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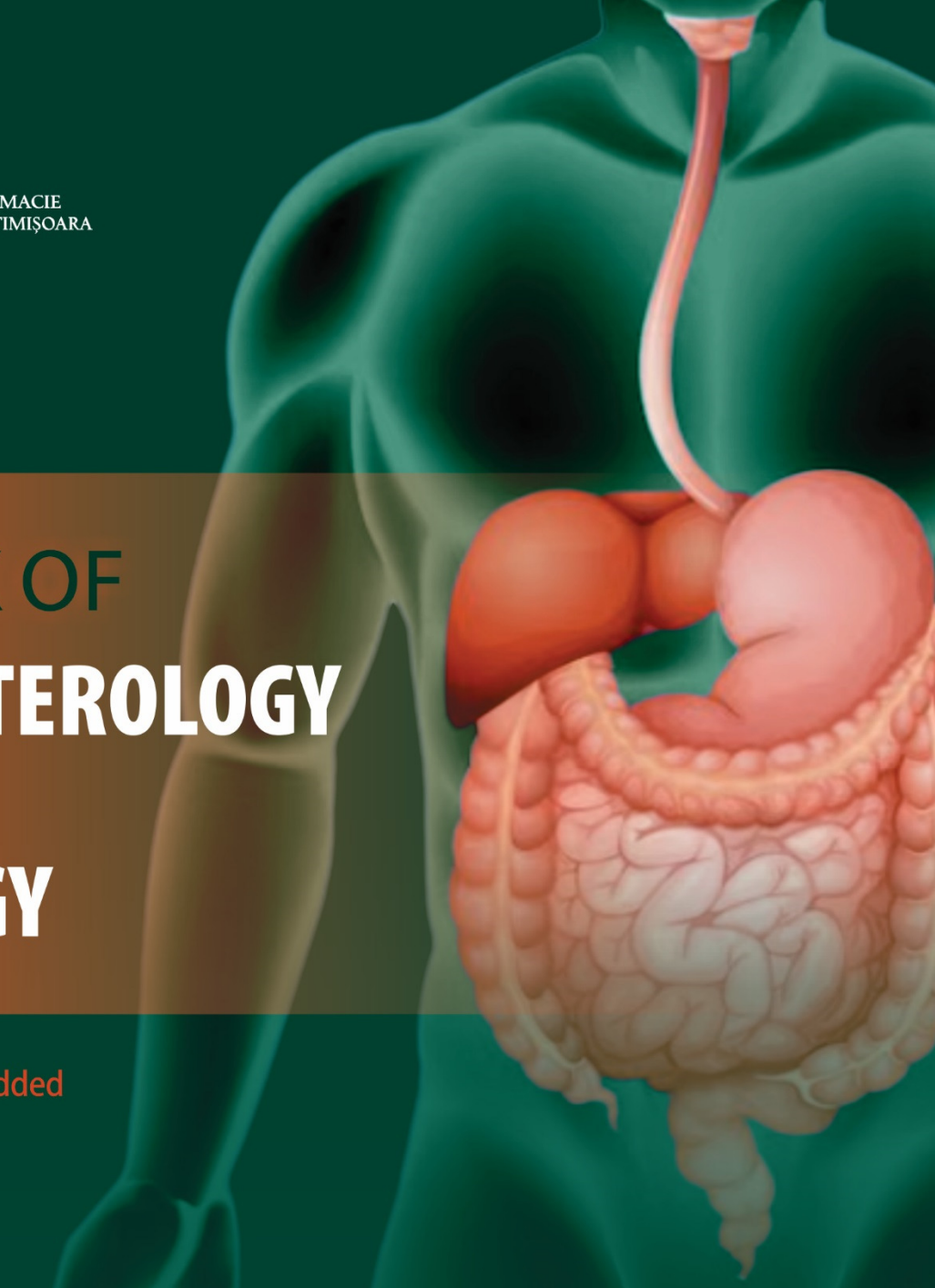

TEXTBOOK OF GASTROENTEROLOGY AND HEPATOLOGY

second edition, revised and added

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MANUALE

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CONTENT

1. GASTROESOPHAGEAL REFLUX

Definitions

Gastroesophageal reflux disease (GERD) is a condition due to the reflux of gastric contents into the esophagus and includes all the clinical manifestations determined by it, with or without the appearance of endoscopic esophageal lesions.

Gastroesophageal reflux disease (GERD) is a physiological phenomenon, which consists of the passage of part of the gastric contents into the esophagus, caused by the transient relaxation of the lower esophageal sphincter (IES). When anti-reflux mechanisms are overcome, the reflux content can reach the oropharynx and airways.

Reflux esophagitis (erosive GERD) includes inflammatory lesions of the esophageal mucosa caused by GERD, visible endoscopically, and are a complication of it.

Other terms that should be considered are:

- *Negative endoscopic reflux disease (non-erosive GERD*), for cases that meet the clinical definition of GERD, but do not show changes in the esophageal lining on endoscopic examination

- *GERD with extra-esophageal symptoms*, in the ENT or respiratory sphere.

Two newly defined entities ingrained in functional esophageal pathology are: *acid-hypersensitive esophagus* – includes symptoms of PPI-refractory GERD without esophagitis or abnormal acid exposure, related to heartburn episodes and normal acid exposure and *functional heartburn* – proton pump inhibitor (PPI) refractory GERD symptoms, no esophagitis, no abnormal acid exposure, and no link between normal episodes of acid reflux and heartburn. Over 90% of the cases of heartburn patients who do not respond to PPI treatment are caused by the two new entities.

Epidemiology

GERD is a common entity in clinical practice and with an increasing incidence, being the most common gastroenterological pathology encountered in developed countries, with prevalence data ranging between 10-20%.

Etiology and pathogenesis

GERD is directly caused by the reflux of gastric contents (acid, pepsin, bile and duodenal contents) into the esophagus, when the anti-reflux mechanisms are overcome. The most common causes are: the presence of hiatal hernia by slipping, increased intra-abdominal pressure (pregnancy, obesity, ascites, abdominal tumors, too tight corsets). Other causes: post-surgery (vagotomy, gastrectomy), systemic conditions such as scleroderma and diabetes.

GERD is more common after the age of 50 and can be accentuated or induced by drug factors (anticholinergics, aminophylline, nitrites, benzodiazepines, calcium channel blockers), food (chocolate, fats, onions, citrus fruits, tomato juice, menthol products), coffee (by xanthine derivatives), smoking, alcohol.

GERD has multifactorial pathogenesis:

I. Incompetence of anti-reflux barrier mechanisms.

1. Tone of the lower esophageal sphincter (IES). Under normal conditions, the pressure of the IES is 20 – 25 mmHg, which relaxes only at the time of swallowing. GERD manifests when one of the following occurs:

a) transient relaxation of the IES (RTSEI) that is not triggered by swallowing, associated with inhibition of contraction of the crural diaphragm, being the major cause of GERD

b) abnormal adaptive response of the IES to the increase in intra-abdominal pressure (intragastric pressure exceeding that of the IES);

c) Hypotensive EES: an average basal pressure of the EES less than 10 mmHg.

2. Absence or shortening of the intra-abdominal segment of the esophagus – it functions under physiological conditions as a valve

3. Widening the angle of His. This angle between the esophagus and the stomach is usually very sharp, acting as a valve at the entrance to the stomach. In obese people it enlarges and loses its physiological role.

4. *The folds of the gastric mucosa* at the level of the eso-gastric junction form a "brake" with a role in the prevention of GERD, and gastric atrophy favors the appearance of GERD

II. Altered esophageal clearance. Esophageal clearance is achieved due to esophageal motor activity (peristaltic waves), gravitational force and swallowing saliva (which neutralizes acid). In clinostatism, the esophageal clearance is prolonged, the contact time of the esophageal mucosa with the reflux acid is longer, the heartburn and acid regurgitation are more severe, and the patients feel the need to adopt the sitting position.

III. Delayed gastric evacuation – as a result of a disorder of gastro-duodenal motility (e.g. diabetic gastro-paresis)

IV. The content of the reflux influences the appearance and intensity of symptoms;

The aggressiveness of the reflux material in the esophagus is mainly related to the presence and concentration of HCl; an important role is also played by bile salts that have

a detergent effect on the esophageal mucus that protects the esophageal mucosa from acid reflux.

V. Decreased defense capacity of the esophageal mucosa as a result of decreased secretion of mucus and bicarbonate by epithelial cells, as well as insufficient release of prostaglandins.

VI. The presence of acid pocket leads to the paradoxically more frequent appearance of reflux symptoms in the postprandial period, even if the intragastric pH decreases during this period due to the neutralization of acid by food. The acid pocket is located at the level of the fornix, under the heart, being the area where stomach acid accumulates and is not neutralized by food (the acid floats over the food bolus), which makes the pH of this area lower than that of the rest of the stomach.

Clinical picture

It is characterized by typical symptoms, atypical symptoms, symptoms due to complications and alarm symptoms.

Typical symptoms are ***acid regurgitation and heartburn****.* These may only be occasional, but in severe forms they may be quasi-permanent. Heartburn is the sensation of retrosternal burning that goes up to the neck, being present in over 75% of patients with GERD. It is accentuated by maneuvers that increase intra-abdominal pressure (bending forward, lifting weights, going to bed immediately after eating), and is sometimes accompanied by acid regurgitation. Regurgitation is the effortless return of gastric/esophageal contents into the mouth and is felt by the sufferer as a sour (acidic) or bitter (alkaline) taste.

Belching, sialorrhea, hypersalivation are other symptoms that occur with varying frequency. *Odynophagia and dysphagia are alarm symptoms*, suggesting the presence of a complication, most commonly a peptic stenosis, but they can also be due to esophageal motor disorders sometimes present in GERD.

Atypical symptoms occur in about 1/3 of patients with GERD and include:

- Atypical digestive symptoms: nausea, vomiting, difficult digestion, early satiety, epigastric pain, bloating.
- Atypical respiratory and ENT symptoms: asthma, wheezing, chronic cough, fibrosis, lung abscess, mouth burns, gingivitis, dental erosions, dysphonia, foreign body sensation in the throat, pharyngitis, laryngitis, laryngospasm, laryngospasm ulcer and polyp, cricopharyngeal dysfunction, subglottic stenosis, sinusitis, rhinitis, otitis media.
- General atypical: retrosternal pain, sleep disturbances.

It is estimated that about 80% of asthmatics and more than half of patients with precordial pain have clear evidence for the diagnosis of GERD.

Symptoms due to complications: retrosternal pain, dysphagia, digestive bleeding, cough and hemoptysis (aspiration lung disease).

Alarm symptoms – weight loss, dysphagia, odynophagia, digestive bleeding, vomiting/persistent pain, anemia, adenopathic masses, dysphonia. They indicate a complication of GERD or other severe disease requiring urgent endoscopic and radiological explorations.

Paraclinical explorations

Paraclinical investigations are usually not necessary for the diagnosis of GERD. In young patients, under 45 years of age, with typical symptoms, the clinical picture is sufficient to start treatment. However, the presence of atypical symptoms and especially alarm symptoms requires paraclinical investigations.

The investigations used to evaluate gastroesophageal reflux are:

- *Barium radiological examination* has low diagnostic value; it may highlight the existence of a hiatal hernia, an esophageal motor disorder, a complication of reflux (stenosis) or gastric stasis.

- *Esophageal ph-metry* – the measurement of esophageal pH over a 24-hour period (usually ambulatory), considered until recently as the "gold standard" for the diagnosis of GERD. The indications are limited and it is used especially in symptomatic patients, non-responsive to PPI treatment, for the correlation between clinical symptoms and esophageal pH or between atypical symptoms (presternal pain, asthmatic crises) with the presence of acid reflux. A reflux episode is defined as a decrease in the esophageal pH below 4 (normally, the esophageal pH is greater than or equal to 6). A new method of assessing esophageal pH is the BRAVO capsule, attached to the esophageal wall by endoscopy, which sends pH information to an external receptor worn by the patient.

- *Esophageal manometry* has no role in the routine diagnosis of GERD, but can be used to measure pressure at the IES level and for differential diagnosis with esophageal motor disorders

- *Upper digestive endoscopy* (EDS) is primarily recommended for patients with alarm symptoms. Esophagitis is present in 30-50% of patients with GERD examined endoscopically. Endoscopy can reveal or exclude possible esophageal lesions (esophagitis, stenosis), possible gastro-duodenal lesions associated with or even causing symptoms, as well as the presence of a hiatal hernia. EDS also allows or highlights lesions that can and should be biopsied (e.g. a Barrett epithelium).

The most common are ***reflux esophagitis (ER)*** lesions, erosions at the level of the distal esophagus (Fig. 1.1), caused by GERD. Depending on the severity of endoscopic lesions, ER is classified according ***to the Los Angeles criteria*** (Table 1.I):

Table 1.I. Los Angeles Classification of Reflux Esophagitis

Grade ER	Description
A	One or more areas of substance loss (erosion) smaller than 5 mm, limited to mucosal folds.
B	At least one loss of substance (erosion) longer than 5 mm, limited to mucosal folds, with no continuity between the tips of adjacent folds.
C	At least one extensive loss of substance (erosion) between adjacent but non-circumferential mucosal folds (≤ 75% of circumference).
D	Loss of substance (erosion) affecting more than 75% of the circumference of the esophagus.

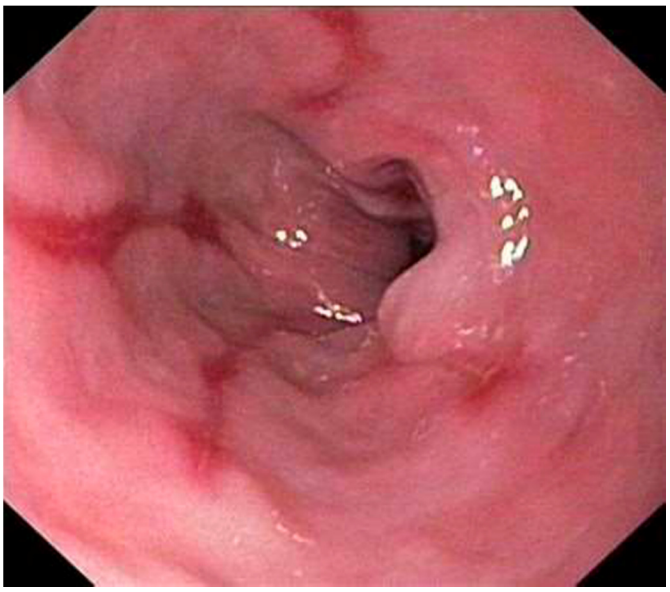


Figure 1.1. Reflux esophagitis grade B, evaluation by EDS.

Hiatal hernia is the condition in which the upper portion of the stomach passes from the abdominal cavity to the thoracic cavity due to the widening of the diaphragmatic hiatus, the natural hole through which the esophagus passes into the abdomen. Hiatal hernia can be by slipping, in which the eso-gastric junction and part of the stomach slide into the thoracic cavity, by rolling, in which the gastric fornix protrudes into the thoracic cavity parallel to the esophagus or mixta, a combination of the two, with a higher risk of complications (Fig. 1.2). According to the endoscopic classification, the lower esophageal sphincter presents itself as follows: Grade I: normal situation; the mucosal fold is tightened around the endoscopic tube. Grade II: the mucosal fold is less prominent, presenting a small space between the endoscope and the mucosa. Grade III: there is an obvious space between the weakened mucosa and the endoscope, presenting a small hiatal hernia and a widened hiatus. Grade IV: migration of the eso-gastric junction into the mediastinum, with a substantial hiatal hernia through the enlarged hiatus.

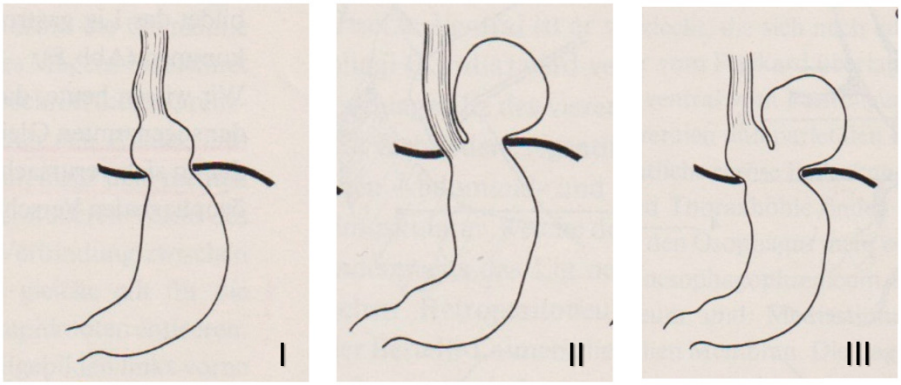


Figure 1.2. Classification of hiatal hernia. I – by sliding. II- by rolling or paraesophageal and III- mixed. Source: https://doi.org/10.3390/life14091145**. Open Access**

Positive diagnosis

In patients under 45 years of age who experience heartburn frequently (more than twice a week) without atypical or alarming symptoms, the positive diagnosis of GERD is easily established on the basis of clinical symptoms, without conducting further explorations. The initial evaluation should include the presence, severity and frequency of heartburn, regurgitation, as well as other typical or atypical symptoms, and, very importantly, the warning signs that require further investigation. Possible precipitating factors should also be sought: diet, physical activity, changes in positions, various pathologies; but also of the factors that lead to the improvement of symptoms: antacids, alkaline foods.

The positive diagnosis is supported by the performance of the above-mentioned paraclinical investigations: upper digestive endoscopy and ph-metry, in selected cases.

Differential diagnosis

The differential diagnosis includes numerous digestive and extradigestive disorders: achalasia cardia, esophageal cancer (endoscopically and radiologically excluded), diffuse esophageal spasm (typical radiological and manometric appearance), ulcerative peptic disease, functional heartburn, angina pectoris (differentiated by pain characteristics, electrocardiographic changes and those evidenced by coronary angiography).

A. With digestive diseases:

- *esophagitis of other etiologies* - the diagnosis is established clinically and endoscopically. For example, in post-caustic esophagitis, the onset is sudden after the ingestion of a corrosive substance, the endoscopic aspect being erosion, extensive ulceration (endoscopy can be done only within a maximum of 24 hours after ingestion, otherwise there is a risk of perforation)

- *esophageal diverticulum* – dysphagia is the dominant symptom, the diagnosis is made endoscopically

- *esophageal ulcer* – dysphagia, odynophagia as well as anemia may be present, the diagnosis is made endoscopically

- *esophageal cancer* - dysphagia is the dominant symptom, followed by weight loss, the diagnosis is made endoscopically and or radiologically

- *achalasia* - the dominant clinical symptom is paradoxical dysphagia (initially for fluids), the radiological appearance being typical. As additional diagnostic methods esophageal manometry, upper digestive endoscopy

- *diffuse esophageal spasm* - dysphagia, odynophagia are the dominant clinical symptoms, diagnosed by esophageal manometry and radiological examination

- *functional heartburn, hypersensitivity to acid* – clinical picture similar to GERD, but not improved by PPI, the positive diagnosis is made by esophageal pH-metry

- *gastric or duodenal ulcer disease* - has epigastric pain as a typical symptom; the presence of heartburn indicating the concomitant acid reflux; The positive diagnosis is made endoscopically

B. With extra-digestive diseases:

- *retrosternal or chest pain* will be differentiated from heart pain (EKG or stress test is necessary; in case of doubt, coronary angiography is useful);

- *the asthma crisis* can sometimes be triggered by acid reflux, so the correlation of asthmatic attacks with pH-metry can be useful for therapy;

Evolution. Complications. Prognosis

The course of GERD is generally good, but symptoms often recur and most patients require maintenance treatment for a period of time.

The complications that occur in reflux disease are:

- *Reflux (peptic) esophagitis*, in varying degrees, going up to esophageal ulcers

- *Esophageal stenosis* - the dominant symptom is progressive dysphagia, and the diagnosis is established radiologically and endoscopically. It usually occurs in patients with a long-term history of GERD.

- *Barrett's epithelium* is a cylindrical epithelial metaplasia of the normal malpigeon mucosa, as a consequence of the cure of reflux disease after exposure to acid and is a premalignant condition for esophageal cancer. Endoscopically, the metaplastic Barrett mucosa appears red, unlike the pink-esophageal mucosa.

- *Esophageal adenocarcinoma*

- *Upper digestive hemorrhage* – usually occurs as a complication of severe ER, it can be externalized by hematemesis and/or melena, sometimes only iron deficiency anemia is present

The prognosis remains generally good, with the mortality of GERD directly reported being very low.

Treatment of reflux disease

1. Hygienic-dietary treatment

Most cases respond well to lifestyle changes. But these changes are sometimes difficult to maintain in the long term, hence the failure of the hygienic-dietary treatment

- *Diet.* Small and repeated lunches are recommended, excluding foods that trigger symptoms: alcohol, fats, coffee, chocolate, citrus fruits, mint, carbonated drinks, tomato juice, spices; weight loss in case of overweight

- *Prohibition of smoking* (nicotine causes a decrease in IES tone).

