3. Ultrastructurally, Paget cells display apocrine, eccrine, and keratinocyte differentiation and presumably arise from primitive epithelial progenitor cells.

4. In contrast to Paget's disease of the nipple, in which 100% of patients show an underlying ductal breast carcinoma, vulvar lesions are most frequently confined to the epidermis of the skin and adjacent hair follicles and sweat glands.

5. The prognosis of Paget's disease is poor in the uncommon cases with associated carcinoma, but intraepidermal Paget's disease may persist for many years, even decades, without the development of invasion.

6. However, because Paget's cells often extend into skin appendages and may extend beyond the confines of the grossly visible lesion, they are prone to recurrence.

7. It is considered as nothing more than a variant of Vulval intraepithelial neoplasia.

7.6. MALIGNANT MELANOMA

1. Melanomas of the vulva are rare, representing less than 5% of all vulvar cancers and 2% of all melanomas in women.

2. Their peak incidence is in the sixth or seventh decade;

3. They tend to have the same biologic and histologic characteristics as melanomas occurring elsewhere and are capable of widespread metastatic dissemination.

4. Because it is initially confined to the epithelium, melanoma may resemble Paget's disease, both grossly and histologically.

5. It can usually be differentiated by its uniform reactivity, with immunoperoxidase techniques, with antibodies to S100 protein, absence of reactivity with antibodies to carcinoembryonic antigen, and lack of mucopolysaccharides.

6. Prognosis is linked principally to depth of invasion, with greater than 60% mortality for lesions invading deeper than 1 mm.

7. Treatment is by wide excision or radical vulvectomy.

8. The overall survival rate is less than 32%, presumably owing to delays in detection and a generally poor prognosis for mucosal melanomas.

7.7. BOWEN'S DISEASES

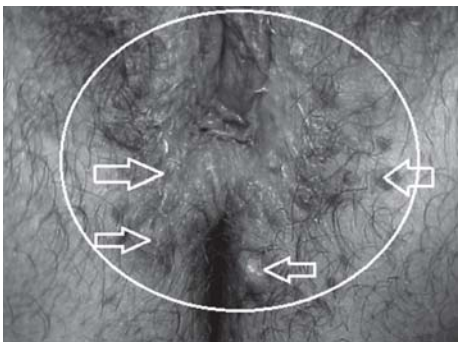


Figure 7.5. *Multicenter pigmented Bowen' s disease of the groin*

• In 1970 Lloid describes this dermatosis for the first time like "multicenter pigmented Bowen' s disease of the groin" (*Fig. 7.5*).

• Subsequently, in 1978, Wade introduced the term "Bowenoid Papulosis" (BP) in order to describe such pathology that is placed between Acuminate Condylomata and Bowen' s disease.

• In the same year Kimura describes a clinical case of viral pigmented papulosis of genitals.

Ethiopatogenesis

1. The BP ethiopathogenesis is not well understood still today.

2. HPV has been linked closely to BP. HPV is a very small DNA-virus with specific tropism for keratinocytes and the mucosas.

3. The more demonstrated in the lesions trough hybridization in situ viral genotypes are: HPV 16, HPV 18, HPV 31, HPV 32, HPV 33, HPV 39, HPV 42, HPV 48, HPV 51.

4. The infection by HPV 16, HPV 18, HPV 31 is an important factor of risk for the squamocellular carcinoma in situ, above all in HIV+ patients and in general in immunodepressed.

Frequency

• BP lesions are related clinically to genital warts. They share the same age of onset and are transmitted sexually.

• Since BP lesions frequently are treated destructively as warts and without histopathologic examination, the true frequency of BP is unknown but is believed to be underestimated.

• A number of case reports associate BP with malignant invasive transformation (2.6%).

• All races are affected equally.

Clinical manifestations

1. The young adults (average age 31 years), sexually active, hetero- and homosexual, are hit, with a light female predilection.

2. The lesions interest more frequently the genital, perianal and perineal areas, but in HIV+ patients also extragenital regions.

3. The morphology is very variable: warty, pink or brown or violet, well delimited macula-papulas, 2–30 mm in diameter; frequently asymptomatic, but it' s possible also itch, erythema, hyperpigmentation and inflammation.

Histopathological features

1. The granular layer is thickening defined with hyperkeratosis, parakeratosis and dyskeratosis.

2. Cellular atypia:

a) pleomorphic keratinocytes, hypercromatic and amassed magnified nucleous; some of them with numerous nuclei;

b) koilocytosis (it' s a cytoplasmatic vacuolation around the thickened nuclear chromatin);

c) numerous mitotic figures and cells in metaphase;

d) if the lesion is coloured, melanin-laden cells;

e) often altered acrosyringia;

f) always integral acrotrichia.

Differential diagnosis

The most important are Bowen's disease and the Condylomatosis of the genitals.

Bowen' s disease

The Bowen' s disease differs for the following clinical and histopathological characteristics:

• has its highest incidence in the older age groups;

• arises mainly in sun-damaged areas;

• usually single lesion;

• it never disappears spontaneously;

• erythematous, scaly patches or plaques that may become hyperkeratotic, crusted, fissured, or ulcerated;

• full tickness dysplasia with loss of the normal maturation of its components;

• large pale keratinocytes with abundant ground glass cytoplasm, so-called pagetoid cells;

• integral acrosyringia;

• altered acrotrichia.

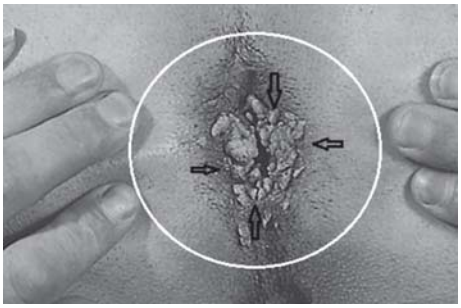


Figure 7.6. *Acuminate condylomata (arrows)*

Acuminate condylomata

• mainly occur on the genital, perianal and perineal regions (*Fig. 7.6*);

• flesh-coloured papular lesions;

• cauliflower lesions;

• hyperkeratosis, parakeratosis, acanthosis;

• koilocytosis;

• viral inclusions in the cytoplasm and the nucleous;

• absence of neoplastic change.

Course

The course is very variable:

• sometimes BP can spontaneously regress;

• in the immunodepressed patients it' s possible a carcinomatous transformation;

• after the first therapeutic assistance relapses are frequent.

Therapy

Several possibilities are available:

• superficial surgery with electrodesiccation;

• cryotherapy;

• surgical excision;

• laser therapy;

• topic immunotherapy with interferon α, β, γ;

• local imiquimod.

Activity

1. Dermatological follow up every 3–6 month because of possibility of transformation in Bowen`s disease of invasive squamoucell CA.

2. Female partners should be evaluated regularly using Papanicolaou smears.

3. In male partners, periodic anogenital examination may be of benefit.

General considerations

• Improve correct diagnosis of BP in order to prevent malignant transformation.

• Patient education regarding the malignant potential of BP and avoidance of direct sexual contact to decrease transmission.

REFERENCES

1. Besa P, Rich ÒÀ, DeklosL, Edwards CL, Ota DM, Wharton JT. Extramammary Paget's disease of the perianal skin. Int J Radiat Oncol Biol Phys 1992; 24:73–8.

2. Braverman IM. Skin Signs of Systemic Disease. 3rd ed. Philadelphia, Pa: WB Saunders Co; 1998:416–423.

3. Butler JD, Hersham MJ, Wilson CA, Bryson JR. Perianal Paget's disease. J Royal Soc Med 1997; 90:688–9.

4. Callen JP. Pyoderma gangrenosum. Lancet. 1998;351:581–585.

5. Coldiron BM, Goldsmith BA, Robinson Æ. Surgical treatment of extramammary Paget's disease. Cancer 1991; 16:387–403.

6. Darier J, Coulillaud P. Sur un cas de maladie de Paget de la region perineo-anale et scrotale. Ann Dermatol Syph 1893;4:25–3.

7. Ehrenpreis ED, Kane SV, Cohen LB, Cohen RD. Thalidomide therapy for patients with refractory Crohn's disease. Gastroenterology. 1999;117:1271–1277.

8. Levitt MD, Ritchie JK, Lennard-Jones JE, Phillips RKS. Pyoderma gangrenosum in inflammatory bowel disease. Br J Surg. 1991;78:676–678.

9. Hamblin TJ. Pyoderma gangrenosum. Lancet. 1998;351:1134.

10. Paget J. On disease of the mammary areola preceding cancer of the mammary gland. St Bartholomew's Hospital Report 1874;10:87–9.