- *Postural recommendations* - during sleep or rest, the patient's head should be raised to 15° or 15-20 cm above the horizontal line. Avoid decubitus at less than 2 hours postprandial.

- *Avoid drugs that lower IES pressure*: nitrites, anticholinergics, euphylline, progesterone, alpha-adrenergic antagonists, beta-adrenergic agonists, calcium channel blockers, etc.

2. Drug treatment.

- *Antacid medication has the* role of neutralizing hydrochloric acid (HCl), inactivating pepsin and having a chelating effect on bile salts. It quickly relieves the symptoms of GERD and is used in mild forms of the disease. The effect of antacids is short-lived (about 30 min) and disappears from the moment they are expelled from the stomach; therefore, it is administered 4-6 times a day, at 1-2 hours postprandial. Medication with a direct neutralizing effect includes preparations containing magnesium and aluminum salts (Maalox, Novalox, Rennie, Dicarbocalm). It should be remembered that those based on aluminum can cause constipation, and those containing magnesium can cause diarrhea.

- *Alginate-based preparations* (Gaviscon) are increasingly used, without a prescription required (OTC). The alginate forms a gel or "foam cork" in the acid pocket, thus preventing reflux. The administration is done 3 times a day.

- *Antisecretory medication* – with the role of decreasing acid secretion at the gastric level.

- *Proton pump inhibitors (blockers).* They are the most potent class of antisecretors. This class includes omeprazole - the first representative of the class, the recommended dose in the ER being 20-40 mg/day), pantoprazole (20-40 mg/day), lanzoprazole (30 mg/day), rabeprazole (10-20 mg/day), esomeprazole (20-40 mg/day). In case of reflux esophagitis, the duration of treatment is 4 – 8 weeks (depending on the endoscopic severity of the esophagitis. In GERD without esophagitis (or without upper digestive endoscopy), in case of intermittent acid reflux, PPIs can be administered as needed, including as a therapeutic sample.

- *H2 histamine receptor blockers.* Their antisecretory effect is achieved by competitive blockade of H2 receptors which leads to a decrease in the concentration of intracellular cyclic AMP and a reduction in gastric acid secretion. Examples: cimetidine,

ranitidine, famotidine, nizatidine and roxatidine. The cure rate after administration of histamine H2 receptor blockers correlates with the severity of esophagitis, ranging from 70-80% for grades A and B and only 50% for grades C and D. Failure in severe forms of GERD is related to the inability of these preparations to maintain for a long time a pH above 4 of the gastric contents refluxed into the esophagus.

- *Prokinetics* – have the role of favoring gastric evacuation and increasing IES tone.

• The classic Metoclopramide, taken 1 cp (10 mg) 30 minutes before a meal. The effect is to increase the tone of IES; It also increases esophageal clearance and gastric emptying rate. But beware of extrapyramidal side effects

• Domperidon (Motilium) has an effect on IES and gastric kinetics. It does not give extrapyramidal phenomena. This prokinetic is preferred to Metoclopramide, having reduced adverse effects. Also take 10 mg 30 minutes before meals.

Drug therapeutic strategy:

1. In patients with rare symptoms (1-2 times/week) it is recommended to modify lifestyle and administer antacids and/or prokinetics.

2. Patients with moderate reflux symptoms, without endoscopic examination or with grade A or B esophagitis, benefit (in addition to lifestyle modification, antacids and/or prokinetics) either H2 histamine blockers or standard dose PPIs.

3. In patients with severe reflux symptoms and grade C or D esophagitis, treatment with standard dose PPIs is recommended from the beginning, and if the response is unfavorable, the dose is doubled for a period of 8 weeks.

The "step-down" strategy is preferred, in which standard-dose PPIs are used from the beginning, for 6-8 weeks, in order to quickly obtain control of clinical symptoms and cure of esophagitis, with subsequent dose reduction, intermittent treatment, if necessary, or switching to other drugs (histamine H2 blockers) if the therapeutic response is favorable.

3. Endoscopic treatment is reserved for complications of GERD, most often being:

- Esophageal stenosis treated endoscopically by dilation with Savary probes or pressure balloons

- Upper digestive hemorrhage. He benefits from endoscopic hemostasis by adrenaline injection, photocoagulation with Argon Beamer or application of hemoclips.

- Barrett's esophagus. Intestinal metaplasia beaches with varying degrees of dysplasia can be destroyed by radiofrequency ablation (RFA), dynamic phototherapy or endoscopic mucosectomy.

- Endoscopic fundoplication. It is a new, less invasive method by modifying the Hiss angle, making it sharper, by endoscopic plication of the gastric face of the IES.

4. Surgical treatment.

The objective of surgical treatment is to reconstruct the reflux barrier. It is performed by Nissen fundo-plication (making a gastric sleeve around the distal esophagus), which, at present, can also be performed laparoscopically.

BARRET ESOPHAGUS

Etiopathogenesis

Barrett's esophagus is considered a premalignant lesion with a risk of developing esophageal adenocarcinoma. In GERD, prolonged exposure to gastric reflux causes erosions of the esophageal mucosa that stimulates the formation of inflammatory cellular infiltrates and, finally, the evolution towards epithelial necrosis. This chronic damage causes the replacement of the normal esophageal epithelium with metaplastic columnar cells, more resistant to acid aggression.

Pathology

From a histopathological point of view, three types of epithelium that can appear in Barrett's esophagus are described: specialized intestinal type, junctional type and fundic gastric type, the maximum risk of malignancy being for the first type.

In patients with symptoms of gastroesophageal reflux, the prevalence of EB varies between 4.5-19%. The risk of developing cancer is quite low, about 0.3% per year.

Clinical picture

There are no symptoms specific to Barrett's esophagus. About 1/3 of the patients are asymptomatic, and in the rest of the cases the symptomatology is similar to GERD (heartburn, acid regurgitation) and its complications. There are no specific changes to the objective examination.

The diagnosis is made by upper digestive endoscopy (the endoscopic aspect being suggestive but not sufficient for diagnosis) and mandatory biopsy sampling. The diagnosis of Barrett's esophagus is established if columnar epithelium is identified in the distal esophagus and if specialized intestinal metaplasia with goblet cells is identified on histopathological examination. After locating the eso-gastric junction, the Barrett esophagus is recognized by the contrast between the gray-pinkish esophageal mucosa and the intensely red columnar mucosa (Fig.1.3), the latter exceeding in height the eso-gastric junction by a length of 1-3 cm (Barrett's esophagus – short segment) or over 3 cm (Barrett's esophagus long segment). The biopsy protocol includes taking one biopsy from each quadrant (4 biopsies), every 2 cm of Barrett's esophagus, and in the case of patients with previously detected dysplasia, 4 biopsies can be collected every 1 cm of Barrett's esophagus. In addition, it is recommended to biopsy any macroscopically suspicious area. For a better recognition of dysplasia areas, the NBI - Narrow Band Imaging endoscopic module can be used, which uses a special lumen filter, to allow a superior image of the digestive mucosa, with special emphasis on the vascular aspect.

Since 2004, a new classification of the Barrett epithelium has been applied - the Prague classification. In this classification there are two parameters: the circumferential

Barrett (the distance from the IES to where the endoscopic changes are circumferential) and the maximum Barrett (the maximum extent of the endoscopic changes), both expressed in centimeters.

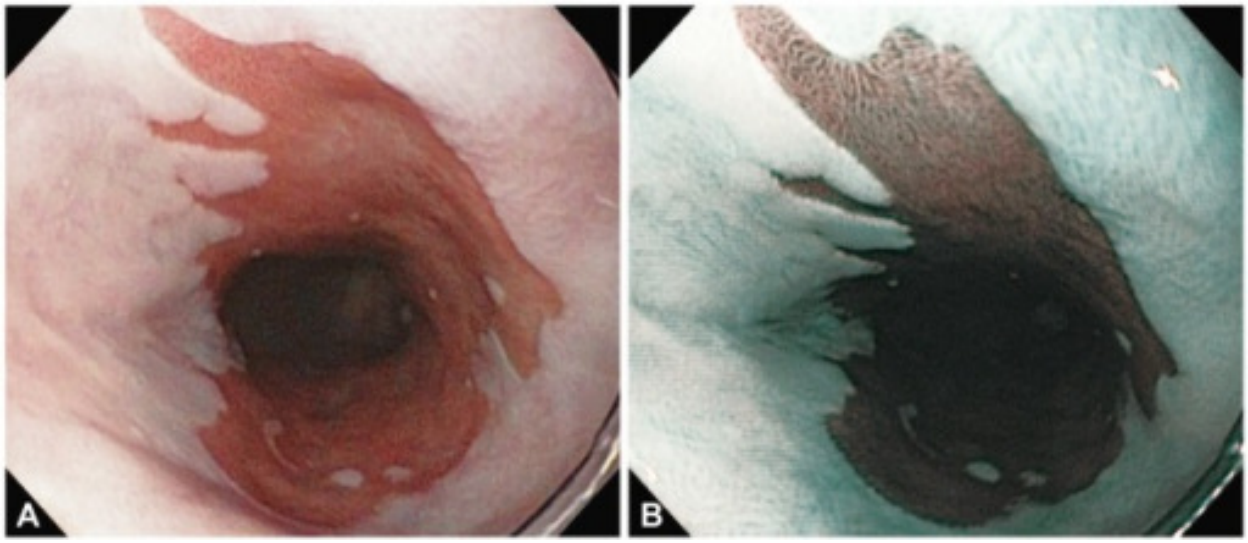


Figure 1.3. (A) Endoscopic image of Barrett's esophagus. (B) The corresponding image of Barrett's esophagus with NBI (narrow band imaging) visualization showing the usual villous architecture. Source: *https://openi.nlm.nih.gov/*. Open Access

The therapeutic and supervisory conduct for the prevention and/or early detection of malignancy of Barrett's esophagus is made according to the histological aspect:

- In patients with intestinal metaplasia, without dysplasia – medical treatment (administration of PPIs to relieve symptoms) with endoscopic surveillance and biopsy at 2 years;

- In patients with dysplasia of any degree – endoscopic treatment (endoscopic mucosectomy or radioablation destruction) or surgical treatment and annual surveillance with biopsies are performed.

To note

- Gastroesophageal reflux disease (GERD) is a condition due to the reflux of gastric contents into the esophagus and includes all the clinical manifestations caused by it, with or without the appearance of endoscopic esophageal lesions.

- It is a common condition, heartburn is the characteristic symptom sometimes accompanied by regurgitation, the triggering factor being frequently food or medication.

- The most common endoscopic lesions are those of reflux esophagitis of different degrees.

- Treatment includes hygienic-dietary measures (avoiding foods that cause reflux, avoiding bedtime, etc.)

- Drug treatment includes alginate-based, antisecretory and prokinetic preparations.

- Barrett's esophagus is a complication of reflux disease, being considered a premalignant lesion, with the risk of turning into adenocarcinoma. Its presence is suspected endoscopically and confirmed bioptically (specialized intestinal metaplasia with goblet cells in the esophageal mucosa).

- The therapeutic and supervisory conduct in order to prevent and/or early detection of malignancy of Barrett's esophagus is done according to the histological aspect.

2. ESOPHAGEAL MOTOR DISORDERS

ACHALASIA

Definition

It is a condition in which insufficient or absent relaxation of the lower esophageal sphincter (SEI) during swallowing, as well as the lack of normal esophageal peristalsis, creates a functional obstacle in the way of food to the stomach, which leads to progressive dilation of the esophagus and the appearance of symptoms.

Epidemiology

The incidence of achalasia is about 1:100,000 individuals, affecting women and men alike, with an increase in incidence with age, being a rarer condition in children.

Etiopathogenesis

The etiopathogenesis is insufficiently known, being incriminated genetic factors (predisposition) and environmental factors (neurotropic viruses). The role of emotion and stress in triggering symptoms is recognized. Autopsy studies have shown impairment of the Auerbach myenteric plexus, responsible for nerve control of esophageal motility, as well as esophageal muscles.

The hypothesis of the involvement of a virus that secretes a neurotoxin that affects the vagus is supported by the existence of secondary achalasia in Chagas disease (infestation with Trypanosoma Cruzi), in which the parasite produces neurotoxic lesions that cause the appearance of the megaesophagus.

A more frequent association with autoimmune diseases (psoriasis, Sjogren's syndrome) and allergic diseases has also been observed in patients with achalasia.

It appears that there are also genetic risk factors for primary achalasia, such as the insertion of 8 bases at the cytoplasmic end of HLA-DQβ1 or genetic variations in the lymphoxin α/tumor necrosis factor α (TNFα) area, regions that mediate immune response and neuronal function.

Clinical picture

The clinical picture is dominated by dysphagia (87%), atypical chest pain (80%), regurgitation (83%), heartburn (59%) and weight loss (58%). Initially, the symptoms are intermittent, later becoming more and more frequent. Dysphagia is often paradoxical, with difficulty swallowing liquid foods, but with good tolerance of solid foods. In the early stages, patients complain of regurgitation, heartburn and retrosternal chest pain, being often labeled as having gastroesophageal reflux and, consequently, are treated with gastric antisecretors, and the diagnosis is delayed.

Hiccups may occur late, due to irritation of the phrenic nerves by significant dilation of the esophagus. Food and saliva regurgitation is quite common, appearing several hours after eating, but over time, by dilating the esophagus, it decreases. Nocturnal regurgitation can trigger coughing and dyspnea. In the advanced stages, the patient takes a typical position (Valsalva position), through which he increases his intrathoracic pressure and facilitates the passage of the food bolus into the stomach. A late complication is aspirase pneumonia.

Diagnosis

The positive diagnosis is clinically suspected by progressive paradoxical dysphagia and will be confirmed by endoscopy, radiology and manometry.

Endoscopy will show a much dilated esophagus, with food debris and abundant saliva, generally without endoscopic lesions, or inflammatory decubitus lesions of the mucosa (due to stagnation of food in the esophagus), which can be classified as "retention" esophagitis. In the early stages, endoscopic changes are minimal – the cardia is punctiform and can be overcome relatively easily with the endoscope by applying slight pressure (unlike organic stenosis). The most important role of endoscopy is to exclude esophageal cancer, whose clinical picture includes diphagia.

The esophageal barium examination is useful and valuable, revealing a much dilated esophagus, which in the lower portion narrows symmetrically, with the appearance of a "bird's beak" or "radish" of the distal esophagus, determined by the axial, symmetrical, regular and short stenosis of the SEI that does not relax during swallowing (Fig. 2.1). The follow-up of swallowing reveals the absence of esophageal peristaltic waves, as well as the lack of relaxation of the lower esophageal sphincter, which opens only under the weight of the barium column.

Esophageal manometry will confirm the diagnosis of achalasia and is especially useful for less advanced or atypical cases. The absence of peristaltic waves in the lower esophagus, the absence of relaxation of the EIS at swallowing and hypertonia of the EIS at rest will be observed.

Conventional manometry describes two forms of cardia achalasia, the common feature of which was incomplete relaxation of the EES: classical achalasia (in which the amplitude of the esophageal waves is < 40 mmHg) and vigorous achalasia (in which the amplitude of the esophageal waves exceeds 40 mmHg).

High-resolution esophageal manometry with pressure topography (MEIR-TP) revealed three subtypes of achalasia, the diagnosis being suggested primarily by the absence of relaxation of the EIS during swallowing.

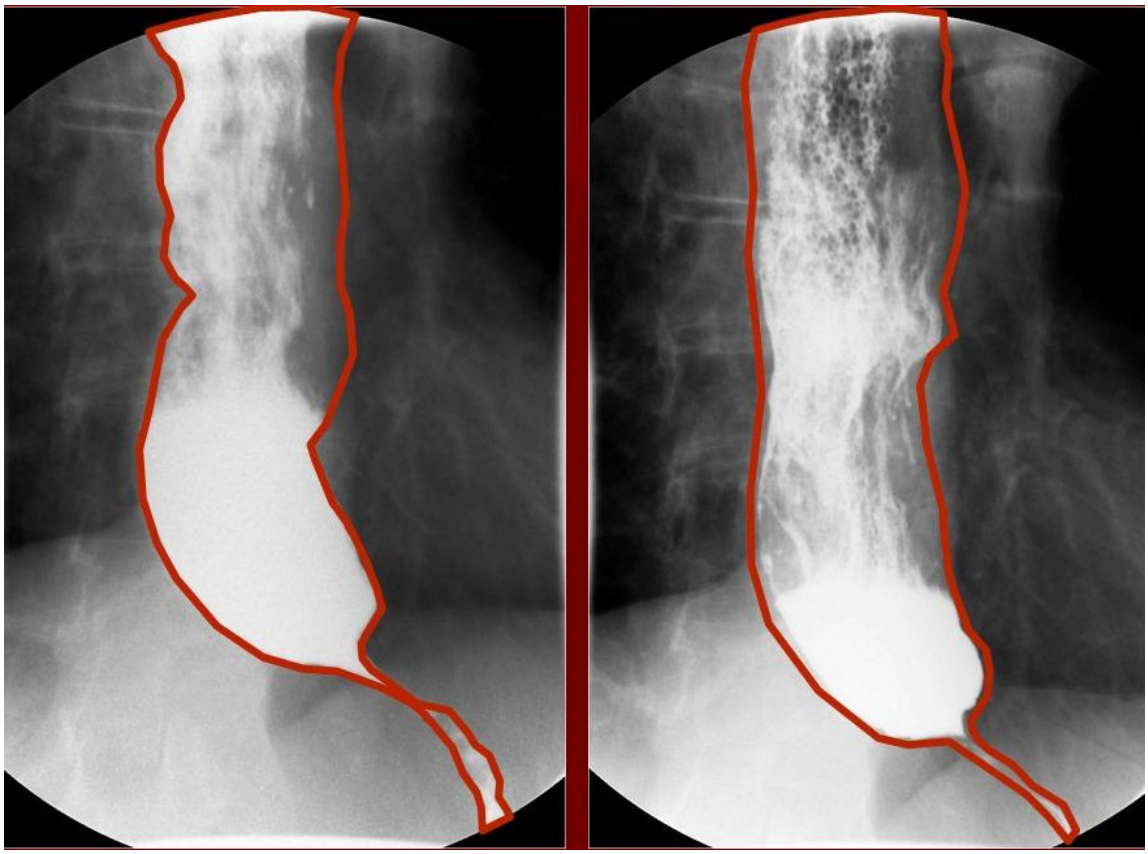


Figure 2.3. Tortuous and marked dilated esophagus, which narrows at the esogastric junction, with the appearance of a "beak". An abnormal accumulation of contrast is observed in the distal esophagus and food debris and residual secretions.
Source: MedPix. (n.d.). *https://medpix.nlm.nih.gov/*. Open Access

Differential diagnosis

It is done with other causes of dysphagia: esophageal neoplasm, postcaustic organic esophageal stenosis, diffuse esophageal spasm and its variant hyperperistaltic esophagus (in "nut-cracker esophagus"). Upper digestive endoscopy with biopsy diagnoses esophageal neoplasm and organic stenosis, respectively, and esophageal manometry differentiates from diffuse esophageal spasm and hyperperistaltic esophagus.

Complications. Prognosis

Acalazia can cause dysphagia with repercussions on the state of nutrition leading to weight loss with malnutrition, vitamin and mineral deficiencies, iron deficiency anemia. Due to the stasis of food in the esophagus there is a risk of aspiration pneumonia. Acalasia is a risk factor for esophageal squamous cell carcinoma.

The prognosis is good. Patients can tolerate the symptoms caused by achalasia for a long time. The application of endoscopic or surgical treatment greatly improves the quality of life.

Treatment

There are three therapeutic alternatives:

1. Drug treatment – preparations that decrease the tone of the SEI are administered, such as: nitrates and nitrites, calcium blockers (nifedipine, diltiazem and verapamil). One or two such preparations are administered, which in the initial phases can lead to an improvement in symptoms. The effects, however, are weak and short-lived. Drug therapy is no longer indicated only in patients who refuse or have contraindications to endoscopic or surgical therapy.

2. Endoscopic Treatment

- *Injection of botulinum toxin* at the level of the SEI. This causes a temporary paralysis of the sphincter muscle. The clinical response occurs in 80% of patients. Since the effect lasts only a few months, repetitive sessions are required. It is preferable that this method, as well as the pharmaceutical one, be tempted before a method with lasting effects. It can be used as an intermediate method before surgery in patients who have lost a lot of weight, with the aim of improving nutritional status and reducing post-surgical risks.

- *Endoscopic dilation* with pneumatic balloon, the goal of the method is to stretch and break the cardial muscle fibers to decrease tone in the SEI. About 50% of patients require one or two more dilation sessions in the first 5 years. The efficiency varies between 70% and 90%. Possible complications are mucosal tearing, digestive hemorrhage, esophageal perforation.