11. Powell FC, Su WP, Perry HO. Pyoderma gangrenosum: classification and management. J Am Acad Dermatol. 1996;34:395–409.

12. Shutze WP, Gleysteen JJ. Perianal Paget's disease, classification and review of management. Report of two cases. Dis Colon Rectum 1990;33:502–7.

13. Thirlby RC, I lammer CJ Jr. Galagan KA, Travaglini JJ, Picozzi VJ. Perianal Paget's disease: successful treatment with combined chemoradiotherapy. Dis Colon Rectum 1990;33:150–2.

14. Von Den Driesch P. Pyoderma gangrenosum: a report of 44 cases with follow-up. Br J Dermatol. 1997;137:1000–1005.

Chapter 8

METHODS OF INVESTIGATIONS OF SURGICAL PATIENTS

8.1. PLAN OF CASE HISTORY

1. Investigation of the subjective state. The complaints of the patient.
2. History of present illness.
3. History of life.
4. An objective study of the patient:

a) external examination: general condition, consciousness, position of the patient, the skin and mucous membranes, subcutaneous tissue, lymph nodes, breast cancer, musculoskeletal system;

b) The study of the circulatory system;

c) A study of the respiratory system;

d) Study of the digestive system and spleen;

e) The study of the genitourinary system;

f) The study of the nervous system;

g) Study of the endocrine system;

h) The musculoskeletal system.

5. Localization of the disease.

6. The preliminary diagnosis indicating the rationale and the need for additional research (laboratory, biochemical, instrumental, X-ray, and others.) And consulting other professionals. Evaluation made from additional research and consultations.

7. Plan of inspection.

8. The clinical diagnosis (basic disease, complications, comorbidities).

9. Treatment of the patient. Justification of the need for surgical intervention. Preoperative preparation and prevention of possible postoperative complications. The choice of method operation, anesthesia. The combination of pathogenetic therapy with other therapies (diet, exercise therapy, replacement therapy, physiotherapy, symptomatic, spa treatment, etc., Diary reflecting the dynamics of the disease and treatment measures for the days of supervision of the patient, the signature of the curator).

10. Epicrisis.

11. Forecast of the disease in relation to the patient's life, his rehabilitation (recovery and disability).

12. References in writing history.

Study of subjective states. Initially, the patient is given the opportunity to state their complaints themselves. In the future, the curator clarifies the major and minor complaints, clarify the sequence in which they occurred, and what relationship exists between them. When there is pain, pay attention to the character, intensity, location and irradiation. It is necessary to clarify the connection of pain with movement, physical exertion, food intake, urination, defecation act, as well as other external factors: hypothermia, change of weather, season, etc. It is important to clarify the

duration of pain, if they are accompanied by feelings of fear, anguish. In severe patient's condition, you should formulate questions so that the patient can answer in one word.

After clarification and detailed complain, it is necessary to undertake a systematic survey of the patient in terms of the basic functions of the body in a specific pattern. Particular attention should be paid to those violations, which may be relevant to the disease. An additional survey of the patient according to the following scheme:

1. *The respiratory system.* Identify the nature of breathing (free, labored through the nose, through the mouth), if there are nasal discharge, the amount and type (transparent, festering, bloody). If nosebleeds, indicate their profusion, duration, frequency and the cause of the alleged. Detailing pain in the chest, state their intensity and location, frequency, in connection with which they arise, where radiating. We attach great importance to factors that increase the pain in the chest (deep breath, cough). In a survey of the patient's complaint, it is desirable to identify those who have ME.

2. *Cardiovascular System.* If you have complaints about the heart it is advisable to clarify its nature, frequency, duration, and, if possible, the causative factors (agitation, fatigue, night work). Pain in the heart may be periodically or continuously, of varying intensity and significance irradiation. Important complaints are those of pain in the lower limbs: their symmetry, location and duration (there in the evening, after sleep or permanent). Detailing the complaints of pain in the lower extremities, find out the cause and time of their appearance. Pain may occur periodically in the form of intermittent claudication, is often accompanied by increased chilliness, feeling of pins and needles, numbness of the limbs. Note the presence of a headache, dizziness, decreased vision, memory impairment.

3. *The digestive system.* After asking what the patient's appetite (good, fair, poor, "wolf"), you should pay attention to taste (bitter, sour, unpleasant), the amount of fluid drunk per day, thirst, salivation, aversion to any.

Food. Most of the diagnostic value is subjective data such as getting liquid food into the trachea, free, difficult or painful passage of food through the esophagus, character.

Regurgitation (air, received food, gastric contents) and its smell (no smell, like rotten eggs, fecal). Full transcript of dyspepsia (heartburn, nausea, vomiting), the determination of their intensity and duration, taking into account the causative factors – an important element in the diagnosis of surgical diseases of the gastrointestinal tract. The curator is to imagine a logical sequence.

These violations specifically focus complaints of the patient and give them some praise. For the diagnosis is extremely important, for example, such data when there was vomiting, whether it is connected.

Write to the reception, the amount of vomit, smell, color, and others. When there are complaints of abdominal pain, you need to know their location (in the pit, hypochondria, iliac or inguinal region, during bowel movement, character (permanent paroxysmal, acute, and obtuse) irradiation (girdle, under the shoulder blade, in the chest), and communication with the meal. It should also take into account the

physiological characteristics of the Board: carminative (not free, in large quantities), defecation (independent after the enema, frequent urge the color of bowel movements (mixed with blood, tarry, with the presence of mucus or pus).

4. *The urinary system.* Characteristics of pain in the lumbar region (paroxysmal, persistent, radiating to the back or external genitalia), should be supplemented by data on urination (free, difficult, painful, constant leakage of urine drop by drop), the amount of urine per day, and those of its features, as color, the presence in urine of mucus, pus, blood. Pay attention to urinary frequency depending on time of day.

5. *The nervous system.* In terms of identifying the main signs and comorbidities, the patient's mood is important (optimistic, cheerful, depression, anxiety), the adequacy of responses to various stimuli, the ability to quickly transition from sleep to wakefulness. In the same section should reflect subjective data concerning the state of the senses (sight, hearing, smell, touch).

6. *Musculoskeletal system.* In case of complaints of pain in the muscles, bones and joints should determine their nature (permanent, acute, obtuse), the relationship with the seasons, weather and other factors.

After completing the study of the subjective complaints of the patient, it is necessary to detail and in a certain sequence to state in history. It should be guided by the following scheme-guide:

1) To describe the complaints of the patient due to the underlying disease and its complications. Reads complaints related to co-morbidity;

2) Obtained in the study of subjective data grouped into complaints of a general nature, local and complaints relating to other organs and systems. For example, complaints of a patient with dumping syndrome can be divided three groups of complaints: general (dizziness, fatigue, drowsiness, tinnitus, tremor of the extremities), local (feeling of pressure and a feeling of fullness in the epigastric region during meals or 15–20 minutes after a meal) and related dyspeptic disorders (salivation, heartburn, belching, rumbling in the abdomen, diarrhea).

History of the disease. In history it is necessary to describe the onset of the disease, as well as the sequence of its clinical manifestations, especially the pre-hospital period. The curator is to find out exactly where the disease originated, and in emergency surgical conditions – how many hours ago. He should also detail and find out how the disease developed: gradually or suddenly, any remedial measures carried out in the pre-hospital period and their effectiveness. Particular attention is paid to establishing possible causes of the disease. Beginning with the first symptoms and admission to detail the growth of the clinical picture of the dynamics of personality and find out the pathological process in this patient. In some cases, medical history include the most characteristic thing about the disease to describe the conclusions of medical institutions, where the patient was before entering the clinic, as well as information concerning the biochemical, laboratory, X-ray and functional investigations conducted before admission.

If the patient is being treated for a long time for chronic diseases, you should describe the disease with all the features and data of diagnostic tests and the results

of the treatment. In those cases where the patient is unconscious, history of the disease should be checked with relatives or medical personnel who accompanied the patient in the clinic.

In describing the history of this disease, be guided by the following scheme:

1) set the beginning of the disease (sudden, gradual);

2) describe the sequence of origin of symptoms and their relationship to each other;

3) present the most likely proposed causes of disease;

4) describe in detail the development and course of the disease before the arrival of the patient to the hospital and during his stay in the clinic before Supervision.

History of life. Details of this important section of the study of the patient should also be systematized and presented in the following order.