- *Peroral endoscopic myotomy* (POEM). This technique is based on the sectioning of the esophageal circular muscle fibers at the level of the lower esophagus, cardial and 2-3 cm subcardial, using special cutting devices (Hook knife, IT knife, triangle knife), the mucosal defect produced being later covered with metal clips. It is a new and effective method of alleviating dysphagia, with a success rate of 90%. Possible complications are damage to the esophageal mucosa resulting in esophageal or gastric perforation, pneumothorax and/or pneumoperitoneum, digestive hemorrhage, gastroesophageal reflux with or without symptoms.

3. Surgical treatment - used when other techniques have not had an effect. Heller cardiomyotomy of the SEI (longitudinal section of the circular fibers of the SEI) is performed. Surgery can then predispose to gastroesophageal reflux.

DIFFUSE ESOPHAGEAL SPASM and HYPERPERISTALTIC ESOPHAGUS ("NUT-CRACKER ESOPHAGUS")

It is clinically manifested by *dysphagia and retrosternal pain*. The diagnosis is made by barium radiological examination, which reveals an esophagus in the "corkscrew", and esophageal manometry highlights intense esophageal contractions during swallowing, with the absence of normal peristalsis. In the hyperperistaltic esophagus, the amplitude of the peistaltic waves is intense, above 200 mmHg, the dominant symptoms being chest pain and odynophagia, and less dysphagia.

Treatment is difficult, with unsatisfactory results and consists of the administration of nitrates, nitrites, antispasmodics, calcium channel blockers, y-aminobutyric receptor (GABA) agonists such as baclofen. Sedative therapy may be helpful. In the absence of response to treatment, balloon esophageal dilation or esophageal longitudinal myotomy may be used.

To note

- Achalasia is a condition characterized by insufficient or absent relaxation of SEI during swallowing, as well as the lack of normal esophageal peristalsis, creating a functional obstacle in the way of food to the stomach.
- The characteristic symptom in achalasia is initially paradoxical dysphagia for liquids, which progresses to dysphagia and for solids, in the advanced stages nutrition being impossible. Vomiting with undigested food is still present several hours postprandial
- The diagnosis of achalasia is made endoscopically and radiologically.
- The treatment is done medically, with nitrates and nitrites, calcium blockers, and in non-responsive cases with endoscopic balloon dilation or botulinum toxin injection at the level of the SEI.
- In diffuse esophageal spasm, the clinical picture is dominated by dysphagia and retrosternal pain.
- The diagnosis is made radiologically and by esophageal manometry.
- Treatment is difficult with nitrates and nitrites, calcium blockers.

3. ESOPHAGEAL NEOPLASM

Definition

Esophageal neoplasm is a malignant tumor that occurs in the esophagus. Histologically, there are two major forms: *squamous cell carcinoma* and *adenocarcinoma*. Esophageal cancer is known for its poor prognosis, usually diagnosed late, being one of the most lethal forms of digestive cancer.

Epidemiology

Esophageal cancer is the 6th most common cancer worldwide. Its incidence varies geographically, with the prevalence of squamous cell carcinoma in Asia, while adenocarcinoma is more common in North America and Western Europe. About 450,000 new cases are diagnosed annually globally, and mortality is almost similar, with 400,000 deaths per year. The average age of onset is 60-70 years, with men being more frequently affected.

Pathophysiology

The pathogenesis of esophageal cancer involves exposure to risk factors such as smoking, alcohol consumption, and prolonged exposure to irritants (e.g., hot drinks, hard alcohol). In the case of adenocarcinoma, gastroesophageal reflux disease (GERD) and Barrett's esophagus are important risk factors, with the presence of GERD symptoms increasing the risk of esophageal adenocarcinoma by about 8 times. In squamous cell carcinoma, chronic inflammatory mechanisms play a significant role, risk factors being smoking, obesity, reduced consumption of fruits and vegetables.

Pathology

Squamous cell carcinoma most often affects the middle and upper third of the esophagus, while adenocarcinoma is located especially in the area of the esogastric junction. Adenocarcinoma accounts for about 70% of newly diagnosed esophageal cancers. Microscopically, squamous cell carcinoma can be keratinizing or non-keratinizing, and adenocarcinoma is frequently associated with esophageal metaplasia in Barrett's esophagus.

Clinical picture

Progressive dysphagia is the most common symptom of esophageal cancer, being present in 90% of cases. Other symptoms include weight loss (which can lead to cachexia), anorexia, odynophagia, and retrosternal pain. Symptoms usually appear in advanced stages of the disease.

Esophageal obstruction can lead to the impossibility of swallowing saliva, with night cough, aspiration pneumonia. In the advanced phases, the clinical picture of neoplastic impregnation is also present, with turous pallor, cachexia, apathy, adynamia.

Biological picture

Patients may experience anemia and changes in nutritional status due to severe dysphagia and malnutrition.

Paraclinic

Upper digestive endoscopy is the main diagnostic method, offering the possibility of taking *biopsies*, which confirm the diagnosis. The endoscopic aspect is of stenosing tumor formation, which can be completely obstructive, making it impossible to pass with the endoscope (Fig 3.1).

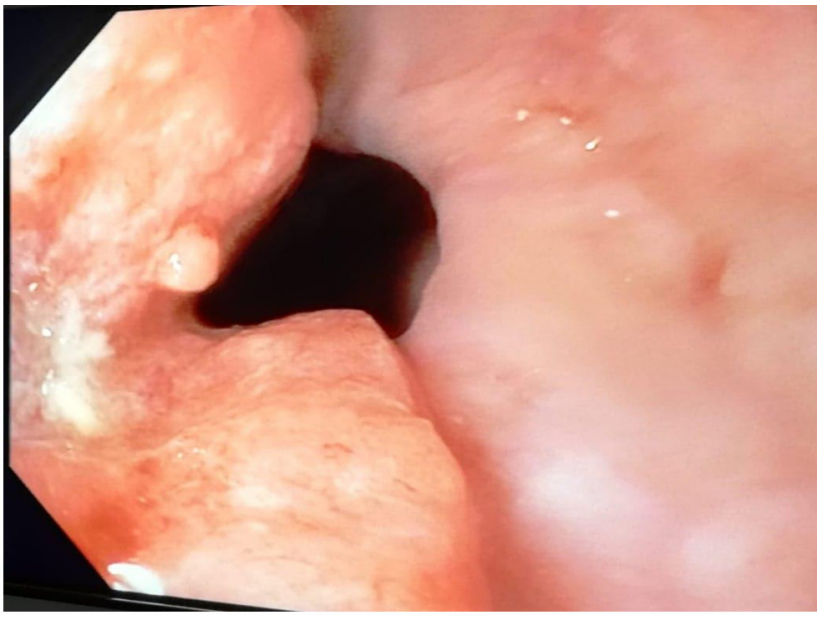


Fig 3.1 Esophageal neoplasm – endoscopic image

Radiological examination with barium or radiopaque oral contrast reveals an area of irregular esophageal stenosis with marginal spikes. It is important to perform in inoperable cancers, to evaluate the length of the stenosis area in order to choose the esophageal prosthesis to be mounted for palliative purposes.

Echoendoscopy (EUS) is extremely important especially in early cancers, for staging and assessment of the transparietal extension of the esophageal tumor, as well as in more advanced cancers for the evaluation of invasion of adjacent structures

CT, MRI, and PET-CT are used for staging and evaluation of tumor extension.

Positive diagnosis

The positive diagnosis is based on the clinical picture (progressive dysphagia being the dominant symptom), endoscopy with biopsy and histopathological examination certifying the diagnosis. One of the sectional imaging methods are mandatory for staging the disease and for establishing the therapeutic strategy. Esophageal tumors are classified according to the TNM system, to assess the degree of invasion and the presence of metastases.

Differential diagnosis

The differential diagnosis includes other esophageal tumors (benign and malignant) such as leiomyoma and lymphoma, but also pathologies that mimic the symptoms of esophageal cancer, such as achalasia, diffuse esophageal spasm. Endoscopy with biopsy are essential for differential diagnosis.

Complications

Common complications include aspiration pneumonia, esotracheal fistulas, and severe malnutrition. Advanced tumors can invade adjacent structures, generating fistulas and hemorrhages, and can metastasize at a distance, with the liver frequently affected.

Evolution and prognosis

Esophageal cancer has a *reserved prognosis*, which also depends on the time of diagnosis, with an average survival time of one year.

Treatment

1. Radiotherapy and chemotherapy are used for palliative purposes or as part of multimodal treatment.

The most commonly used standard chemotherapy is with Cisplatin and Fluorouracil. Recently entered into the therapeutic regimens for locally advanced or metastatic neoplasms with positive biomarkers (PD-1 and HER2) is the check-point inhibitors and monocline antibody medication. The most commonly used in these groups are Nivolumab and Pembrolizumab.

External chest irradiation or brachytherapy is used as radiotherapy, concomitantly with systemic chemotherapy. In principle, the dose should not exceed 50 Gray at the same time as systemic chemotherapy (usually 5 Fluorouracil + Cisplatin). Squamous cell carcinoma responds better to radiation therapy than adenocarcinoma. It has been observed that the survival rate increases if radiochemotherapy is applied compared to adjuvant chemotherapy before surgery in patients with locally advanced esophageal cancer.

2. Endoscopic therapy is recommended in cases of *early cancer*, with a curative role or in advanced stages, with a palliative role. *Endoscopic mucosal resection* (mucosectomy) is reserved for superficial tumors, limited to the mucosa, without invasion into the submucosa. By injecting saline and adrenaline into the submucosa, the mucosa is lifted for a more precise resection, with curative purposes.

In advanced cases, endoscopic therapy has a palliative role to relieve dysphagia and improve quality of life. *Endoscopic prosthesis* is performed in cases with dysphagia secondary to tumor stenosis, by fitting expandable metal esophageal prostheses, which help to resume nutrition and improve quality of life (Fig. 3.2). An alternative when the esophageal tumor is very high, close to the upper esophageal sphincter, under these conditions an expandable stent is not tolerated, is *the endoscopic installation of a gastrostomy* (Fig. 3.3) to introduce food directly into the stomach.

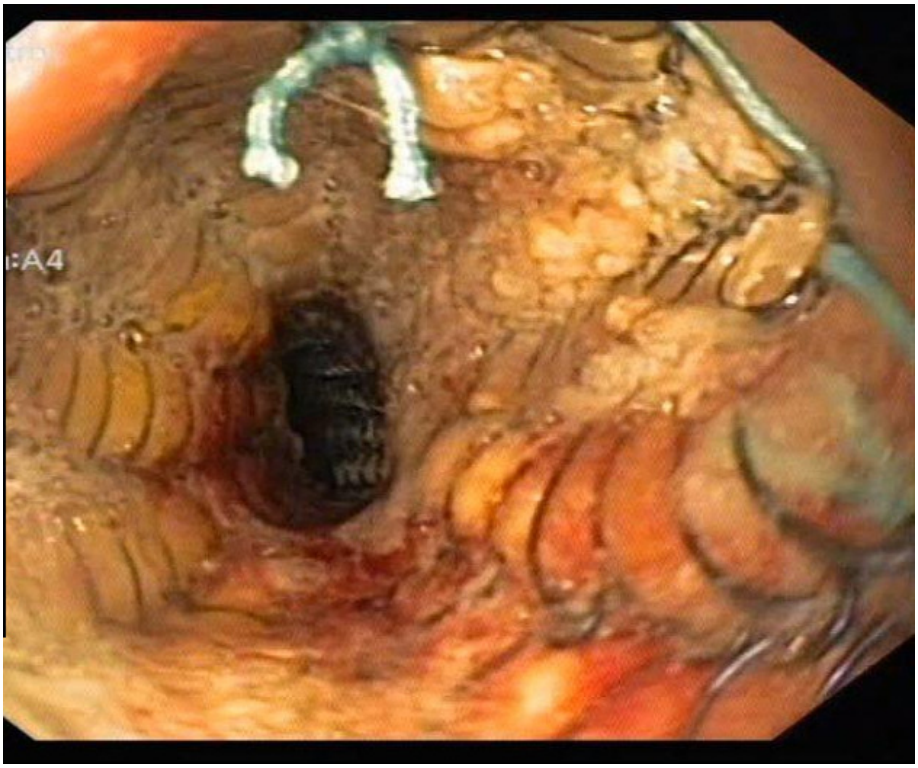


Fig. 3.2. Endoscopic prosthesis

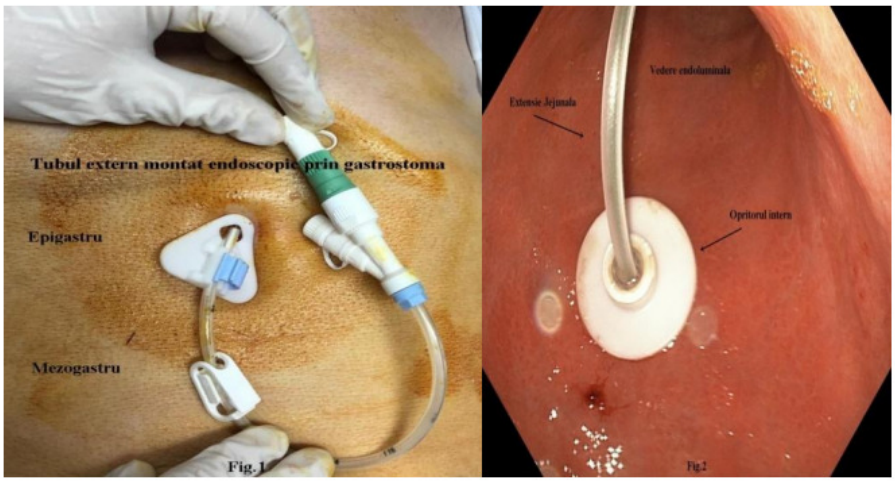


Fig. 3.3 Percutaneous gastrostomy

3. Surgical treatment involves esophagectomy with eso-gastric, eso-jejunal or eso-colic anastomosis. The intervention is a difficult one and must be carried out in experienced centers.

4. Nutritional therapy is essential for maintaining adequate nutritional status, especially in patients with severe dysphagia.

To note

- Esophageal cancer is more common in men, the onset being in the 6th decade of life.
- The suggestive clinical picture is progressive dysphagia for solids, which ultimately leads to significant weight loss.
- The diagnosis is usually made late, by endoscopy with biopsy, when curative treatment is no longer possible, the prognosis being reserved.

4. GASTRITES

Gastritis refers to inflammatory conditions of the gastric mucosa, short-term (acute gastritis) or long-lasting (chronic gastritis).

ACUTE GASTRITIS

Definition

Acute gastritis is a rapid and short-term inflammation of the gastric mucosa, characterized from a morphopathological point of view by the presence of an inflammatory infiltrate consisting predominantly of polymorphonuclear neutrophils. The inflammation can involve the entire stomach (pangastritis) or just a specific region, such as the gastric antrum (antral gastritis).

From the point of view of endoscopic appearance, acute gastritis can be classified into:

- *Erosive gastritis* - characterized by the presence of erosions of the gastric mucosa, friability and bleeding. Erosions are superficial and do not exceed the muscularis mucosae- *Nonerosive gastritis* - in which there are no obvious structural lesions of the mucosa, but histopathological examination reveals inflammatory infiltrate with polymorphonuclears.

Epidemiology

The epidemiology of acute gastritis varies depending on etiological and geographical factors. Although there is little precise data, it is estimated that between 10-20% of patients who use chronic nonsteroidal anti-inflammatory drugs (NSAIDs) develop dyspeptic symptoms and acute gastritis. In the case of *Helicobacterpylori* infection, it is more common in developing countries, being influenced by socio-economic conditions, poor hygiene and virulence of bacterial strains.

Etiology

Acute gastritis has various causes, including:

- *Drug causes.* As shown above, nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, naproxen, diclofenac, phenylbutazone, and, to a lesser extent, selective NSAIDs such as coxibs, can cause acute gastritis. Also, corticosteroid therapy.

- *Infections* of various types. Of *the bacterial infections*, the most common is Helicobacter pylori, less often with Helicobacter heilmannii. Rare are also streptococcal gastritis, staphylococcal gastritis, with species of Proteus, Clostridium, Escherichia coli, tubercular gastritis or secondary syphilis. *Viral infections* – cytomegalovirus. *Fungal infections* - Candida, Histoplasma, fungal gastritis being rare, in immunocompromised

individuals. *Parasitic infections* – anisakidosis, associated with the consumption of insufficiently thermally prepared seafood.

- *Food and non-food* allergies.

- *Food poisoning* - consumption of concentrated alcoholic beverages (whiskey, gin, vodka) with an irritating effect on the mucosa, or ingestion of irritating and toxic substances.

- *Bile reflux* - through the cleansing effect of bile on the protective gastric mucus, thus exposing the mucosa to the irritating effect of gastric acid.

- *Acute stress* - shocks, extensive burns, polytrauma.

- *Other systemic conditions* - congestive heart failure, respiratory failure, intracranial hypertension, renal failure.

Pathogenesis

1. Acute erosive and hemorrhagic gastritis

The pathogenesis of this form of gastritis involves direct aggressions on the gastric mucosa caused by factors such as the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, shock (trauma, major surgery, burns), severe infections or ischemia. These factors reduce the mucosa's natural defenses by decreasing the production of protective mucus and bicarbonate, increasing vulnerability to stomach acid and proteolytic enzymes.

2. Acute non-erosive gastritis

- Acute gastritis caused by Helicobacterpylori *(HP).* This type of gastritis occurs in the context of a recent H. Pylori *infection*. After colonizing the gastric mucosa, *HP* releases enzymes (such as urease) and toxins that induce local inflammation by attracting polymorphonuclear and monocytes to the affected area. The activation of these inflammatory cells causes the release of pro-inflammatory cytokines, such as IL-8, which amplify the immune response and contribute to the damage of the gastric mucosa.

- Phlegmonous gastritis. It is a rare form of acute purulent gastritis, associated with severe bacterial infections (usually *E. coli, Proteus*, staphylococci).

- Acute food-toxic gastritis. It is caused by bacterial toxins such as staphylococcal toxin or botulinum toxin.

- Acute gastritis induced by caustic substances. It occurs following the ingestion of caustic chemicals (acidic or alkaline).

- Acute allergic gastritis. This type of gastritis is induced by food allergies and is characterized by the presence of an eosinophilic infiltrate in the gastric mucosa.

Clinical picture

Patients with acute erosive gastritis may be completely asymptomatic or may experience symptoms such as epigastric pain, nausea, and vomiting. Upper gastrointestinal bleeding can complicate the clinical picture, although in most patients, the bleeding is occult. Depending on the underlying pathology involved in the etiology of gastritis (septic shock, polytrauma, organ failures), the symptoms may vary, the clinical picture being dominated by the specific manifestations of the associated pathology.

Clinical manifestations in acute *Helicobacter pylori* infection may be absent or minimal, consisting of nausea, vomiting, and epigastric pain.

In *allergic gastritis*, we encounter the same spectrum of symptoms, but they are triggered after eating the offending food.

In *phlegmonous gastritis*, the clinical picture presents as an acute abdomen, accompanied by signs of sepsis. The pain is initially localized in the epigastrium, but becomes diffuse as the inflammation spreads to the peritoneum.

The clinical manifestations in *eosinophilic gastritis* are nonspecific and depend on the location of the inflammatory infiltrate. If it is localized in the mucosa, the patient will experience epigastralgia, nausea, vomiting, occult bleeding, iron deficiency anemia, malabsorption. Localization in the muscle layer can lead to manifestations such as subocclusive syndrome or intestinal occlusion. Localization at the level of the serosis leads to the appearance of ascites.

In *acute foodborne gastritis*, symptoms appear 4-8 hours after ingestion of contaminated food and may include fever and diarrheal stools. *Botulinum toxin* causes gastrointestinal symptoms such as epigastralgia, nausea and vomiting, but also neurological signs such as blepharoptosis, diplopia, mydriasis, osteotendinous hyporeflexia, hypotension and tachycardia.

Diagnosis

The diagnosis of acute gastritis involves both clinical elements and paraclinical investigations. Clinically, symptoms such as dull epigastric pain, nausea, vomiting and abdominal discomfort may suggest the presence of gastritis. The diagnosis is confirmed, however, by upper digestive endoscopy, which allows direct visualization of the gastric mucosa. In this form, the mucosa is congested, edematous and friable when touched with the endoscope (Fig. 4.1). In addition, endoscopy allows biopsy of the gastric mucosa, the histopathological examination revealing the morphological substrate of gastric lesions.

The positive diagnosis consists of different diagnostic elements, depending on the type of acute gastritis:

- *Acute gastritis with Helicobacter pylori.* At endoscopy, mucosal congestion is observed, predominantly in the antrum, and histological examination reveals an inflammatory infiltrate with polymorphonuclear neutrophils in the gastric submucosa. H. Pylori can be identified either by histological sections or by common tests (urease test, anti-H.Pylori antibodies, fecal H. Pylori antigen).

- *Phlegmonous gastritis.* The diagnosis of this rare form of gastritis is based on a set of clinical, imaging and laboratory criteria. Clinically, patients experience severe epigastric pain, fever, nausea, vomiting and, in advanced cases, signs of peritonitis. Imaging plays a crucial role: abdominal X-ray can highlight air in the gastric wall, and computed tomography (CT) and abdominal ultrasound can show gastric wall thickening and purulent collections. Bacteriological examination (blood cultures or cultures from gastric aspirate) can identify the pathogen.

- *Acute allergic gastritis*. The diagnosis is based on the fulfillment of the Engelkinger criteria:

- Rapid onset of symptoms after eating small amounts of food.
- Recurrence of symptoms upon a new consumption of the offending food.
- Positive skin tests.
- Proof of the allergic mechanism by the presence of eosinophilia and increased serum levels of immunoglobulin E.

- *Eosinophilic gastritis*. The diagnosis involves both endoscopic changes (erythema, whitish exudate, erosions, ulcers, thickened folds) and histopathological confirmation. Histopathological examination reveals an inflammatory infiltrate with a large number of eosinophils (over 20 eosinophils/field under high-power magnification) in the mucosa.

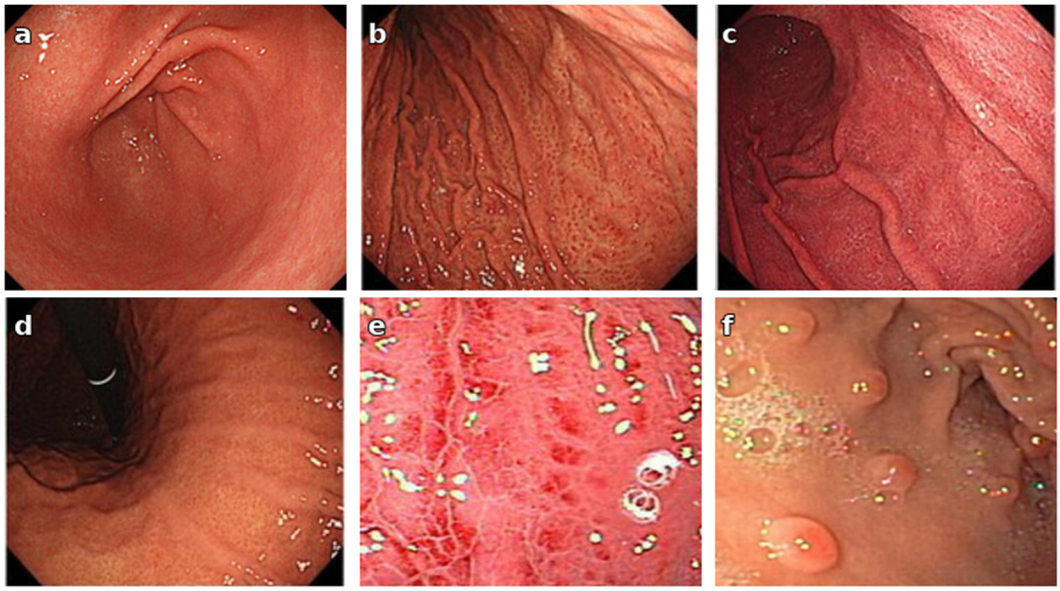


Figure 4.1. Endoscopic aspects of acute gastritis

a. Normal gastric mucosa, with a smooth surface and visible vascularization, without signs of inflammation; **b. c. d.** Punctiform/diffuse redness: the appearance of multiple reddish spots, a sign of extensive inflammation, often associated with *Helicobacter pylori infection*; **is.** Vascular congestion and accentuated inflammation, with hyperemia and edema of the mucosa, indicating a more severe form of acute gastritis; **f.** Suggestive of **eosinophilic gastritis**, characterized by edema and nodular lesions.

Differential diagnosis

The differential diagnosis is made, first of all, between the forms of acute gastritis previously presented. The following gastric disorders must also be taken into account, the differential diagnosis being made endoscopically: hyperplastic gastropathy (Menetrier's disease), granulomatous gastropathy.

Other conditions with which the differential diagnosis is made include: peptic ulcer, acute cholecystitis, gastric neoplasm, gallstones, Crohn's disease, acute pancreatitis, lower myocardial infarction, functional dyspepsia, pregnancy. Abdominal ultrasound, gastroscopy with biopsy, specific biological tests are used for differentiation.

Treatment

General treatment of patients with acute gastritis includes the administration of antisecretory drugs: *PPIs* (pantoprazole 20-40 mg/day, esomeprazole 40-80 mg/day, lansoprazole 30 mg/day, rabeprazole 10-20 mg/day) or *H2 blockers* (ranitidine 150-300 mg/day, famotidine 20-40 mg/day, nizatidine 150-300 mg/day). *Prostaglandin E* (misoprostol) 200 mcg 3-4 times/day taken orally, with the role of stimulating mucus secretion, as well as *Sucralfate* 1 g 4 times/day taken orally, which forms a barrier at the mucosa, preventing its contact with stomach acid, can also be administered.

In the case of digestive bleeding, gastroscopy is essential, allowing endoscopic hemostasis to be performed.

In addition to general and symptomatic treatment, the therapy of acute gastritis depends on the etiological factor responsible for the appearance of the disease:

- *Acute gastritis with Helicobacter pylori* - The H.Pylori eradication cure is administered according to the therapeutic guidelines.

- *Allergic gastritis* - Treatment involves avoiding foods responsible for triggering symptoms.

- *Eosinophilic gastritis* - Treatment involves eliminating foods that have caused skin tests to be positive. Sometimes an elementary diet is necessary. In cases with occlusive manifestations, oral corticosteroid therapy (prednisone 40-60 mg/day) is administered. If the response to corticosteroid therapy is insufficient, surgery may be necessary.

- *Phlegmonous gastritis* - This must be treated in an intensive care unit, with the administration of broad-spectrum antibiotics, with the correction of hydro-electrolyte and acid-base imbalances and with the maintenance of vital functions. In case of unfavorable evolution, despite the appropriate conservative treatment, surgery is indicated.

Complications

The main complications of acute gastritis include:

- *Upper digestive bleeding* is caused by erosions or ulcers. The most common manifestation is iron deficiency anemia (iron deficiency anemia due to chronic occult blood loss), less often with the appearance of melena.

- *Gastric evacuation disorder* caused by edema in the antral or pyloric area, which is most commonly manifested by the sensation of nausea with the appearance of vomiting.

- Acute dehydration secondary to persistent vomiting.

- *Acute renal failure,* secondary to dehydration.

Prognosis

The prognosis of acute gastritis varies depending on the etiological agent involved. In general, they tend to heal spontaneously or with minimal treatment. However, phlegmonic gastritis has the worst prognosis, with a mortality rate of over 50%.

Prophylaxis

Certain categories of patients are at increased risk of developing acute gastritis, such as those admitted to intensive care units, patients with polytrauma, extensive burns, undergoing major surgery, in shock or with organ failure. In these cases, prophylaxis is essential. This consists of administering antisecretory drugs such as H2 blockers.

Other general prevention measures include cessation of smoking and alcohol, avoiding spicy foods and fizzy drinks, monitoring the effectiveness of the therapeutic regimen to eradicate Helicobacter pylori infection, avoiding the consumption of NSAIDs, especially without medical recommendation. If NSAIDs are necessary, H.Pylori testing and eradication is recommended, possibly NSAIDs in combination with an antisecretor.

CHRONIC GASTRITIS

Definition

Chronic gastritis is a long-lasting inflammation of the gastric mucosa, which can be diffuse or localized. The diagnosis is confirmed by clinical, endoscopic and histopathological evaluation. Over time, chronic gastritis increases the risk of developing severe conditions, such as gastric ulcers, gastric adenomas or even gastric neoplasm, especially in chronic gastritis subtypes with malignant potential, considered premalignant conditions.

Epidemiology

Population epidemiological studies have shown that chronic gastritis is more common than acute gastritis, its prevalence being closely correlated with *Helicobacter pylori infection. According to epidemiological data on H. pylori infection,* chronic gastritis is more common in geographic regions with a low socioeconomic status.

Etiology

Chronic gastritis is classified according to the etiological factor, endoscopic appearance or histological classification into two main categories: non-infectious gastritis and chronic infectious gastritis (Table 4.I).

Table 4.I. Classification of chronic gastritis

Chronic non-infectious gastritis	Chronic infectious gastritis
Autoimmune gastritis	Gastritis caused by PH infection - the most common form
Biliary reflux gastritis	
Gastritis caused by NSAID consumption	Granulomatous gastritis secondary to infection with Mycobacterium, syflis, etc
Granulomatous gastritis (in Crohn's disease, sarcoidosis, Wegener's granulomatosis)	Gastritis caused by viral infections: cytomegalovirus, herpes virus
Lymphocytic gastritis	
Eosinophilic gastritis	Gastritis caused by parasitic infections: Strongyloides, Schistosoma, Diphyllobothriumlatum
Ischemic gastritis	
Post-radiotherapy gastritis	

Pathophysiology

The pattern of onset of chronic gastritis is a progressive and sequential one, being a long-term process.

1. Chronic gastritis associated with Helicobacter pylori infection

HP infection causes the appearance of acute gastritis, which, in the absence of appropriate therapy, progresses slowly (in years or decades) to chronic atrophic gastritis. It is characterized by the progressive loss of glandular structures at the level of the antrum, the gastric body or even at the level of the entire gastric mucosa.

Extensive inflammation inhibits parietal cells, secondarily reducing acid secretion, ultimately leading to gastric atrophy. Antral inflammation affects the function of gastrin-secreting G cells and somatostatin-secreting D cells, generating an imbalance between gastrin and somatostatin.

Depending on the location, chronic gastritis associated with H.Pylori infection is classified into:

- *Antral atrophic gastritis,* in which the inflammatory process and atrophy are limited to the antral level, often having a favorable evolution.

- *Multifocal atrophic gastritis,* which, progresses over time through the metaplasia–dysplasia sequence. Patients may develop gastric ulcers, MALT lymphoma, or gastric carcinoma.

2. Chronic gastritis due to chemical aggression

It occurs most commonly due to the consumption of NSAIDs, aspirin or enteral reflux. NSAIDs inhibit the enzyme cyclooxygenase (COX), which is responsible for the synthesis of prostaglandins. Inhibition of COX-1 and COX-2 reduces the production of prostaglandins, causing mucus and bicarbonate secretion to decrease, increase mucosal permeability, and reduce gastric blood flow. These factors make the gastric mucosa vulnerable, favoring chronic inflammation, which can progress over time to gastric atrophy.

3. Chronic gastritis caused by bile reflux

It occurs as a result of prolonged exposure of the gastric mucosa to duodenal contents (bile, pancreatic enzymes and bile salts). Normally, the pyloric sphincter prevents the reflux of these substances into the stomach. However, under certain conditions (surgery, pyloric dysfunction), bile salts and pancreatic enzymes irritate and destroy the gastric mucosal barrier, generating chronic inflammation.

4. Autoimmune gastritis

This type of gastritis is characterized by the presence of anti-parietal and anti-intrinsic factor antibodies. The progression of gastric atrophy leads over time to intrinsic factor deficiency with secondary pernicious anemia as well as decreased acid secretion, which causes G-cell hyperplasia and hypergastrinemia. Patients with autoimmune gastritis may develop carcinoid gastric tumors, due to the stimulating effect of gastrin on enterochromaffin-like (ECL) cells.

Clinical picture

The clinical signs and symptoms of chronic gastritis are in close correlation with the etiological factor involved.

- *HP-positive chronic gastritis* may be completely asymptomatic or may be diagnosed based on non-specific symptoms, such as dyspepsia, epigastric pain, postprandial fullness, nausea, and vomiting, leading to gastroscopy and testing for H. Pylori infection.

- *Autoimmune gastritis* in which the symptomatology is mainly determined by vitamin B12 deficiency, with megaloblastic anemia and may include paresthesias, ataxia, memory disorders and adynamia. The occurrence of complications (gastric ulcer, MALT lymphoma, gastric adenocarcinoma) is suggested by warning signs such as weight loss, anemia and upper digestive hemorrhage.

Paraclinical Investigations

Biological tests.

Laboratory changes are related to the etiology of gastritis. In *atrophic gastritis*, the serum PGI/PGII ratio is low, megaloblastic anemia is present. In *autoimmune gastritis*, suggestive analyses include positive anti-parietal cell antibodies, anti-intrinsic factor antibodies, achlorhydria (basal and stimulated), hypergastrinemia, decrease in serum vitamin B12 levels below 100 pg/ml, megaloblastic anemia.

Upper Digestive Endoscopy (UDE)

UDE is the essential diagnostic method for chronic gastritis, allowing direct visualization and localization of gastric mucosal changes, evaluation of gastric atrophy, areas of metaplasia, dysplasia and protrusive lesions (Fig. 4.2), taking of biopsies for histopathological examination. New endoscopic examination techniques, such as autofluorescence, magnification endoscopy and narrowband endoscopy (NBI), allow for a more accurate assessment of atrophy and mucosal and vascular changes.

The European Society of Endoscopy recommends taking 5 biopsies from the gastric mucosa: 2 from the gastric anthrum, 2 from the gastric body, 1 from the gastric angle.

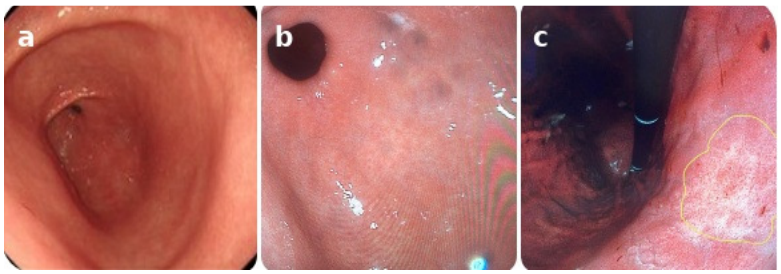


Figure 4.2. Endoscopic aspects of chronic gastritis a. Gastric mucosa with the deletion of the vascular drawing; b. Diffuse areas of discoloration, with the appearance of mucosal pallor and hyperpigmented spots, characteristic of atrophic changes and chronic inflammation; c. Area delimited by mucosal atrophy (outlined in yellow), where the loss of the normal architecture of the gastric mucosa is observed

Histopathological examination

The results of the histopathological examination depend on the etiology of gastritis. Thus, in *chronic HP-positive gastritis*, H.Pylori infection, chronic inflammatory lesions, in advanced stages atrophy of the gastric glands and intestinal metaplasia (replacement of gastric epithelium with intestinal-type epithelium) are highlighted. In *autoimmune gastritis,* the sequence of inflammation-atrophy-metaplasia can be highlighted. In the early stages, the predominant accumulation of mononuclear and eosinophilic cells is observed. In advanced stages, lymphocytic inflammation becomes dominant.

The OLGA (Operative Link on Gastritis Assessment) and OLGIM (Operative Link on Gastric Intestinal Metaplasia) criteria are used to establish the severity of gastric atrophy and intestinal metaplasia, being essential for identifying patients at high risk of developing gastric neoplasm.

Positive diagnosis

It starts from the clinical picture and is based on the mentioned biological, endoscopic and histopathological data.

Differential diagnosis

The differential diagnosis of chronic gastritis includes *other pathologies that are manifested by dyspeptic syndrome*, such as gastric or duodenal ulcers, functional dyspepsia, gastroesophageal reflux, as well as with *conditions that can evolve with megaloblastic anemia*, such as vitamin B12 deficiency, malabsorption syndrome. Infectious conditions such as bacterial infections (tuberculosis, syphilis), parasitic infections (giardiasis), viral infections (cytomegalovirus) should also be considered.

Evolution, prognosis, complications

The evolution is usually long-lasting and the prognosis is generally good, but affected by possible complications. Gastritis HP is a risk factor for the development of ulcerative disease, which can in turn be complicated by upper digestive hemorrhage, perforation. HP gastritis can also progress to atrophy, metaplasia, dysplasia, with the risk of MALT lymphoma and gastric adenocarcinoma.

Treatment

Treatment of chronic gastritis includes both symptomatic therapy and etiological treatment.

1. Symptomatic therapy includes antisecretory drugs of the PPI class - pantoprazole (20-40 mg/day), esomeprazole (40-80 mg/day), lansoprazole (30 mg/day), rabeprazole (10-20 mg/day); or H2 blockers - ranitidine (150-300 mg/day), famotidine (20-40 mg/day), nizatidine (150-300 mg/day). Prokinetics and antiemetics can be administered to combat nausea and vomiting.

2. Etiological therapy is the most important

- *Chronic gastritis with Helicobacter pylori - the goal of treatment is to eradicate the infection, confirmed by* respiratory test or by determination of fecal Ag HP one month after the completion of therapy. One of the treatment regimens recommended by the Maastricht guidelines is used.

- *Chronic autoimmune atrophic gastritis.* Long-term intake of vitamin B12 and folic acid are essential. Due to the increased risk of carcinoid tumors, early initiation of screening for gastric neoplasm is recommended. It is also recommended to search for and eradicate HP infection.

- *Reflux gastritis.* Treatment involves the administration of prokinetics (metoclopramid, domperidone) to prevent reflux. It is also important to neutralize bile secretion (cholestyramine, aluminum hydroxide, ursodeoxycholic acid) and use agents that restore the functionality of the mucosa (sucralfat, vitamin A, prostaglandins).

- *Chronic atrophic gastritis induced by environmental factors*. This condition is caused by dietary factors, environmental factors and HP infection. Specific treatment is limited to monitoring the disease and adopting a low-sodium and basic diet,excluding foods rich in nitrites, in addition to eradicating HP, if present.

- *Lymphocytic gastritis***.** Although the pathogenesis of this condition is unclear, it is frequently associated with PH infection. Treatment involves eradicating the infection if it is confirmed. Further studies are needed to better understand the mechanisms and therapeutic options.

- *Eosinophilic gastritis.*Treatment includes taking Prednisone and avoiding foods that trigger symptoms, if they have been identified.

- *Menetrier's hyperplastic gastritis.* This rare form, also known as giant hyperplastic gastropathy, is characterized by severe hypertrophy of the gastric folds, hypoproteinemia, and hypochlorhydria. First-line treatment includes cetuximab, a monoclonal antibody that acts against the epidermal growth factor receptor. Other options are anticholinergic medication, proton pump inhibitors, prostaglandins, H2 blockers, prednisone. In severe, refractory cases, total gastrectomy is necessary due to the high risk of malignant transformation.

- *Granulomatous gastritis.* This rare form is characterized by the presence of granulomas in the gastric mucosa and is associated with diseases such as Crohn's disease, sarcoidosis, tuberculosis, fungal or parasitic infections. Treatment depends on the underlying cause, which must be identified.

To note

- Acute gastritis is a rapid and short-term inflammation of the gastric mucosa, characterized from a morphopathological point of view by the presence of an inflammatory infiltrate consisting predominantly of neutrophil polymorphonuclears.

- Acute gastritis can be erosive (characterized by the presence of superficial erosions of the gastric mucosa, friability and bleeding) or non-erosive (without endoscopic lesions, but on histopathological examination inflammatory infiltrate with polymorphonuclear glands is highlighted)

- The main causes of acute gastritis are non-steroidal anti-inflammatory drugs, infections (bacterial, viral, fungal, parasitic), allergic, toxic, caustic.

- The clinical picture ranges from completely asymptomatic to symptoms such as epigastric pain, nausea and vomiting, upper digestive hemorrhage (rare).

- The positive diagnosis starts from the clinical, endoscopic, morphopathological picture and it is ideal to demonstrate the cause for an effective treatment.

- Treatment includes the administration of antisecretors (proton pump inhibitors), *prostaglandin E* (misoprostol - with the role of stimulating mucus secretion), as well as *sucralfat*- which forms a barrier at the level of the mucosa, preventing its contact with gastric acid.

- Chronic gastritis is long-lasting inflammation of the gastric mucosa, with the potential to evolve into ulcers, gastric atrophy and neoplasia.

- Chronic gastritis can be infectious (most commonly involving Helicobacter pylori) or non-infectious.

- The clinical picture ranges from completely asymptomatic to symptoms such as epigastric pain, nausea and vomiting.

- Megaloblastic anemia is a consequence of atrophic and/or autoimmune gastritis.

- The endoscopic and histological diagnosis is made by applying the OLGA (Operative Link on Gastritis Assessment) and OLGIM (Operative Link on Gastric Intestinal Metaplasia) criteria to establish the degree of severity of gastric atrophy and intestinal metaplasia, in order to identify patients at high risk of developing gastric neoplasm.

- Treatment is symptomatic (antisecretory, prokinetic) and etiological (eradication of PH infection, if it exists is mandatory in atrophic gastritis; corticosteroid therapy in eosinophilic gastritis; supplementation with vitamin B12 and folic acid, if there are deficiencies, etc.)

5. PEPTIC ULCER DISEASE

Definition

Peptic ulcer is a circumscribed, single or multiple defect in the gastric mucosa (gastric ulcer – GU) or duodenal mucosa (duodenal ulcer – DU), extending beyond the muscularis mucosae, accompanied by inflammatory and fibrotic reaction, and potentially penetrating to the serosa.