1. *Medical Biography of patient:* the conditions of his work and life, attitude toward military service, especially family life. It should describe in detail, the birthplace of the patient as the child grew in comparison with their peers, as he learned. Pay attention to children's and youth periods of physical and mental formation of the personality of the patient, conditions of school and work. Detailed description of puberty in women, indicate the time of occurrence of menstruation, their recurrence, number of pregnancies, births, abortions, miscarriages. Characterizing marital status, describe the health of his wife (husband), children. The information about participation in wars, serve in the army is important. This section ends with a description of life history, character, work, sick lately.

2. *Transferred to the chronological* order of illness and injury. It should be mentioned, the use of antibiotics, hormones, blood transfusions, anticoagulant in treatment and their complications. Special mention of diseases such as tuberculosis, syphilis, allergic reactions to the use of drugs.

3. *Hereditary diseases.* Anamnesis of the immediate family, to find out sickness of parents, father and mother of the patient (cancer, metabolic disorders, mental illness).

4. *Bad habits*. It is necessary to elaborate on details of the abuse of alcohol, smoking, drugs and drinking habits indicate strong coffee, tea, and pay attention to the excesses in the diet.

Objective research

1. *External examination of the patient.* First describe the general condition of the patient (satisfactory, moderate, severe, agony), his consciousness (clear, confused, unconsciousness) and position in bed (active, passive, involuntary). Be sure to pay attention to the expression of the patient (calm, excited, indifferent, mask-like), figure (normosthenic, asthenic, hypersthenic), fixed height in centimeters, weight in kilograms and body temperature. Giving a general characteristic of the skin, note the color (pink, pale pink, pale, red, icteric, cyanotic, earthy, bronze), turgor and elasticity, as well as the presence of areas of depigmentation, scars, rashes, tumors, bruises; especially hair growth (male or female type). Examination of the mucous membranes, conjunctiva, nose, lips, mouth and pay attention to the color, the presence

of lesions, erosions, ulcers, leukoplakia. Tongue may be wet, dry and dryish, surrounded by white, gray or brown coating. In describing the tonsils determine their color and value; give a characterization of dental formula. Along with the determination of the degree of development of the subcutaneous tissue (weak, satisfactory, excessive) note the uniformity (or unevenness) of its distribution, and skin pastosity or edema. During inspection and palpation of lymph nodes (submandibular, cervical, axillary, inguinal, and retroperitoneal) find out their cohesion with subcutaneous fat, texture, size, tenderness.

In the same section provide data from examination of mammary glands: the symmetry, size, shape and the presence of nipple discharge (serous, hemorrhagic, and purulent). On palpation of the prostate in vertical and horizontal position of the patient, it is impracticable to determine the development of adipose tissue, the nature of lobular structure, the presence of seals and tumor formations.

2. *Study of the respiratory system.* After inspection of the chest, describe its shape (cylindrical, conical, barrel-shaped, narrow, flat, etc.). Type of breathing (thoracic, abdominal, combined), and the participation of both halves of the chest in the act of breathing. Pay attention to the state of the intercostal spaces with a deep breath and exhalation. On the chest is determined painful places, swelling, compression and voice tremor (weakened, unaltered, increased). The method of comparative percussion in symmetrical parts of the chest determines the nature of the sound (clear lung, blunted, tympanic, and boxed), height standing tops, the boundaries of the lungs. Auscultation produces symmetrical sites, starting with the subclavian pits. At the same time determine the character of breath sounds (vesicular breathing, rigid, bronchial, amphorae mixed), quantity, and location of the sonority of wheezing (dry, wet, coarsely and finely) and pleural rub.

3. *Study of the circulatory system.* The study of the circulatory system begins with the definition of pulse on the arteries (radial, temporal, carotid, brachial, femoral, subclavian, tibial, the back of the foot), frequency, and voltage of pulse filling. Pay attention to the presence of varicose veins in the thorax, abdomen, extremities, as well as seals and pain along the vein. Important are pastose and asymmetric limb edema. Determine blood pressure (maximum, minimum, pulse), and the border of the heart. Percussion is impossible to define the boundaries of relative and absolute cardiac dullness. Auscultation, pay attention to heart sounds (clear, the deaf, the splitting of the second tone), their frequency, rhythm and attitude to heart-phase activities. Pericardial noises are heard in different positions of the patient. Non-cardiac noises are determined by their relation to the phases of respiration.

4. *Investigation of the digestive system.* On examination of the abdomen define its shape (round, retracted, asymmetrical), part of the front wall in the act of breathing, the presence of visible peristalsis. In addition, it is possible to detect the visible pulsation in the epigastric region, the divergence of the abdominal muscles, hernial protrusion, straining and coughing. The method of determining the state of the superficial palpation of the abdomen, its resistance, strain of abdomen muscles, tenderness and its location, area of skin hypersensitivity and pain points. It is necessary

to identify and fix the medical history and condition of the umbilical inguinal rings and the presence of Blumberg's sing. With deep methodical sliding palpation method Obraztsov–Strazhesko and consistently determine the location, condition and pain of the sigmoid colon, the cecum. Determine soreness at the points Mc Burney and Lanza, Rovsing's sing, Sitkovsky's sing, Voskresensky's sign, Krymov's, Obraztsova's, and others. In the same manner and subject to the same data examine ascending, transverse colon, descending colon, determine the presence of tumors, infiltrates.

With deep sliding palpation of the epigastric region palpate stomach, define pain (local, diffuse) of individual sections of the small and large curvature, pyloroduodenal region, bulbs of duodenum, ulcer, note the presence of visible peristalsis, infiltrates, tumors, deformities, asymmetries. A study of the liver begins with a tour of the lower third of the chest and right upper quadrant. Palpating particular edge of the liver (sharp, dull, soft, smooth, dense, and lumpy) and its borders. Exploring the gallbladder, pay attention to its character, value, mobility, pain, and hypersensitivity zone.

In the study of pancreatic area, inspect the epigastric region. Palpably determine the shape, size and consistency of the prostate, pay attention to the presence of infiltration, tuberosity, and tumors. In determining the boundaries of the spleen palpation start with left groin, scrutinize the state of the left side of the abdomen and the left hypochondrium in the supine position on the right side. The history record, data from studies on the consistency of the spleen (firm, elastic, soft), the surface (smooth, nodular) and pain. When viewing the anus, note the presence of external hemorrhoids, prolapse of the rectal mucosa, the presence of warts, fistula, and fissures. At manual study, it is impracticable to determine the tone of the sphincter, the presence of internal hemorrhoids, infiltrates, polyps, tumors. It is extremely important to be considered in the identification of rectal mucus, pus, bleeding.

5. *Investigation of the genitourinary system.* After inspecting the psoas and groin, by palpation determine the lower pole of the right and the left kidney of the patient in the supine position, resting on the side. Pay attention to the location of the kidneys, their size, mobility (smooth, bumpy), and tenderness; define Pasternatsky's sing. Inspection, palpation and percussion of the bladder reveal the presence of infiltrates asymmetries tumors. Perform digital examination of prostate through the rectum and describe its size, consistency, indicate the presence of the tuberosity, and other fluctuations.

6. *A study of the nervous system.* Determine the patient's mood (cheerful, depression, anxiety) and sociability, his orientation in the environment. Identify reflexes (conjunctival, corneal, tendon), pain along the nerve trunks, muscle stiffness, and skin sensitivity (pain, tactile, temperature), hyperesthesia, paresis, paralysis. Explore demographics, its character (red, white) and length.

7. *Study of the endocrine system.* After inspection and palpation of the thyroid gland define its borders, shape, texture, surface, displaceability during swallowing, fusion with the surrounding tissue and pain. Note the presence of obesity, gigantism, exhaustion, pigmentation (with Addison's disease).

8. *Musculoskeletal system.* Determine the overall development of the muscular system, the tone, the presence of infiltrates tumors, atrophy, and hypertrophy. During inspection and palpation, pay attention to the symmetry of limb bones, skull shape, deformation of the chest and spine (kyphosis, lordosis, and scoliosis), and pelvic bones. It is necessary to check the amount of active and passive movements of the joints, pain under pressure, the presence of deformities of the joints, fluctuations, and other tumors.

Site of disease. The localization of the disease after a careful stud, described in a certain sequence: data inspection, palpation and auscultation. For example, when describing patients with abdominal pathology should start with the skin, tongue, visual inspection of the abdomen, and so on. Then describe the main symptoms of the disease. In describing the wounds, fistulas, be sure to note the size, nature, number.