It is commonly associated with Helicobacter pylori (HP) infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Peptic erosions are more superficial lesions, confined to the mucosa and not extending beyond the muscularis mucosae.

Epidemiology

The prevalence of DU is approximately 10% in the general population, and of GU 3–5%. The incidence has decreased in younger populations due to successful eradication of *H. pylori* infection. In the elderly, prevalence remains high, mainly because of widespread NSAID use. DU is more common in men, while GU is more common in women and the elderly.

Pathophysiology

Peptic ulcers result from an imbalance between aggressive and defensive factors of the gastroduodenal mucosa.

Factors of aggression

1. Helicobacter pylori infection

In 1983, Australian researchers J. Robin Warren and Barry Marshall first described the role of H. pylori in the pathogenesis of gastritis. They were awarded the Nobel Prize in 2005 for this discovery. H. pylori is a spiral, flagellated, microaerophilic, Gram-negative bacterium (Fig. 5.1, Fig. 5.2). Transmission is thought to be primarily fecal–oral, with contaminated water being an important source in developing countries. The bacterium colonizes exclusively the gastric mucosa and areas of gastric metaplasia in the duodenum, residing between the epithelial apical membrane and the mucus layer, thereby adapting to the acidic environment.

HP infection causes gastritis in all infected individuals. Complications (peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, MALT lymphoma) can be prevented by eradication therapy. HP infection is considered an infectious disease, whether symptomatic or not, complicated or not, and is classified as a group I carcinogen.

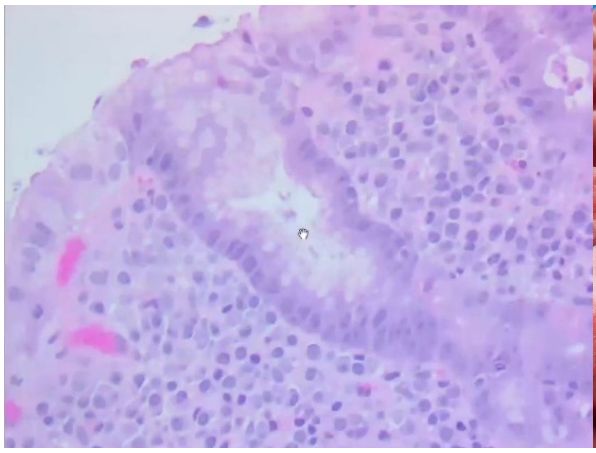


Figure 5.1 Helicobater Pylori - AI generated image

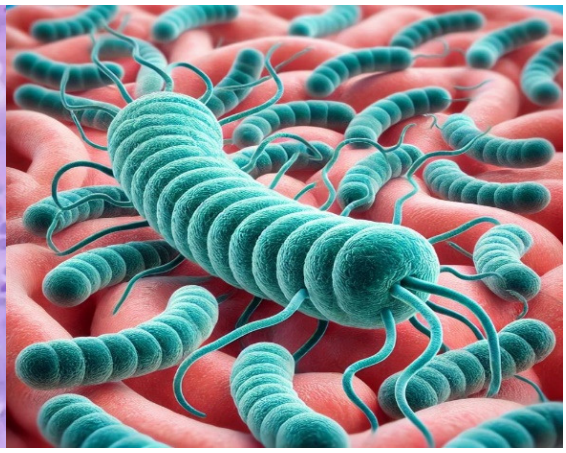


Figure 5.2 Helicobacter Pylori - histopathological appearance

The pathogenicities of HP are the enzymes and cytotoxins it secretes:

- **Urease** – hydrolyzes urea into bicarbonate and ammonium, which have direct cytotoxic effects. Locally increased pH leads to hypergastrinemia and stimulates acid secretion.
- **Phospholipases, proteases** – degrade the protective mucus and epithelial surfaces.
- **Vacuolating cytotoxin (VacA)** – induces apoptosis and inflammation.
- **CagA-positive strains** – cause more severe disease, with higher rates of ulcer complications.

Ulcerogenesis is mediated both directly (via mucosal inflammation and damage) and indirectly (via acid hypersecretion induced by gastrin stimulation).

2. Gastric acid and pepsin hypersecretion

Both GU and DU require acid for development, but DU is more closely associated with hypersecretion. Mechanisms include increased parietal cell mass, hypergastrinemia, vagal hyperactivity, parietal cell hypersensitivity to vagal stimuli, and altered gastric motility (accelerated emptying in DU with excess acid exposure to the duodenum; delayed emptying in GU with stasis). Pepsin secretion is also increased.

3. Bile acids

Refluxed bile salts have an ulcerogenic effect by disrupting lipid membranes of mucosal cells, decreasing resistance to acid injury.

Defensive factors

1. *Preepithelial: Surface mucus*, which opposes H+ retrodiffusion, *and bicarbonate* protects the mucosa from the action of acid, creating a neutral pH in the epithelium.
2. *Epithelial: The integrity of the* gastric and duodenal epithelium are essential to prevent erosion of the mucosa.
3. *Post-epithelial: Capillary blood flow* provides nutrients, bicarbonate intake and eliminates and takes up H+ and toxic products of inflammation.

Predisposing factors

Major risk factors include NSAID use, advanced age, prior ulcer history, and concomitant corticosteroid or anticoagulant therapy. Additional aggravating factors are smoking, alcohol, and stress.

- **NSAIDs and aspirin** cause direct mucosal injury (penetrating epithelial membranes and releasing H+) and indirect injury (inhibition of cyclooxygenase, reduced prostaglandin synthesis, and decreased mucus/bicarbonate secretion). COX-2 selective NSAIDs (coxibs) are less ulcerogenic but not risk-free.
- **Corticosteroids** also inhibit prostaglandin synthesis, though their ulcerogenic potential is lower than that of NSAIDs.
- **Smoking** decreases pancreatic bicarbonate secretion and impairs acid inhibition mechanisms.

Pathology

Macroscopically, ulcers appear as sharply demarcated mucosal defects with clean edges, sometimes with bleeding or perforation. Hemorrhage occurs when an artery at the ulcer base is eroded; the vessel caliber (1.5–4 mm) determines severity. Microscopically, ulcers show a necrotic center surrounded by acute and chronic inflammation, with fibrous tissue developing during healing.

Clinical presentation

Patients often experience *epigastric pain*, which manifests as burning or stinging, feeling of fullness or hunger-like pain in the case of duodenal ulcers. It is usually a dull, continuous pain, accentuated by the consumption of acidic foods. Sometimes rhythmicity is present – the relationship with meals, in UD the pain can improve after food ingestion and occurs late postprandial, and in UG the pain usually occurs immediately postprandial. The evolution over time is characterized by painful periods lasting days or weeks, alternating with asymptomatic periods (periodicity of the ulcer). This pattern is becoming less and less common with the advent of treatments to eradicate PH infection. Duodenal ulcers can also manifest as periumbilical pain.

Some patients with ulcers are *asymptomatic*, and in other cases the onset of symptoms is directly *caused by a complication* such as upper digestive hemorrhage, externalized by hematemesis or melena, or by a perforation. This is especially the case

of elderly patients, treated with NSAIDs, their administration having an analgesic effect, in addition to promoting ulcerogenesis.

Vomiting may also be present, generally acidic, *changes in appetite*, *dyspeptic symptoms* such as belching, meteorism, early satiety.

Biological picture

The blood count may show *anemia* due to chronic bleeding.

Tests for Helicobacter pylori are essential and may include direct and indirect methods.

1. Direct tests involve endoscopy with biopsy from which HP is determined by:

- *Histopathological examination with hematoxylin-eosin staining*. It has the advantage of being able to diagnose, in addition to PH infection, the changes induced by it in the gastric mucosa (gastritis, atrophic gastritis, metaplasia, adenocarcinoma).

- *Urease test (CLO test).* Immediately after retrieval, the biopsy fragment is inserted into a medium containing urea and a color indicator. The test is based on changing the color of the pH indicator. In the presence of HP, under the action of urease, urea is split with the release of ammonia, alkalizing the pH of the solution, and changing the color of the solution. The sensitivity of the urease test is approximately 90%, with specificity of 95–100%.

- *Culture* involves taking over and seeding the biopsy fragment as quickly as possible in a microaerophilic environment. It is not a routine test, being reserved for treatment-resistant HP infections for testing susceptibility to antibiotics.

- *Molecular tests* (real time-PCR, genomic sequencing and digital PCR) allow the detection of HP mutations associated with antibiotic resistance.

2. Indirect tests do not involve endoscopy and highlight Helicobacter infection by testing biological products.

- *Serological test* – determination of anti-Helicobacter Pylori antibodies (anti-HP Needle) in the serum. Due to the long persistence of anti-HP Needle in the serum, even after eradication, it is not recommended to use the serological test to check the effectiveness of the eradication cure.

- Urea breath test (UBT). It is based on the detection of the isotope 13C or 14C in exhaled air. The patient ingests a substrate containing labeled urea. In the stomach, the labeled urea is cleaved by the urea secreted by HP, with the release of CO_2 including that isotope, which will be detected and measured in the exhaled air. It can be used for infection diagnosis and verification of HP eradication.

- *The fecal Helicobacter Pylori antigen (fecal HP Ag)* is a simple test, which involves the determination of the HP antigen in the stool. The test has sensitivity and specificity comparable to that of UBT, and can be used for the diagnosis of infection and verification of HP eradication. Like UBT, fecal Ag HP testing should be done at least 4

weeks after the end of the eradication course and at least 14 days after treatment with proton pump inhibitors.

- *Anti-HP needle detection tests in urine and saliva, respectively*. They have good specificity, but low sensitivity given by the low level of antibodies in these biological fluids, which makes them unsuitable for the routine diagnosis of infection, let alone for checking eradication.

- *Molecular tests* use PCR (polymerase chain reaction) to amplify bacterial DNA in the stool or saliva. They are used in particular to identify strains resistant to different classes of antibiotics.

Paraclinic

Upper digestive endoscopy is the basic investigation for the diagnosis of ulcers, allowing direct evaluation of lesions. It also allows the treatment of a possible hemorrhage, as well as the taking of biopsies, mandatory in the case of a UG (to differentiate from a possible ulcerated gastric cancer), but not recommended in the DU (the malignancy of the DU being exceptional)

Barium radiological examination is an outdated method of diagnosis. It does not highlight superficial ulcers and does not allow the biopsy of gastric ulcers, which is mandatory for diagnosis. It can be used as an adjuvant method when a gastric evacuation disorder is suspected.

Positive diagnosis

The diagnosis is based on clinical suspicion and is confirmed by upper gastrointestinal endoscopy (EGD), which provides precise evaluation of the lesion and allows biopsy in the case of a gastric ulcer (GU). In complicated cases presenting with upper gastrointestinal bleeding, endoscopy also enables hemostatic interventions and risk stratification of rebleeding according to the Forrest classification, which is essential for guiding therapy. Active ulcers classified as Forrest Ia and Ib carry the highest risk of rebleeding and therefore require immediate endoscopic treatment.

Differential diagnosis

The differential diagnosis includes all conditions presenting with predominant upper abdominal pain, such as gastric cancer, erosive gastritis (diagnosed by EGD), chronic pancreatitis, and gallstone disease (with abdominal ultrasound as the first-line diagnostic method). Functional dyspepsia and irritable bowel syndrome are diagnoses of exclusion, in which EGD, gastroscopy, and colonoscopy reveal no abnormalities. Biopsy of any suspicious lesion is mandatory to exclude malignancy.

Complications

Upper gastrointestinal hemorrhage (UGIB) – the most common complication, resulting from erosion of a blood vessel at the base of the ulcer. Gastric ulcers bleed more frequently than duodenal ulcers. Clinical manifestations of bleeding include:

- **Hematemesis** – vomiting of blood, often described as resembling “coffee grounds.”
- **Melena** – passage of black, tarry stools.
- **Hematochezia** – passage of bright red or partially digested blood per rectum, in cases of massive bleeding.

Sometimes, symptoms of acute hemorrhagic anemia—such as cold sweats, pallor, dizziness, or near-syncope—may precede overt bleeding. In severe cases, clinical signs of hemorrhagic shock may also be present.

Ulcer perforation – the most severe complication (Fig. 5.3) and a surgical emergency. It typically presents with sudden, intense abdominal pain, initially localized to the epigastrium or right periumbilical region, but rapidly becoming generalized. On physical examination, abdominal wall rigidity due to muscular guarding (contracture) is observed, which prevents deep palpation—classically referred to as a “board-like abdomen.

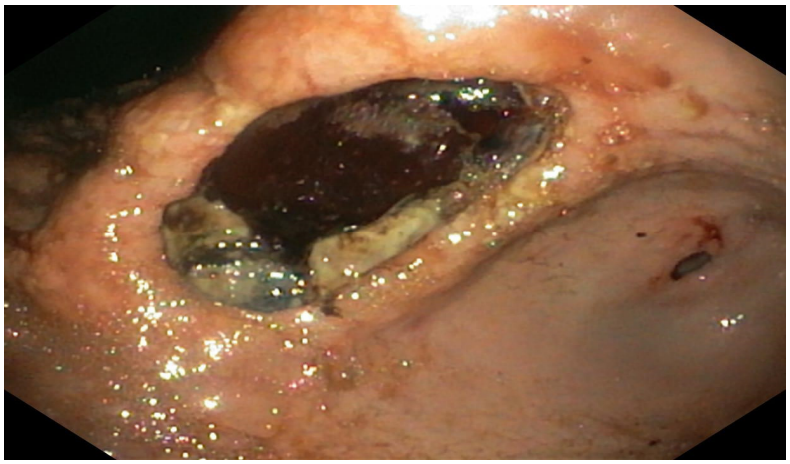


Figure 5.3. Perforated ulcer. Deep ulcerative crater with a blood clot and peritoneal fat.

Pyloric stenosis can occur in the evolution of juxta-pyloric ulcers. The typical manifestation is unforced vomiting, with undigested food several hours after ingestion. The treatment is surgical or by endoscopic balloon dilation.

Evolution and prognosis

The natural course of peptic ulcer disease has been fundamentally altered by the introduction of Helicobacter pylori eradication therapy. Before this, peptic ulcer was characterized by frequent recurrences, with painful flare-ups alternating with asymptomatic intervals. Eradication of HP now prevents recurrences in approximately 90% of cases.

The prognosis depends largely on the occurrence of complications and on comorbidities. In young individuals, even when complications are present at diagnosis, the overall prognosis is generally favorable. In contrast, in elderly patients with cardiovascular comorbidities, the disease is more likely to be complicated by hemorrhage or perforation, particularly due to the use of NSAIDs and antiplatelet or anticoagulant therapy.

Treatment

Lifestyle and dietary measures

There is no evidence to support overly restrictive diets, especially in the era of modern and highly potent antisecretory therapy. However, smoking cessation, abstinence from alcohol, and avoidance of spicy foods can accelerate healing. A diet that excludes acidic, spicy, or very hot foods, carbonated beverages, and fruit juices is recommended. In patients with active ulcers, the use of aspirin, NSAIDs, and corticosteroids is strictly contraindicated.

Drug therapy

Medical treatment includes several classes of drugs:

Antacids – provide symptomatic relief by neutralizing excess gastric acid. They are the oldest agents used in ulcer disease and include various combinations of aluminum and magnesium hydroxide, calcium carbonate, and magnesium salts (e.g., Maalox, Almagel, Dicarbocalm).

Mucosal protectants – particularly useful in gastric ulcer, where sucralfate 4 g/day (in 4 divided doses) may be added. Sucralfate is a polysulfated aluminum sucrose complex that promotes healing by binding bile salts and pepsin and by stimulating prostaglandin secretion.

Antisecretory agents – the mainstay of therapy, as they inhibit acid secretion. Two major classes are used:

Proton pump inhibitors (PPIs) – the most potent and effective agents.

The first representative was omeprazole, marketed under several trade names (Losec, Omeran, Omez, Antra, Ultop). The usual dose is 40 mg/day.

Other PPIs include pantoprazole (Controloc) 40 mg/day, lansoprazole (Lanzul, Lanzap) 30 mg/day, rabeprazole (Pariet, Relitaz) 20 mg/day, and esomeprazole (Nexium, Helides, etc.) 40 mg/day.

PPI therapy is highly effective, rapidly relieving pain, which is why PPIs are the treatment of choice for active ulcers. The duration of therapy is typically 6–8 weeks (6

weeks for GU and 8 weeks for DU), which corresponds to the time required for ulcer healing.

In superficial ulcers, therapy may be shorter, but in complicated cases—such as those associated with upper GI bleeding—the full recommended duration should be used.

In bleeding ulcers requiring endoscopic hemostasis, PPI therapy should begin intravenously (e.g., omeprazole 80 mg IV bolus followed by continuous infusion of 8 mg/h for 72 hours), after which oral therapy should continue until the expected healing time (6–8 weeks). Continuous infusion is necessary to maintain intragastric pH above 4, since fibrin clots essential for physiological hemostasis are unstable in a more acidic environment.

Histamine H2-receptor antagonists – their effect is achieved through competitive blockade of H2 receptors, reducing intracellular cyclic AMP levels and thus decreasing acid secretion. Examples: cimetidine (the first of the class, now rarely used), ranitidine (usual dose 300 mg/day), famotidine (Quamatel, 40 mg/day), nizatidine (Axid, 300 mg/day), and roxatidine. The duration of administration is also 6–8 weeks.

Treatment to eradicate Helicobacter pylori infection. Eradication therapy for *H. pylori* infection is an essential step in the treatment of peptic ulcer disease, as it prevents ulcer recurrence and the development of associated complications. Over the years, eradication regimens have evolved due to the emergence of bacterial resistance to the various antibiotics used. Groups of international experts regularly review data on resistance patterns and publish updated treatment recommendations, known as the **Maastricht Consensus**.

The general principle of eradication therapy is to combine a proton pump inhibitor (PPI) with two or three antibiotics. After the treatment has been completed, it is mandatory to confirm eradication, either by a urea breath test or by detection of *H. pylori* antigen in the stool. In case of treatment failure, patients should be switched to a second-line regimen, as repeating the same scheme is ineffective.

The **Maastricht III Consensus**, published in 2007, recommended as first-line therapy the triple combination of a PPI, administered in standard dose twice daily (omeprazole 20 mg BID, pantoprazole 20 mg BID, or esomeprazole 20 mg BID), together with:

- amoxicillin 1,000 mg BID, and
- either metronidazole 500 mg BID or clarithromycin 500 mg BID,

for a duration of 7–14 days. These were known as the OAM regimen (omeprazole + amoxicillin + metronidazole) and the OAC regimen (omeprazole + amoxicillin + clarithromycin).

Second-line regimens at that time included substitution of levofloxacin for metronidazole or clarithromycin. However, with the increasing use of antibiotics in recent

years, response rates to these classic triple therapies have declined, and therefore the consensus has been revised multiple times. A major advance was the addition of **bismuth subcitrate** at a dose of 240 mg BID to triple therapy, creating bismuth-based quadruple regimens with improved efficacy.

In **Romania**, a country considered to have a high prevalence of resistance to both clarithromycin and metronidazole, the recommendations of the **Maastricht VI Consensus (2022)** specify the following treatment regimens:

- **First-line therapy** – quadruple regimen:
  - Omeprazole 20 mg BID + bismuth subcitrate 240 mg BID + metronidazole 500 mg TID + tetracycline 500 mg QID, administered for 14 days.
- **Second-line therapy** – triple or quadruple therapy (including bismuth) based on levofloxacin, with double-dose PPIs:
  - Omeprazole 40 mg BID + levofloxacin 500 mg BID + amoxicillin 1,000 mg BID ± bismuth subcitrate 240 mg BID.

An important point is not to confuse the treatment of ulcer disease itself (which consists of PPI therapy for 6–8 weeks) with the treatment of H. pylori infection (which requires a combination of PPI and antibiotics, with or without bismuth, for 10–14 days). If H. pylori infection is diagnosed in association with an active ulcer, eradication therapy should be given first, followed by continuation of PPI treatment until the ulcer has healed. If H. pylori infection is diagnosed outside of an ulcer flare, a 10–14 day regimen combining a PPI with antibiotics, with or without bismuth, is sufficient for the treatment of the infection.

In cases where the first two lines of therapy fail, other therapeutic strategies can be considered. These include:

- Rifabutin-based therapy, in which rifabutin replaces metronidazole or clarithromycin.
- Sequential therapy, in which treatment is initiated with a PPI plus one antibiotic for 7–10 days, followed by another 7–10 days of PPI combined with a different antibiotic.
- Hybrid therapy, in which a PPI plus amoxicillin are administered for 14 days, and during the last 7 days metronidazole and clarithromycin are added to the regimen.

Nevertheless, the optimal approach in cases of eradication failure is to select therapy based on an antibiogram (culture with susceptibility testing) or on molecular testing for resistance mutations.