8.2. PRELIMINARY DIAGNOSIS

On the basis of patient complaints (are the main complaints), the history and objective examination (describe the main symptoms of the disease), as well as the laboratory, radiological, instrumental and other additional methods of investigation, reflecting the underlying disease, its complications and comorbidities, we can supply the following diagnosis. In order to establish the clinical diagnosis of patient we need to survey

Plan of inspection:

1. Clinical analysis of blood platelet indication.
2. Urinalysis.
3. Analysis of urine (daily) for sugar.
4. The residual nitrogen, urea, creatinine of blood.
5. The contents of potassium, calcium, sodium, chloride in the serum.
6. Key indicators of acid-base balance.
7. General protein and protein fractions.
8. Expanded coagulation.
9. Blood group and Rh affiliation.
10. The content of bilirubin levels.
11. Diastase blood, urine.
12. Blood glucose.
13. Determination of aldolase transaminases.
14. Scan.
15. Determination of the main exchange.
16. Test for unconjugated bilirubin.
17. ECG.
18. Analysis of gastric juice with histamine load.
19. Duodenal intubation.
20. Special methods of examination: endoscopy, X-ray, ultrasound, CT, X-ray, bronchoscopy, cholecystitis, cholangiography, cystochromoscopy, sigmoidoscopy, colonoscopy, laparoscopy, and others.

8.3. CLINICAL DIAGNOSIS

Based on the above patient complaints, anamnesis of disease and life, as well as the results of additional research methods, we can put a clinical diagnosis.

In justifying the clinical diagnosis, only those studies that were obtained after the description of the preliminary diagnosis, reflecting the underlying disease, its complications and comorbidities are used.

Treatment and prevention. If the diagnosis reveals complications and comorbidities, the physician must determine the surgical approach and develop a plan for comprehensive treatment.

Description of therapeutic interventions should be done in the following order: patient treatment, diet, preparation and conduct of surgery, physiotherapy and medication.

The surgical hospitals generally carry out the following treatments: 1) surgery, 2) diet, 3) physical therapy, 4) substitution therapy, 5) symptomatic therapy, 6) rehabilitation.

One of the important stages of treatment - rational preoperative preparation of the patient, is aimed at improving the body's immune-biological and sanitation foci of chronic purulent infection.

1. *Preoperative preparation.* The duration and content of remedial measures in the preoperative period is determined by the main indicators of the functional activity of vital organs and systems, as well as the estimated volume of surgical intervention.

Preoperative preparation is to correct the identified violations of the water and electrolyte balance and protein, acid-base balance, as well as to stimulate the body's defenses (due to blood transfusion, dietary, vitamin-monotherapy, etc.). Much attention should be paid by the curator to the treatment of concomitant diseases that can be in the postoperative period which create an unfavorable background for the recovery of the patient. In order to prevent various complications in the postoperative period before surgery is necessary to sanitize all the centers of a chronic purulent infection (tonsillitis, carious teeth, otitis, pyoderma), which, where appropriate, should be invited to another specialist (dentist, otolaryngologist). This section, preoperative medical history, complete case history, which indicates the underlying disease, its complications and comorbidities, justify the need for surgical intervention.

The preoperative epicrisis should list the main indicators of laboratory, instrumental and radiological studies on the organ, which will be produced by surgery, indicated and justified incision access and the method proposed transaction. In conclusion, the curator notes consent of the patient for surgery, type of anesthesia, and substantiates the need for sedation.

In addition to these studies, in each case perform targeted analysis, enabling to find out the function of the body, which is supposed to surgery. For example, in complicated ulcer (penetration, bleeding) or in diseases of operated stomach additionally should undertake the following studies: an analysis of stomach contents, empty stomach and with the stimulation of histamine and insulin, X-rays and X-rays

of the gastrointestinal tract, with evidence – gastroscopy, biopsy of mucosa and study of washing water, the content of diastase in blood and urine, propensity for dumping syndrome, and others. In this case, additional research will allow doctors to determine the surgical approach and choose the most efficient method of surgery (resection of 1/2, 2/3, 3/4 gastric vagotomy with drainage surgery, gastrectomy, vagotomy and supplemented by others).

2. *Minutes of the operation.* The minutes of the curator is to articulate the postoperative clinical diagnosis, the name, date, and duration of surgery, type of anesthesia, as well as to record the name and patronymic of the surgeon, assistant, anesthesiologist, and surgical nurses.