Endoscopic treatment. Endoscopic therapy is essential in the management of hemorrhagic ulcers.

- **Endoscopic hemostasis** is indicated in upper gastrointestinal bleeding caused by ulcer disease, specifically in Forrest stages Ia, Ib, and IIa (Table 5.I). Techniques include thermal methods (such as electrocoagulation with a bipolar probe) and mechanical methods (such as hemostatic clips).

- As an adjuvant technique, injection of adrenaline (epinephrine) at a dilution of 1:10,000 can be used, but always in combination with another hemostatic method, in order to achieve effective bleeding control.

Further details are provided in the chapter dedicated to upper gastrointestinal bleeding.

Table 5.I. Forrest classification of hemorrhagic ulcers:

Forrest Classification	Endoscopic elements	Risk of rebleeding
Forrest Ia	Spurting arterial bleeding	80-90%
Forrest Ib	Oozing (oozing venous or capillary bleeding) (Fig. 5.4)	10-30%
Forrest IIa	Non-bleeding visible vessel	50-60%
Forrest IIb	Adherent clot	25-35%
Forrest IIc	Ulcer base covered with hematin (black) (Fig. 5.5)	0-8%
Forrest III	Clean ulcer base	0-2%

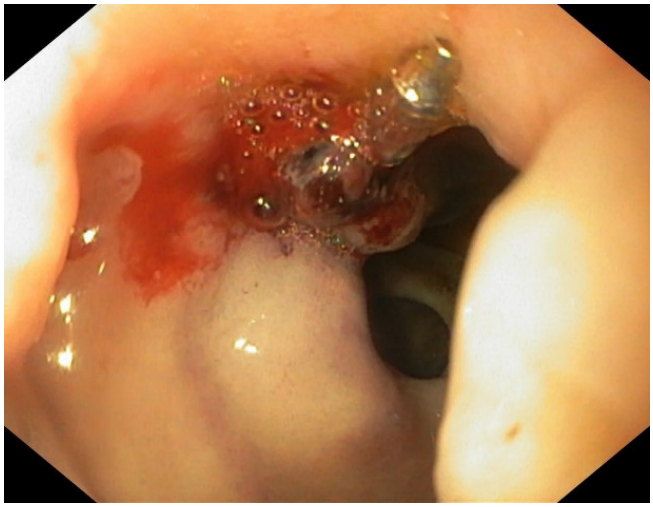


Figure 5.4. Forrest IB bulbar ulcer – endoscopic hemostasis – hemoclip application

The Forrest classification is essential for assessing the risk of rebleeding and for guiding both endoscopic and medical management. Patients with Forrest Ia and Ib ulcers (active spurting or oozing bleeding) and those with Forrest IIa ulcers (non-bleeding visible vessel) require immediate intervention in order to reduce the risk of mortality associated with recurrent bleeding.

Angiographic treatment – This modality is rarely used and is reserved for cases of upper gastrointestinal bleeding in which endoscopic treatment has failed. It can provide both diagnostic localization of the bleeding source and therapeutic embolization of the responsible vessel.

Surgical treatment – Surgery is indicated in patients with upper gastrointestinal bleeding who do not respond to endoscopic and angiographic therapy, as well as in cases of perforated ulcers or gastric outlet obstruction secondary to ulcer-related stenosis.

To note

Peptic ulcer is a circumscribed lesion, either single or multiple, representing an interruption of the continuity of the gastric and/or duodenal mucosa. The lesion extends beyond the muscularis mucosae and is accompanied by an inflammatory and fibrotic reaction.

It is commonly associated with Helicobacter pylori (HP) infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

The appearance of gastric and duodenal ulcers is explained by the imbalance between the aggressive factors and the defensive mechanisms of the mucosa.

The clinical presentation includes epigastric pain, which is usually dull and continuous, and often becomes more intense after the ingestion of acidic foods. Sometimes rhythmicity, meaning the relationship of pain with meals, is present—for example, “hunger pain” in the case of duodenal ulcer. Some patients with ulcers may remain asymptomatic, while in other cases the very first manifestation of the disease may be a complication such as upper gastrointestinal hemorrhage, this being particularly common in patients treated with NSAIDs.

The diagnosis begins with the patient’s symptoms, is confirmed by endoscopy, and must always include testing for *Helicobacter pylori* infection as well as evaluation of possible NSAID use.

The diagnosis of HP infection can be established by **direct tests**—which require endoscopy with biopsy, such as the rapid urease test and histopathological examination—or by **indirect tests**, such as the urea breath test, serological detection of anti-HP antibodies in serum, or stool antigen testing.

Differential diagnosis must always be taken into account and includes all other potential causes of epigastric pain.

The main complications of ulcerative disease are hemorrhage, perforation, and stenosis.

Drug treatment of peptic ulcer disease is based on antisecretory therapy. This can be achieved with proton pump inhibitors (esomeprazole, pantoprazole, omeprazole, rabeprazole), administered for 4–6 weeks, or with H2-receptor antagonists, which are less potent (nizatidine, ranitidine, famotidine).

Treatment of *Helicobacter pylori* infection must follow the currently accepted clinical guidelines and consists of either quadruple therapy or triple therapy. In all cases, eradication must be confirmed after treatment, using either a urea breath test or stool antigen testing.

Peptic ulcer disease complicated by hemorrhage requires endoscopic treatment, which may include the application of hemoclips, thermocoagulation, and adrenaline (epinephrine) injection. This must always be combined with parenteral PPI therapy, such as an intravenous bolus of omeprazole 80 mg followed by continuous infusion at 8 mg/hour for 72 hours.

6. FUNCTIONAL DYSPEPSIA

Definition

Functional dyspepsia (FD) is a condition without an organic substrate, characterized by a symptomatology located in the upper abdomen, with epigastric pain, fullness, bloating or discomfort as manifestations. It is a recurrent chronic condition, without complications, but with a significant impact on the quality of life, being considered a functional digestive disorder.

Epidemiology

Functional dyspepsia is the most common functional gastro-duodenal disorder, affecting quality of life, productivity and increasing medical expenses, with an overall prevalence between 4.8% and 7.2%. It is more common in women and young adults, being associated with irritable bowel syndrome, gastroesophageal reflux disease, and risk factors such as acute gastrointestinal infections and anxiety.

Approximately 70-80% of patients who go to the gastroenterologist have symptoms located in the upper abdomen, but modern explorations cannot reveal the presence of organic lesions (gastro-duodenal ulcer, gastric neoplasm, gallstones, chronic pancreatitis, etc.). These patients are those classified as having functional dyspepsia, that is, without an organic substrate. The remaining 20-30% of patients with upper abdominal symptoms have organic dyspepsia (organic lesions that generate suffering).

Pathophysiology

There are many insufficiently elucidated aspects regarding the etiopathogenesis of functional distress in the upper abdominal floor. Among the known mechanisms are the role of Helicobacter Pylori or hypersecretory status in cases with ulcer-like symptoms; In those with bloating-type symptoms, a gastric evacuation disorder (dysmotility) or even digestive sensory perception disorders are incriminated - the patient perceives a normal amount of gas in the digestive tract as abnormal.

Functional dyspepsia involves a disruption of the gut-brain interaction and can be caused by mechanisms such as dysmotility, visceral hypersensitivity, low-grade mucosal inflammation, damage to the gut microbiota, or altered processing in the central nervous system. Depression and anxiety also play an important role.

Pathology

From a morphopathological point of view, FD does not cause obvious structural abnormalities. Endoscopy and gastric biopsies are generally normal. Thus, morphopathological investigations confirm the functional character of the disease and exclude other pathologies with organic substrate.

Clinical picture

The clinical diagnosis starts from a more or less noisy epigastric symptomatology, but which lacks weight loss, digestive bleeding or anemia (considered alarm signs - in their presence we must think of an organic disease). The type of symptoms that prevail will allow you to fall into one of the forms of dyspepsia.

Biological picture

Laboratory tests are performed to exclude anemia (blood count, ferritin, sideremia) and inflammation (PCR). Testing for Helicobacter Pylori infection is recommended. The presence or absence of infection does not exclude the diagnosis of FD, but testing is mandatory in patients with dyspepsia. In dyspeptic patients in whom the eradication of PH infection does not relieve symptoms for a period of more than 6-12 months, they are considered to have functional dyspepsia.

Paraclinic

The paraclinical diagnosis consists of a series of explorations that will demonstrate the absence of organic lesions. It starts with an abdominal ultrasound that will demonstrate a gallbladder without stones, a normal-looking pancreas, a liver without changes. Upper digestive endoscopy will reveal a normal esophagus, stomach, and duodenum. Colonoscopy, performed when indicated, will not reveal colonic changes. So the functional character of dyspepsia will be demonstrated by the absence of organic lesions. It should be noted that the use of barium passage does not allow a diagnosis of functional dyspepsia, since superficial gastro-duodenal ulcers cannot be highlighted by this method.

Positive diagnosis

DF is defined based on 3 criteria:

1. *The presence of upper abdominal floor symptoms:* post-prandial fullness, early satiety, epigastric pain, which occur after food ingestion, but also in the absence of nutrition.

2. *Chronic, recurrent evolution, with impairment of quality of life.* Symptoms must be present 3 days a week for the last 3 months and with onset 6 months ago.

3. *Absence of organic, systemic or metabolic lesions* explaining symptoms on routine investigations (including upper digestive endoscopy).

Table 6.I. Diagnostic criteria in functional dyspepsia

	Diagnostic symptoms	Temporal criterion	Associated symptoms	Exclusion criteria
Postprandial distress syndrome (PDS)	- Postprandial fullness - Early postprandial satiety - The intensity is enough to affect the usual activities or the ingestion of an average lunch.	3 days/week in the last 3 months, with onset of 6 months	-epigastric pain/burning, bloating, belching, nausea -heartburn is not a typical symptom but may coexist with FD -vomiting falls under other functional disorders -symptoms relieved by the elimination of gas or feces are not part of FF	-absence of organic, systemic or metabolic lesions explaining the symptoms on routine investigations (including upper digestive endoscopy).
Epigastric pain syndrome (ESP)	- Epigastric pain and/or - Epigastric burn - The intensity of the pain is enough to influence the usual activities. - Symptoms can be produced by food ingestion, can be relieved by food, or can occur without eating.	3 days/week in the last 3 months, with onset of 6 months	- postprandial upper abdominal floor meteorism, belching, nausea; - persistent vomiting suggests another functional syndrome - heartburn is not a dyspeptic syndrome, but it can coexist - epigastric pain is not of the biliary type - symptoms relieved by gas/fecal elimination are not part of FD	-absence of organic, systemic or metabolic lesions that explain the symptoms at routine investigations (including upper digestive endoscopy).

Functional dyspepsia includes:

- *postprandial distress syndrome (PDS)* - in which symptoms appear predominantly postprandial, as discomfort. The main mechanism of occurrence would be gastric dysmotility.

- *epigastric pain syndrome (ESP)* - with ulcerative symptoms. The main mechanism of action would be visceral hypersensitivity.

The diagnostic criteria for Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome are given in Table 6.I**.**

Differential diagnosis

The differential diagnosis of functional dyspepsia should be made with all organic lesions of the upper abdomen (reflux esophagitis, esophageal neoplasm, achalasia, gastro-duodenal ulcer, chronic gastritis, gastric neoplasm, gastric lymphoma, acute or chronic pancreatitis, gallstones, etc.). Also, the differential diagnosis must be made with another functional entity, but with localization in the lower abdomen, namely irritable bowel syndrome (IBS)(characterized by transit disorders, bloating, feeling of incomplete stool, discomfort in the lower abdomen, etc.). There are authors who include functional dyspepsia and irritable bowel in the same entity - the "irritable digestive tract".

Evolution, complications, prognosis

Functional dyspepsia evolves without organic complications. The evolution of functional dyspepsia is favorable, with better and less good periods, generally related to nutrition, stress, etc. The prognosis of this disease is favorable.

Treatment

1. Hygienic-dietary treatment - involves the adoption of a healthy lifestyle and the patient's awareness of the fact that it is a benign but recurrent pathology. It is recommended to eat 5 meals a day (3 main meals and 2 snacks) at regular times, with a personalized diet, without excessive restrictions. It is advisable to avoid NSAIDs, excessive consumption of alcohol, tobacco and coffee.

2. Drug treatment.

- *The eradication of H. Pylori infection* can cause the disappearance of symptoms in some patients with FD, without being able to know in advance which of them will respond. Dyspeptic syndrome can be attributed to H.Pylori gastritis (infection-associated dyspepsia) if the eradication of H. Pylori leads to sustained amendment of symptoms, for more than 6-12 months.

- *Antisecretory medication* with PPIs (proton pump inhibitors – e.g. Esomeprazole 20-40 mg/day) and H2 blockers (histamine H2 blockers – e.g. ranitidine 300 mg/day, or famotidine 20-40 mg/day) are administered during periods of symptoms. They are ineffective in those with PDS, but of choice in those with EPS.

- *Prokinetics* such as Metoclopramide or Motilium are administered before main meals. Domperione (Motilium) is preferred because it has fewer side effects (it does not cause drowsiness or extrapyramidal manifestations). Pokinetics are effective in those with PDS type DF. Debridate (trimebutin maleate) accelerates gastric emptying, stimulates the release of motilin and has a possible antimicrobial role.

- Digestive ferments can *also be administered* at meals (Digestal, Mezym forte, Festal, Creon, etc.) or *absorbents of intestinal* gases, such as symethicone (Espumisan, Sab-simplex) or charcoal.

- *Psychotropic drugs*, *antidepressants* - they are used as a 2nd line treatment (Levosulpiride, Amitryptyline, Mirtazapine).

To note

- FD is a common condition, without an organic substrate, characterized by a symptomatology located in the upper abdomen, having as manifestations epigastric pain, fullness, bloating or discomfort in the upper abdominal floor.

- The diagnosis is a clinical one, biological and paraclinical tests being used to exclude organic diseases.

- The evolution is long, with periods of exacerbation and periods of calm, without organic complications, but affecting the quality of life of patients.

- Drug treatment is symptomatic, focused on antisecretors in epigastric pain syndrome and prokinetics in postprandial distress. Dietary treatment can relieve symptoms.

7. GASTRIC CANCER

Definition

Gastric cancer is defined as a malignant tumor that arises from the epithelial cells of the gastric mucosa. It can manifest as local invasion, extension to adjacent structures, and distant metastases in the lymph nodes, liver, lungs, or peritoneum. From a clinical point of view, the disease can have a slow or aggressive evolution, depending on the histological type and the stage at diagnosis.

Epidemiology

Gastric cancer is the fifth leading cause of cancer worldwide and the third leading cause of cancer death. Its incidence varies significantly between regions, being particularly high in East Asia (Japan, South Korea), but low in North America and Africa. This geographical distribution reflects the influence of environmental factors, lifestyle and access to healthcare. Although the global incidence is decreasing due to advances in prevention and treatment, gastric cancer continues to be a major cause of mortality, especially in high-risk regions such as East Asia.

Pathophysiology

The pathophysiology of gastric cancer involves a combination of environmental, genetic and inflammatory factors. The process begins with chronic gastritis, most often caused by Helicobacter pylori, which induces persistent inflammation. It progresses to atrophic gastritis, intestinal metaplasia and epithelial dysplasia, culminating in the development of gastric adenocarcinoma.

Major risk factors for gastric cancer are:

- *Helicobacter pylori infection.* It is the most important risk factor for gastric adenocarcinoma, especially CagA-positive HP infection. Chronic infection causes atrophic gastritis, intestinal metaplasia and, finally, malignant transformation. The WHO considers HP a first-grade oncogen.

- *Diet* with an increased intake of foods preserved by salting, smoking or added nitrites is associated with an increased risk.

- *Smoking significantly* increases the risk of gastric cancer, especially in chronic smokers.

- *Genetic factors.* Mutations in the CDH1 gene are implicated in hereditary diffuse gastric cancer. The disease is more common in men than in women, and the risk increases with age, being most commonly diagnosed after the age of 60.

Predisposing gastric disorders. Several chronic gastric conditions are associated with an increased risk of gastric cancer.

- *Atrophic gastritis.* The progressive loss of gastric glandular cells contributes to intestinal metaplasia, with the risk of dysplasia and malignant transformation.

- *Megaloblastic (pernicious) anemia* is associated with autoimmune atrophic gastritis and vitamin B12 deficiency, increases the risk of malignant transformation.

- *Barrett's esophagus* caused by severe gastroesophageal reflux disease can lead to Barrett's metaplasia in the esogastric transition zone.

- *Zollinger-Ellison syndrome*. Hypersecretion of gastrin causes excessive stimulation of parietal gastric cells, favoring carcinogenesis.

- *Gastric resection* more than 10-15 years postoperatively, the pathophysiological mechanism probably being chronic inflammation caused by chronic reflux of intestinal juice.

- *Gastritis with gigantic folds Menetrier.*

- *Gastric polyps,* especially associated with dysplasia.

The pathophysiological mechanisms involved in carcinogenesis are:

- *Chronic inflammation* – Pro-inflammatory cytokines and oxidative stress contribute to cellular DNA damage and genomic instability.

- *Genetic alterations* - Microsatellite instability and mutations in the *p53* gene are common.

- *Environmental factors* - Diet rich in nitrites and alcohol consumption intensify the carcinogenic process.

Pathology

Gastric cancer presents important variations from a macroscopic and histological point of view.

Macroscopic. From a macroscopic point of view, gastric cancer is described

- *protrusive (polypoid)* – the endoscopic aspect being a tumor protruding into the gastric lumen, it is the most typical appearance, but requires biopsy confirmation.

- *ulcerative* – with endoscopic appearance of deep ulcer with irregular edges and infiltrative bottom. However, the diagnosis cannot be made only endoscopically, the biopsy being mandatory.

- *infiltrative (linitis plastica)* – in which there is a diffuse thickening of the gastric wall, characteristic of diffuse adenocarcinoma. The appearance of the mucosa at endoscopy is quasi-normal, but the stomach is stiffer, less distensible to insufflation, transabdominal ultrasound and sectional imaging methods highlighting a thick and unstructured gastric wall.

Microscopic. Adenocarcinoma is the most common type of gastric cancer, being responsible for over 90% of cases. Other types include gastric lymphoma, gastrointestinal stromal tumors (GIST), and squamous cell carcinomas.

Depending on the microscopic histopathological appearance, gastric adenocarcinoma is classified into two types: intestinal and diffuse (Lauren histological classification).

- *Intestinal type* - Well-differentiated tumors, commonly associated with intestinal metaplasia. It occurs more often in the elderly and is closely related to environmental factors. The endoscopic appearance is polypoid or ulcerated, metastasizes mainly to the liver and has a somewhat better prognosis than the diffuse type.

- *Diffuse type* **-** Poorly differentiated tumors with extensive invasion into the gastric wall (linitis plastica) and poorly defined margins. It is more common in young women, associated with genetic predisposition. It metastasizes early peritoneally and has a severe prognosis.

Early gastric cancer

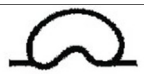
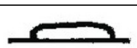
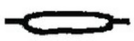
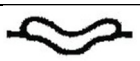
Incipient gastric cancer (CGI) is an early form of gastric cancer, defined by the presence of a tumor limited to the mucosa and/or submucosa, regardless of the presence or absence of lymph node metastases. This form of cancer is particularly important because it has a significantly better prognosis compared to advanced forms of the disease.

CGI is more commonly diagnosed in countries with advanced screening programs, such as Japan and South Korea, due to the widespread use of upper digestive endoscopy. Risk factors include *Helicobacter pylori* infection, diet rich in smoked, salted, or nitrate-preserved foods, alcohol consumption and smoking, family history of gastric cancer, and premalignant conditions such as intestinal metaplasia or atrophic gastritis. Clinical manifestations are often nonspecific, including persistent dyspepsia, vague epigastric pain, iron deficiency anemia, and unexplained weight loss.

Diagnosis is based on upper digestive endoscopy with multiple biopsies, chromoendoscopy and confocal laser endomicroscopy to improve the identification of suspicious lesions, as well as histopathological examination, which determines the histological type according to the Lauren classification. Treatment is aimed at complete resection of the tumor and may include endoscopic resection, by endoscopic submucosal dissection (ESD) or endoscopic mucosectomy (EMR), or partial or total gastrectomy with lymphadenectomy, indicated in cases at high risk of lymph node metastases. The prognosis is excellent in the case of early diagnosis, with 5-year survival rates exceeding 90% after appropriate treatment. Postoperative monitoring is essential for detecting recurrences or metachronous lesions. Raising awareness and implementing endoscopic screening in high-risk populations can help reduce mortality from gastric cancer.

The Paris classification (Table 7.I) is a system used to describe and classify superficial lesions of the digestive tract, including gastric polyps. It has an essential role in assessing the risk of malignancy and in guiding the therapeutic decision, being widely adopted in modern endoscopy.