If the operation is performed under local anesthesia, or potentiated, you must specify the concentration and amount of spent solution of Novocain. Inhalation (intubation) and intravenous anesthesia neuroleptanalgesia data, and the amount of spent narcotic drugs should be detailed in the anesthetic map.

Driving protocol operations:

- Treatment of the surgical field (iodine, film-forming substances).
- Skin incision (shape, length, height).
- Particular surgical approach.
- Data audit and inspection bodies (thoracic, abdominal).
- A detailed description of the detected organic changes.
- The final choice of method of surgical intervention and its rationale.
- Sequence of the various stages of operation.
- A description of any complications during surgery (bleeding, wounded nearby organs, perforation of hollow organs, hematoma, and others).
- A description of the operated organ after its reconstruction (sutured stump leak, anastomotic patency, and others).
- A description of the remote organ or a part thereof (macro preparations).
- Particular transaction (increased bleeding, pronounced adhesions, etc.).
- Particular closure of surgical wounds (plugging, drainage).

3. *Postoperative period.* After surgery in severe condition of the patient is 3–4 days in the intensive care unit under the supervision of the surgeon and the anesthesiologist. With a view to the prevention and timely detection of various complications (internal bleeding, peritonitis, pneumonia, thromboembolism) curator systematically monitors the patient. It should be every day to observe and record the history of the disease, blood pressure, heart rate and breathing, to describe the state of the chest and abdomen, physiological functions. It is mandatory registration of water-electrolyte and protein metabolism, acid-base balance, blood coagulation properties and their correction. In the postoperative period to determine the function of the cardiovascular, respiratory and other systems as well as before the operation, widely used laboratory, instrumental and radiological diagnostic methods. Postoperative treatment generally should be multidimensional and include diet, pathogenetic, symptomatic, physiotherapy and other treatments. Assigned medications should be recorded in the history of the disease in the form of prescription formulations

with an indication of the concentration, dosage and time of medication. In the event of post-operative complications is necessary to describe in detail the features of their clinical manifestations, to justify the additional therapeutic measures. One of the essential conditions for rational postoperative patient – physiotherapy; this kind of preventive therapy must be reflected in history.

4. *Diary of patient care*. The disease is reflected in the diary of observations of patients in which the curator series presents the dynamics of the subjective condition of the patient and the data of objective research. The diary should describe the general condition of the patient, his sleep, appetite, tolerability and efficacy of therapeutic interventions. In addition to blood pressure, heart rate and respiration, Entries should reflect the data inspection, palpation and auscultation, on the chest and abdomen. One of the important sections of the diary – dynamic observation and description of the location of the disease (post-surgical wounds, fistulas, scar infiltrate). It should describe in detail the state of the dressing, the quantity and nature of the secretions from the wound, indicate the presence of necrotic tissue, granulation, infiltrates. In a diary note the removal of the drainage tubes and micro-irrigators, application of dressings with antiseptic solutions, the nature of the healing of surgical wounds. During Supervision 4–5 to write a diary, reflect the objective and the subjective condition of the patient.

8.4. EPICRISIS

This section is a detailed extract from the case where the surname, name and patronymic of the patient's age when he entered, with any diagnosis, conducted survey, treatments, surgery, when issued and what the final diagnosis is.

8.5. PROGNOSIS

- prognosis of complications;
- death prognosis;
- prognosis for work;
- prognosis for life.

Навчальне видання

Криворучко Ігор Андрійович
Лісовий Володимир Миколайович
Бойко Валерій Володимирович
Тонкоглас Олександр Аркадійович

SURGERY
Part II
SURGICAL GASTROENTEROLOGY AND PROCTOLOGY
Textbook for medical students

ХІРУРГІЯ
Частина ІІ
ХІРУРГІЧНА ГАСТРОЕНТЕРОЛОГІЯ І ПРОКТОЛОГІЯ
Навчальний посібник для студентів медичних закладів

Відповідальний за випуск І. А. Криворучко

Комп'ютерний набір і верстка Н. І. Дубська

Формат В5. Папір офсетний. Друк – цифровий.
Наклад 300 прим. Зам. №18-33621

Редакційно-видавничий відділ ХНМУ,
пр. Науки, 4, м. Харків, 61022
izdatknmurio@gmail.com

Свідоцтво про внесення суб'єкта видавничої справи
до Державного реєстру видавництв, виготівників і розповсюджувачів
видавничої продукції серії ДК № 3242 від 18.07.2008 р.