Table 7. I. Paris Classification of Gastric Polyps

Endoscopic appearance	Paris Classification	Schematic representation	Description
Protrusive lesions	Ip		Pedicled polyps
	Ips		Subpedicled polyps
	Is		Sessile polyps
Superficial lesions	IIa		Flat elevation of the mucosa
	IIb		Flat change in the mucosa
	IIc		Lesion with mild depression
Excavated lesions	III		Deep depression lesion at high risk of malignancy

The Paris classification plays a fundamental role in the management of gastric polyps, having direct implications on the therapeutic decision:

- **Ip, Ips, and Is lesions** are most commonly benign (e.g., hyperplastic, adenomatous polyps) and are often endoscopically resected.
- **Lesions II and III** are more commonly associated with severe dysplasia or early adenocarcinoma, requiring advanced techniques such as endoscopic mucosal resection (EMR) or endoscopic submucosal resection (ESD).
- Correctly identifying the type of lesion allows for personalized treatment, reducing the risk of complications and improving patients' prognosis.

Therefore, the systematic use of the Paris classification in digestive endoscopy contributes to a better stratification of the risk and to the optimization of therapeutic strategies in the case of gastric polyps.

Clinical picture

This disease has a silentonset, with initial non-specific symptoms, which delays the diagnosis and allows the progression of the disease, that most cases are identified at advanced stages

Common symptoms include persistent dyspepsia, especially after meals, nausea, vomiting and lack of appetite, sometimes with aversion to meat, unexplained weight loss, fatigue and pallor, associated with iron deficiency anemia.

The warning signs that require EDS are iron deficiency anemia, dyspepsia that no longer yields to regular medication, selective lack of appetite for meat, involuntary weight loss.

In advanced stages, clinical signs are usually related to complications. These include upper digestive hemorrhage (manifested by hematemesis and/or melena), Virchow adenopathy (palpable left supraclavicular lymph node, due to lymph node metastasis), Krukenberg tumor (ovarian metastases), carcinomatous ascites (from peritoneal dissemination).

Paraclinical investigations

The diagnosis of gastric cancer requires a multidisciplinary approach, including endoscopy, imaging, and biological and histological evaluation.

- *Biological analyzes* can bring valuable information about the patient's status and can guide diagnosis and staging. Iron-deficiency anemia is the most frequent laboratory abnormality -, indicating chronic blood loss from the gastrointestinal tract; as well as thrombocytosis that frequently occurs in a paraneoplastic setting and may suggest advanced disease. Among *the biochemical tests*, the most common changes are hypoalbuminemia **-** indicative of malnutrition or protein loss through the affected gastric wall; increased alkaline phosphatase values, suggestive of the presence of bone or liver metastases; increased bilirubin and transaminases - suggestive of the presence of extensive liver metastases. Signs of *systemic inflammation* are increased ESR and C-reactive protein (CRP) – indicative of chronic inflammation and/or paraneoplastic response. *The tumor markers* evaluated are carcinoembryonic antigen (CEA) – used to monitor treatment response and detect recurrence, as well as CA 19-9 and CA 72-4 – markers with moderate sensitivity, often used in combination for monitoring.

- *Upper digestive endoscopy* is the method of choice, allowing direct visualization of the tumor (Fig. 7.1) and biopsy sampling for histological confirmation.

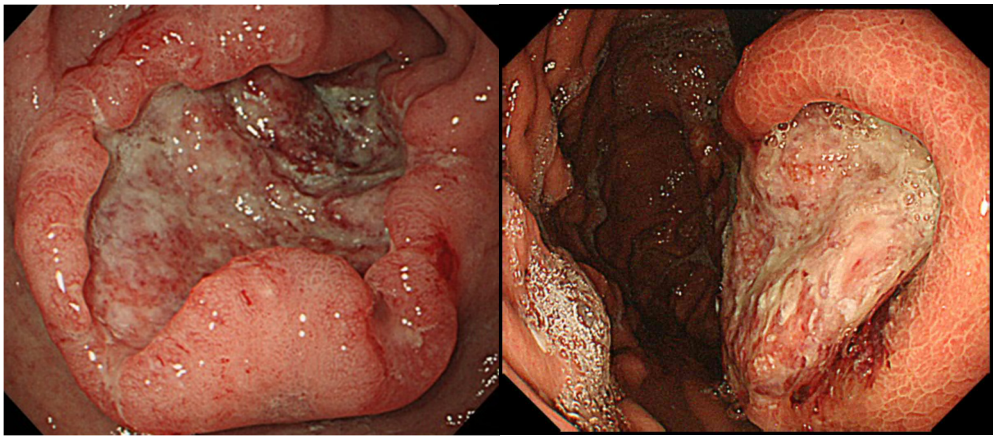


Fig. 7.1. Endoscopic aspects of gastric cancer. Left- Ulcerated antral gastric tumor. Right – Ulcerated gastric tumor located at the level of the small curvature.

- *Imaging methods*. Transabdominal ultrasound can highlight thickening and destructuring of the gastric wall, possible liver and lymph node metastases, carcinomatous ascites. Contrast computed tomography (CT) or contrast MRI allows the evaluation of loco-regional extension and metastases, being indispensable for correct staging. Echoendoscopy – is extremely important in early cancer, providing information about the invasion of the gastric wall and perigastric lymph nodes.

Positive diagnosis

The integration of clinical, biological, endoscopic data with imaging and histological investigations contributes to a complete and accurate diagnosis. The diagnosis of certainty requires histological confirmation (Fig. 7.2).

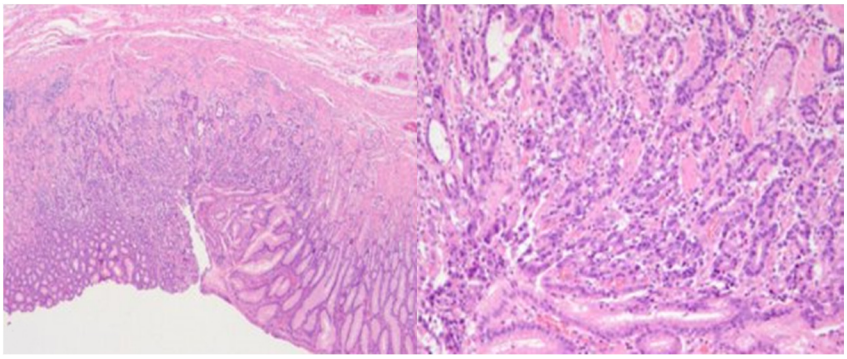


Fig. 7. 2. Histological features of gastric adenocarcinoma (Hematoxylin, Eosin staining). Left - Gastric adenocarcinoma limited to the mucous layer (×40). Right - Has distorted tubular glands, made up of epithelial cells with atypical nuclei, suggesting an intestinal-type adenocarcinoma according to the Lauren classification (×100).

Part of the positive diagnosis is mandatory staging of the disease, classification in TNM system (Tumor, Nodules, Metastases) which is essential for the therapeutic and prognostic plan (Table 7.II).

Table 7.II. cTNM staging for gastric cancer

cTNM staging	Description
T1	Invasion limited to the mucosa or submucosa
T2	Invasion of one's own muscle layer
T3	Serous invasion without touching adjacent organs
T4a	Serous invasion with damage to adjacent organs
T4b	Extensive invasion of neighboring structures and organs
N0	No lymph node metastases
N1	1-2 lymph nodes affected
N2	3-6 lymph nodes affected
N3	More than 7 lymph nodes affected
M0	No distant metastases
M1	Distant metastases present

Differential diagnosis

The differential diagnosis of gastric cancer is mainly based on EDS with biopsy and includes: *gastric* ulcer – endoscopic this has net margins, unlike ulcerated cancer, in which the edges areirregular, but differentiation is made by multiple biopsies; *gastric lymphoma* - requires immunohistochemistry for confirmation; *gastrointestinal stromal tumors (GIST)* – frequently appear as submucosal tumors (normal covering mucosa or with "decubitus ulceration", requires biopsy with immunohistochemistry and identification of the c-KIT marker).

Complications

Gastric cancer can cause *acute or chronic bleeding* – which can lead to severe anemia; *gastric obstruction* – more frequent in antral tumors, the clinical picture being dominated by gastric evacuation failure phenomena; *the appearance of distant metastases* , frequently affecting the liver, lungs and peritoneum; *perforation* – with a clinical picture of acute peritonitis, a surgical emergency.

Evolution and prognosis

The prognosis of gastric cancer is closely related to the stage at diagnosis and the histological type. Patients with early gastric cancer have a 5-year survival rate of over 70%, while advanced forms have a rate of less than 20%. Early screening and diagnosis are essential to improve the prognosis.

Treatment

The treatment of gastric cancer involves a multimodal approach, adapted to the stage of the disease and the characteristics of the patient. Curative treatment is possible in cases detected early, but in late stages only palliative treatment is possible, with the aim of prolonging survival and improving quality of life.

1. Surgical treatment. Surgery is the basic treatment for localized gastric cancer. Surgery is recommended for stage T1, ineligible for endoscopic resection, and for stages T1b – T3, associated with perioperative chemotherapy (pre- and postoperative).

Depending on the location and extension of the tumor, the following types of interventions can be performed: *subtotal gastrectomy* - indicated in antrally localized tumors; *total gastrectomy* - necessary in large or proximally localized tumors, at the level of the gastric body; *gastrectomy with extended lymphadenectomy* - it is performed to remove the affected lymph nodes and reduce the risk of recurrence.

In clinically advanced stages, without obvious metastases, it is recommended to perform exploratory laparotomy, in 50 – 60% of cases patients may be unresectable, having peritoneal carcinomatosis, which must be evidenced by imaging methods if it is not accompanied by ascites.

In advanced stages, with metastases, curative surgery cannot be performed, but it can be used for the management of complications, such as gastric obstruction and bleeding, as well as palliatively, for tumor mass reduction. Radiotherapy with polychemotherapy can also be used to reduce the tumor mass by up to 50% and extend life expectancy.

2. Chemotherapy. Commonly used chemotherapy regimens include combinations based on fluorouracil, cisplatin and taxanes. Chemotherapy can be administered as neoadjuvant therapy, to reduce the size of the tumor before surgery; *adjuvant,* after surgery, to remove residual tumor cells and prevent recurrence; *palliative,* in cases of advanced disease, to prolong survival and control symptoms.

3. Radiotherapy is rarely used as a single treatment, but it can be combined with adjuvant chemotherapy - to improve local control after surgery or it can be performed for palliative purposes - to reduce pain caused by metastases or large tumors.

4. Endoscopic treatment is indicated in the early stages of gastric cancer, when the lesions are limited to the mucosa or submucosa, without lymph node invasion. Techniques used include *endoscopic mucosal resection (EMR)* – a minimally invasive method that allows for complete excision of precancerous lesions or early cancer, and *endoscopic submucosal dissection (ESD)* – which allows for the excision en bloc of lesions that are more extensive or deeper than those treatable by EMR. These techniques are preferred due to their curative nature and the reduced risk of complications compared to traditional surgery.

5. Immunotherapy. In recent years, immunotherapy has become a promising option for advanced gastric cancer. PD-1 inhibitors (e.g. nivolumab) have demonstrated efficacy in certain cases of metastatic disease.

6. Palliative therapy is indicated in advanced cases, it aims to relieve symptoms and improve quality of life. *Endoscopic prosthesis* – is used in inoperable antral tumors that cause gastric obstruction with evacuatory insufficiency. *Pain management* – it is mandatory for quality of life, it is done progressively, starting with common analgesics such asmetamizole (dipyrone), paracetamol, to opioid analgesics. *Enteral nutrition* – by placing a gastrostomy or jejunostomy, if oral feeding is not possible. This integrated approach gives patients the best chance of controlling the disease while improving their quality of life.

Prophylaxis and screening in the high-risk population

Gastric cancer screening is essential in regions with high incidence, such as East Asia. Upper digestive endoscopy is the primary method used for the early detection of

precancerous lesions or early gastric cancer. The populations that benefit the most from screening include people over 40-50 years old, especially in high-risk regions; patients with a history of severe atrophic gastritis or intestinal metaplasia; people with a family history of gastric cancer; patients with known Helicobacter pylori infection. Regular screening can significantly improve the prognosis, as it allows diagnosis in the early stages, when curative treatment is more effective.

Prophylactic measures include eradicating H.Pylori infection, stopping smoking, avoiding foods preserved by smoking, salting, a diet rich in greens, antioxidants.

To note

- Gastric cancer is a common neoplastic pathology, the fifth leading cause of cancer worldwide and the third leading cause of cancer death.
- Predisposing conditions include: atrophic gastritis, megaloblastic anemia, Barrett's esophagus, Zollinger-Ellison syndrome, gastric resection more than 10-15 years postoperatively, gastritis with giant Menetrier folds, gastric polyps, especially associated with dysplasia.
- The clinical picture at onset is often erased, with decreased appetite, selective meat intolerance, anemia, weight loss being major alarm signs.
- The positive diagnosis necessarily involves endoscopy with biopsy, as well as staging for optimal treatment.
- The treatment must be multidisciplinary, depending on the stage of the disease and the histological type, the ideal being the surgical resection associated with the oncological treatment

8. INFLAMMATORY BOWEL DISEASES

Definition

Inflammatory bowel diseases (IBD) are chronic conditions characterized by inflammation with an autoimmune mechanism in the gastrointestinal tract. The two major forms of IBD are ***Crohn's disease (CD)*** – which can affect any segment of the digestive tract and ***ulcerative colitis (UC)*** – in which inflammation affects the rectum and can extend proximally to the colon without going beyond the ileocecal valve.

In 10% of cases, the features of UC and CD overlap, the history of the disease, the endoscopic, histopathological and radiological appearance do not allow the differentiation between UC, CD or other forms of colitis (***indeterminate colitis***).

Microscopic colitis is another form of chronic inflammatory bowel disease in which the diagnosis is histopathologically established in patients with chronic watery diarrhea and normal colonoscopy (macroscopic absence of inflammation). Microsocpic colitis comprises two entities: *lymphocytic colitis* and *collagen colitis*.

Epidemiology

The incidence of IBD shows geographical variability, being increased in industrialized countries: Northern Europe, Great Britain and North America. In Romania, UC predominates in the north-eastern area, while in the south and west CD it is more frequent.

Both race and ethnicity influence the incidence and prevalence of IBD. Thus, in North America, the prevalence of CD is lower in the Hispanic and Asian races compared to the white race. Jews are more prone to IBD than other ethnic groups. The incidence increases with the migration of the population from low-risk areas to high-risk areas, and in terms of gender distribution, it is approximately equal, with a slight preponderance of males in UC.

The onset of IBD at a young age is associated with extensive and more aggressive forms of the disease compared to the disease that occurs in elderly patients, who, in general, are moderate forms of the disease, with few exacerbations and the need for surgery.

Etiopathogenesis

The etiopathogenesis of IBD is incompletely elucidated and involves the interaction of several cofactors: individual genetic predisposition, environmental factors and intestinal microbiota, with the initiation and maintenance of an abnormal host immune response.

1. Genetic factors. UC and CD are complex polygenic diseases, with a positive family history being the largest independent risk factor for developing IBD. Thus, up to 1 in 5 patients with CD and 1 in 6 patients with UC have first-degree relatives with IBD. The concordance rates for monozygotic twins and dizygotic twins for CD are 20-50% and 10%, respectively.

2. Shipping: Environmental and other risk factors are responsible for the increase in the prevalence of IBD in developed countries. Among them we mention the following:

- diet low in fiber and rich in processed foods, high in carbohydrates and fats, insufficient nutrition at the breast.

- *smoking* has a protective effect in the case of UC, unlike CD. Smoking, active or passive, seems to lead, through an incompletely elucidated mechanism, to milder forms of disease in UC, reducing the need for surgery. In CD, smoking plays a role in exacerbating the disease and increases the risk of recurrence after surgery.

- *the use of NSAIDs* is correlated with the onset of IBD but also with the periods of exacerbation.

- e*xcessive hygiene*, which limits the exposure of the intestine to antigens in childhood, is another risk factor.

- *psychological factors* such as chronic stress and depression, increase the risk of recurrence in patients with IBD in remission.

- *appendectomy* has a protective effect for UC, but not for CD.

3. The intestinal microbiota intervenes in the regulatory mechanisms that maintain the balance between the host's immunological tolerance and the permanent stimuli coming from the existing flora and its metabolic products. The individual gut microbiota is determined by genetic factors and external factors. In patients with IBD, it undergoes quantitative and qualitative changes, with a role in perpetuating inflammation. The possible mechanisms by which the intestinal microbiota intervenes in the etiopathogenesis of IBD are: intestinal dysbiosis (decrease and alteration of microbiota diversity); specific pathogenic organisms (Escherichia coli, Mycobacterium paratuberculosis - MAP); bacterial antigens; deficient chemical barrier or decrease of intestinal defensins (decrease α defensin-1) and impairment of mucosal barrier function.

4. Immunological factors – the intestinal immune system. The normal mucosal immune system has the ability to recognize immunogens to which it is tolerant and to reject others. This is achieved through a fine balance between pro-inflammatory and anti-inflammatory mechanisms. Intestinal epithelial cells have the ability to produce cytokines through the activation of macrophages. These pro-inflammatory cytokines are TNF alpha (tumor necrosing factor), inter-leukins IL-1, Il-6, IL-8, etc. Lymphocytes also participate in the immune mechanism.

Although the picture of the two conditions often resembles, sometimes even overlapping, however, they have quite a few differences and that is why we will treat them separately.

ULCERATIVE COLITIS (UC)

Definition

UC is an inflammatory bowel disease characterized by recurrent episodes of diarrhea with mucus and blood, alternating with periods of calm. The traditional term ulcerative *colitis* illustrates the extent of the disease (inflammation necessarily affects the rectum and can extend proximally to the colon to the level of the ileo-cecal valve), clinical and endoscopic aspects (rectal infections, ulcerations, presence of blood in the lumen). Currently, the term used in the literature is *ulcerative* colitis.

Pathology

Macroscopically, the recto-colonic mucosa is erythematous, bleeds slightly (it is friable), with superficial ulcerations, with the loss of the typical vascular design, covered with mucus and pus. The typical appearance is that of a "blood-crying mucosa". In chronic forms, the appearance of inflammatory pseudopolyps appears.

Microscopically, superficial inflammation limited to the mucosa, inflammatory infiltrate with polymorphonuclear membranes in the mucosa, the presence of cryptic abscesses, exulcerations, depletion of goblet cells is highlighted.

Clinical picture

The clinical picture in UC is correlated with the extent of the disease and the severity of inflammation, being dominated by *recta, diarrhea with mucus, blood and pus*. UC can start acutely, mimicking infectious enterocolitis, or insidiously. In the lower forms (proctitis), rectal bleeding can be the only symptom or can be associated with *rectal tenesma, proctalgia*, *urgency to defecation, up to fecal incontinence*. In extended forms, blood mixed with feces is associated with the emission of mucus and pus. Diarrhea is both diurnal and nocturnal, with over 6 emissions/24 hours in severe forms.

Abdominal pain is not characteristic of UC, but discomfort, embarrassment or abdominal cramps with localization in the lower abdomen may occur. The presence of intense abdominal pain usually means the appearance of a complication such as toxic megacolon or perforation.

General manifestations include asthenia, anorexia, weight loss, fever, chills, and growth delays occur in children.

Ecstatic manifestations can occur in both UC and CD, they can be concomitant, can precede or succeed the diagnosis of IBD. The main extraintestinal manifestations of IBD are summarized in Table 8.I.

The objective examination may be normal, possibly slightly relaxed abdomen and sensitive to palpation on the colic frame, meteorism, signs of associated extraintestinal manifestations. Rectal examination can be painful and highlights blood and mucus on the examining finger. In fulminant forms of UC, the abdomen is relaxed, painful on palpation,

with the abolition of hydro-air noises and systemic manifestations (tachycardia, tachypnea, hypotension, dehydration).

Table 8.I. Extraintestinal manifestations in patients with IBD.

Ocular manifestations	- Uveitis - episcleritis - scleritis
Joint manifestations – the most common	- arthropathy type I (pauciarticular) - arthropathy type II (polyarticular) - arthralgia - ankylosing spondylitis - sacroileitis - spinal inflammatory pain
Skin manifestations	- Erect nodes - Pyoderma gangrenosum
Hepato-biliary manifestations	- primary sclerosing cholangitis with evolution to cirrhosis of the liver - non-alcoholic fatty liver - chronic hepatitis - lithiasis
Thromboembolic manifestations	- venous thrombosis
Other cardiovascular, neurological, pulmonary, urogenital extraintestinal manifestations - rare	- ischemic heart disease, stroke, COPD, renal lithiasis, etc.

Biological picture

- *Biochemical* and hematological tests can highlight in patients in relapse the presence of iron deficiency anemia, with hypochromia and low sideremia, leukocytosis, thrombocytosis, hypoalbuminemia by loss, inflammatory syndrome present (increased C-reactive protein, increased ESR, increased fibrinogen).

- *Serological tests* may reveal positive anti-neutrophil cytoplasm (pANCA) perinuclear antibodies and negative anti-Saccharomyces cerevisiae (ASCA) antibodies.

- *Stool tests* are necessary to rule out an infectious cause. Thus, stool culture, testing for toxin A and B Clostridium difficile, stool examination will be performed. *Increased fecal calprotectin* expresses inflammation in the intestine and is also useful for monitoring treatment.

Paraclinic

- *Lower digestive endoscopy - colonoscopy with multiple biopsies of the mucosa* is useful for positive and differential diagnosis, appreciates the extent and activity of the disease, has a role in monitoring therapy, in the diagnosis of dysplasia and colorectal

cancer. *Typical for UC are the obligatory involvement of the rectum (recto-colitis) and the continuous nature of endoscopic lesions*. Therefore, by performing a simple rectoscopy, the diagnosis can be suggested macroscopically, and then it will be confirmed biooptically.

In the flare-up, the endoscopic appearance is typical of the mucosa that "cries blood". The mucosa is friable, with superficial ulcerations, with diffuse erythema, with loss of typical vascular design, covered by mucus and pus (Figure 8.1, 8.2).

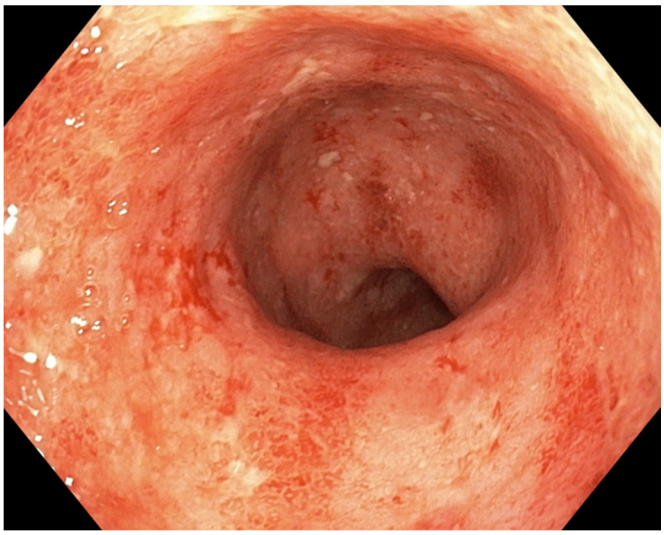


Figure 8.1. Endoscopic appearance in UC (diffuse erythema, superficial ulcerations, friable mucosa).

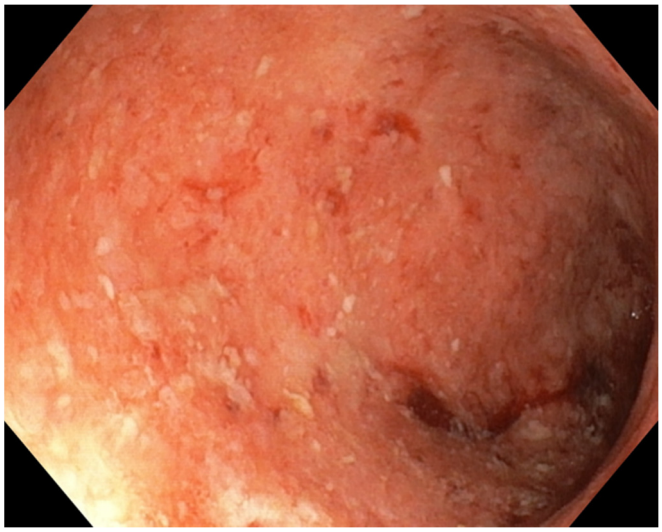


Figure 8.2. Endoscopic appearance in UC (diffuse erythema, superficial ulcerations, erased vascular drawing).

In chronic forms, the appearance of inflammatory pseudopolyps appears. During remission, the appearance is different, since the fragility of the mucosa is reduced,

possibly persisting bleeding when touched with the endoscope. The mucosa has a faded or absent vascular pattern, and pseudopolyps may be present.

Performing a total colonoscopy is mandatory for *the evaluation of the extension*. Often, in the face of a severe flare-up of colitis, we start the exploration with a simple rectoscopy, which makes the endoscopic diagnosis, and later, when there is a clinical improvement, we perform a total colonoscopy, to establish the exact extension, thus avoiding the increased risk of perforation in a severe UC.

- *Biopsy* of the recto-colonic mucosa is mandatory for diagnosis, demonstrating inflammatory infiltrate with polymorphonuclear limited to the mucosa, the presence of cryptic abscesses, exulcerations. The biopsy also allows the severity of the lesions to be assessed.

- *Transabdominal ultrasound* is useful in evaluating extension in the acute phase of the disease, when colonoscopy may have an increased risk of perforation. Normally, the colonic wall is a maximum of 3-4 mm on transabdominal ultrasound examination. The colon route will be followed by ultrasound and the length of the affected segment will be evaluated - colonic wall thicker than 5 mm (most often 7-10 mm thick) (Fig. 8.3), thus being able to appreciate the colonic extension quite well. However, the transabdominal ultrasound assessment of colon changes requires an ultrasound technician with good experience in this field.

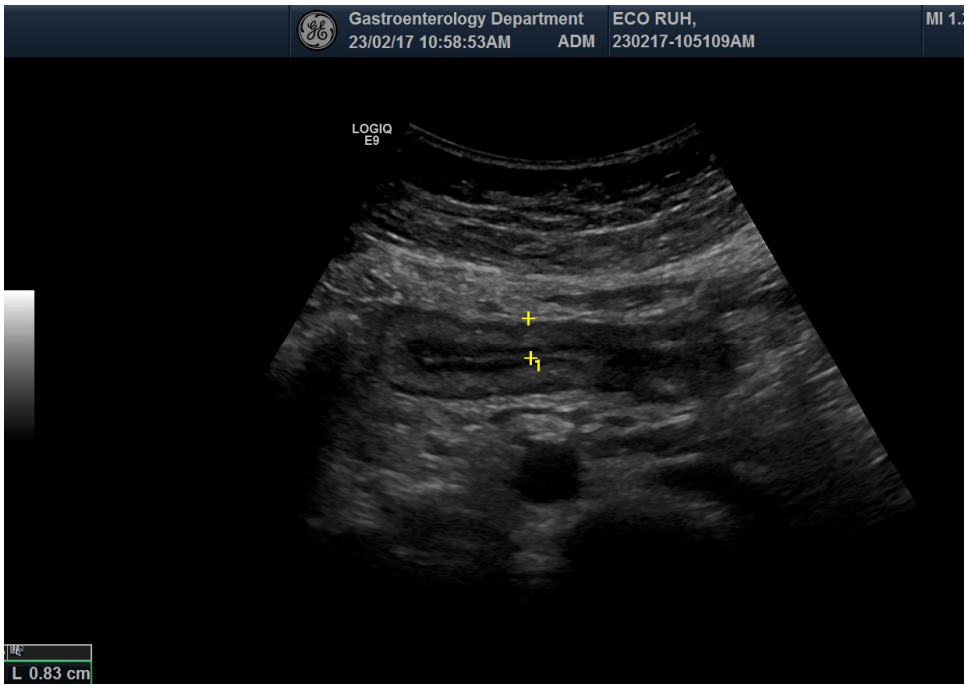


Fig. 8.3. Ulcerative colitis. Transabdominal ultrasound – descending colon with thickened wall.

- *Simple abdominal X-ray* highlights complications: perforation (pneumoperitoneum) and toxic megacolon (dilation of the lumen of the transverse colon over 6 cm). Barium enema has lost its usefulness in the diagnostic algorithm. In chronic forms, irrigography will reveal a granular appearance of the affected mucosa, inflammatory pseudopolyps, loss of normal colonic haustrations, with the appearance of a tubular appearance of the colon.

The positive diagnosis is made by corroborating the clinical data (diarrhea, rectaria, abdominal pain), with the biological data (inflammatory syndrome, anemia), colonoscopic and histological data. The positive diagnosis includes the clinical form, extent and severity of the disease.

1. Clinical forms.
- From a clinical-evolutionary ***point of view***, UC can present as
  - *Fulminant form* (severe acute flare-up lasting less than 6 months);
  - *Intermittent chronic form* (with acute episodes, against the background of almost complete or even complete remissions);
  - *The chronic form continues* (rarer, but increasing lately, in which the disease has no signs of remission).
  - An isolated flare-up, with definitive healing after treatment, without relapse.

- From the point of view of ***severity,*** the classification of the disease is made according to the number of stools and the intensity of clinical signs (Trulove - Witts classification - Table 8.II). Thus, mild, medium and severe forms are described.
- *the mild form* presents up to 4 stools/day, with only a little blood and mucus, the general condition is good, without fever or malnutrition, and the anemia is discreet;
- *moderate form*, with 4-6 stools/day, anemia, subfebrilities;
- *severe form* with more than 6 stools/day, fever over 38 degrees C, anemia and hypoalbuminemia, large amount of blood in the stool, poor general condition.

Table 8.II Trulove-Witts classification of UC by severity

Parameter/Shape	**Easy**	**moderate**	**Severe**
Daily bloody stools	<4	2-4, < 6	≥ 6
Pulse	< 90/min	≤ 90/min	> 90/min or
Temperature	< 37.5°C	≤37.8° C	> 37.8°C or
Hb	> 11.5 g%	≥ 10.5 g%	< 10.5 g% or
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h or
PCR	Normal	≤30 mg/L	> 30 mg/L

- After ***localization***, there are several forms:
  - *proctitis or proctosigmoiditis* (rectal or rectosigmoid localization);
  - *left colitis* (damage up to the splenic angle);
  - *extensive colitis* that includes *pancolitis* (damage to the entire colon). In pancolitis, some patients may experience *reflux ileitis ("backwash ileitis")* by expanding inflammation in the cecum.

Differential diagnosis will be made with the following pathologies:

- *Crohn's disease,* in which the clinical picture is dominated by diarrhea and abdominal pain, weight loss, abscesses, fistulas, stenosis. Endoscopically, the lesions are discontinuous and can affect any segment of the digestive tract. Histologically, the inflammation is transmural and is characterized by lymphocytic infiltrate and granulomas.

- *bacterial dysentery or other infectious colitis* (Salmonella, Shigella, Entamoeba histolitica, Campylobacter, etc.) the diagnosis is established by stool culture, immuno-enzymatic techniques, mucosal biopsy, etc. *Clostridium difficile infection (pseudomembranous colitis)* is frequently associated and should be excluded in any outbreak of activity. The diagnosis is made by highlighting the Clostridium toxin in the stool exam. Treatment is done first-line with Metronidazole, and in case of failure with oral vancomycin (7-10 days). There are also fatal cases in patients with severe co-morbidities. In cases with relapse, there is an indication for fecal transplantation, which would reduce the risks of recurrence. Any exacerbation of the disease under immunosuppressive treatment requires exclusion *of cytomegalovirus infection* (histopathological examination).

- *Colorectal cancer* is excluded by colonoscopy with biopsy and histopathological examination.

- *ischemic colitis* – endoscopic and biotic diagnosis (segmental localization, usually in the descending colon), in an elderly patient with associated atherosclerotic pathology.

- *irradiation colitis* – history of therapeutic abdominal irradiation.

- *microscopic colitis (collagen or lymphocyte)* – watery diarrhea (but without blood emission), in which the endoscopic appearance is normal, but the biopsy will reveal the presence of a submucosal collagen band or a rich lymphocyte infiltrate.

- *indeterminate colitis* – an inflammatory bowel disease in which we cannot specify from the beginning whether it is CD or UC.

- *irritable bowel syndrome* - does not present recta, weight loss, and the biological and colonoscopic picture is normal.

Complications

- *toxic megacolon* or acute toxic dilation of the colon - usually occurs in severe, pancolic forms (empty abdominal X-ray highlights the dilated colon over 6 cm in the context of signs of systemic toxicity – fever, tachycardia, leukocytosis, hypotension, hydro-electrolyte disorders).

- *colonic perforation* with a clinical picture of acute abdomen, abdominal radiography or computed tomography highlights pneumoperitoneum.

- *massive lower digestive hemorrhage* with severe anemia;

- *intestinal stenosis* - rare, generally in chronic forms with a long evolution;

- *colorectal cancer* – patients with UC have an increased risk of developing cancer, usually after an evolution of more than 10 years, especially in pancolic forms.

Evolution and prognosis

The evolution of UC is in the form of episodes of exacerbation, of variable duration, usually weeks or months, followed by remission. There are several criteria for assessing the severity of the disease, in current practice the most often used is the Truelove-Witts score (Table 8.II). The mortality of UC patients is similar to the general population, except for those with severe colitis or over 60 years of age at the time of diagnosis. The risk of colorectal cancer is 2 times higher compared to the general population.

Treatment

The goal of treatment in IBD is to induce and maintain clinical remission.

1. Hygienic-dietary regimen. The diet in the flare-up will be one of digestive sparing, avoiding milk and dairy products (cream, fermented cheeses), raw vegetables and fruits, concentrated sweets. In particularly severe flare-ups, parenteral nutrition can be used for a few days.

2. Drug treatment includes the following classes of medicinal products:

- *Aminosalicylates* have an anti-inflammatory effect, being used in inducing and maintaining remission in UC. The preparations are Salazopyrin and Mesalazine (the latter being the active metabolite of the former, non-sulfated 5-ASA preparation - Salofalk, Pentase, Asacol), available in the form of 500 mg tablets or topical preparations (suppositories, enemas) for the treatment of distal forms. The dose is 3-4 g/day, minimum 6 months.

- *Corticosteroids* (prednisone, medrol for p.o. administration; solumedrol, dexamethasone, hydrocortisone for IV administration; enemas and foams for rectal administration) have multiple anti-inflammatory and immunosuppressive effects. Prednisone is usually administered in doses of 40-60 mg/day (depending on gender, body weight, flare-up intensity). After 4-6 weeks, the doses are decreased by approximately 5-10mg/week, so that after a few weeks, after achieving remission, corticosteroid therapy can be interrupted. Corticosteroids cannot be used as a maintenance treatment due to multiple side effects (Cushing's sd., acne, hirsutism, high blood pressure, diabetes, osteoporosis, osteonecrosis, cataracts, psychosis, obesity).

- *Immunomodulators* are used to maintain corticosteroid-induced remission. The therapeutic effect sets in slowly (after 1-4 months). *Azathioprine* (Imuran) is the preparation of choice, but it has adverse effects (bone marrow suppression, hepatitis,

acute pancreatitis, nausea, vomiting, diarrhea, flu-like symptoms), which is why it is necessary to monitor liver and pancreatic tests and blood count during treatment. *Ciclosporine* may be recommended in severe UC.

- *Biological therapy* has a role in inducing and maintaining remission, as well as in the treatment of extraintestinal manifestations. Basically, biological therapy has revolutionized the treatment of IBD, both in UC and CD. The main side effects of anti-TNF therapy are: allergic reactions, infections, and sepsis. Biological agents are represented by:

- Anti TNF agent class: with representatives *Infliximab* (administered as an intravenous infusion, with an induction dose of 5 mg/kgc at week 0, 2, 6, subsequently the same dose for maintenance, but administered at 8 weeks) and *Adalimumab* (with subcutaneous administration, the induction dose being 160 mg at week 0; 80 mg at week 2 and maintenance treatment at a dose of 40 mg s.c. at 2 weeks).
- Anti-integrin antibody class: with the representative *Vedolizumab*, 300 mg is administered ivly, for induction at 0, 2 and 6 weeks, then 300 mg every 8 weeks, as maintenance treatment.
- Januskinase inhibitor class: with the representative *of Tofaticinib*, administered orally, being used in UC for induction treatment at a dose of 10 mg x 2/day at week 0-8 and for maintaining remission at a dose of 5 mg x 2/day. Newer generations are *Upacitinib, Filgotinib***.**
- Interleukin antagonist monoclonal antibody class 12 and 23: with the representative *Ustekinumab*, which has the same indications as the rest of the biological therapies, the induction dose being 260-520 mg depending on body weight, the maintenance dose being 90 mg s.c at 8 weeks. Newer generations are *Risankizumab, Mirikizumab***.**
- Inhibitor of the intracellular adhesion molecule-1: *Alicaforsen*.
- Oral sphingolipase 1-phosphate receptor agonist: *Ozanimod***.**
- Biosimilars are drugs with safety, composition and efficacy similar to the original biologic product, but at a lower cost, which increases patients' access to therapy.

3. Treatment according to extension and activity

Treatment in UC is done depending on the location: proctitis, procto-sigmoiditis, left colitis, pancolitis (extensive colitis), and the activity of the disease.

Proctitis (strictly rectal localization), suppositories with 5-ASA (mesalazine) are the first-line treatment, 5-ASA preparations per bone can also be added to increase the rate of remission.

Left colitis (maximum extension to the level of the splenic angle), local treatment with suppositories, foam or microenemas with salazopyrine or 5-AS) or with a topical corticosteroid (Budesonide) to which 5-ASA per bone is also associated.

Pancolitis - treatment with Mesalazine (5-ASA) 3-4 g/day or Salazopirine 4-6 g/day is administered, enemas with 5-ASA may also be associated.

In severe flare-ups, parenteral nutrition begins, with hydro-electrolyte rebalancing, with corticosteroid therapy as an attack treatment, usually administered i.v., in doses of 250-500 mg hydrocortisone hemisuccinate/day (then oral Prednisone, maximum 1 mg/kg body/day, which is maintained until clinical remission, usually 4 weeks, then with progressive decrease by 5-10 mg/week). Heparin with low molecular weight s.c. should be associated for the prophylaxis of thromboembolism. *In toxicoseptic forms* , antibiotic therapy is added, especially for anaerobes (Metronidazole). In *severe forms*, which after 3-5 days of treatment *do not respond* to the previous measures, biological rescue therapy is administered with Infliximab at a dose of 5 mg kg/body at 0, 2 and 6 weeks, this treatment acts quickly and can save the patient from possible surgery. There is also an alternative immunosuppressive treatment with Ciclosporin 2-4 mg/kg iv., subsequently p.o. 5-7 mg/kgc.

4. Surgical treatment can be *emergency* (in case of complications) or *elective* (in cases not controlled with drug therapy or in those with dysplasia or colorectal cancer). Indications for emergency surgery are: toxic megacolon, perforation or therapeutically uncontrolled bleeding. The most commonly used surgical techniques are total proctocolectomy with permanent ileostomy and total proctocolectomy with ileoanastomosis and the creation of an ileal reservoir (pouch) - the preferred technique. Up to 50% of patients develop postoperative complications of the ileal reservoir (pouchitis), requiring therapy with antibiotics, corticosteroids, anti-TNF.

CROHN'S DISEASE (CD)

Definition

Crohn's disease (CD) is an IBD characterized by persistent or recurrent chronic inflammation that can affect any segment of the gastrointestinal tract, the most common location being at the level of the terminal ileum (ileitis) and colon (ileo-colitis). Inflammation in CD has a segmental ("jumped"), asymmetrical (lesions are not circumferential) and transmural (affects all layers of the intestinal wall) distribution and can extend to peri-intestinal tissues and satellite lymph nodes). Thus, CD evolves with intestinal complications such as intestinal stenosis or fistulas between the intestine and neighboring organs (entero-enteral, entero-bladder, entero-vaginal, etc.)

Pathology

Macroscopic - the typical changes are segmental inflammation, aphthoid ulcers and deep ulcers, of various shapes and sizes, most commonly interconnected, longitudinal and serpentine, which can form with the surrounding edematous mucosa the typical appearance of "paving stone". Edema, erythema, spontaneous bleeding and when touched with the endoscope, inflammatory pseudopolyps can be found in both CD and UC.

Microscopically, transmural inflammation with discontinuous distribution, focal distribution of chronic inflammation, with lymphoid hyperplasia, in 50-60% of cases granulomas are present – non-caseifying aggregates of epithelioid cells and Langhans cells.

Clinical picture

The clinical picture may sometimes be erased or absent, and at other times it may be suggestive of the disease. Typical clinical signs are:

- *digestive* – including diarrhea, abdominal pain, malabsorption syndrome (in neglected forms), perianal lesions (often languorous perianal fistulas, typical for this disease).

- *extradigestive* - fever or subfebrilities, asthenia, weight loss (sometimes important), arthritis, erythema nodosum, uveitis, etc

CD may begin insidiously or acutely, sometimes as an emergency with significant acute pain in the right iliac fossa, mimicking appendicitis.

On *physical examination*, dehydration, malnutrition, skin pallor (a sign of anemia), subfebrile/febrile state, the presence of palpable abdominal masses, usually in the right iliac fossa, can be detected. Over 30% of patients have perianal manifestations of CD (skin tag, fissures, fistulas, abscesses) which is why it is absolutely necessary to examine the perianal region. The clinical picture can be completed by the presence of extraintestinal manifestations (Table 8.I).

Biological picture

- *Biochemical and hematological tests* may reveal the presence of chronic normochromic normocytic anemia, or iron and/or folate deficiency, megaloblastic anemia due to vitamin B12 deficiency being rare. Inflammatory syndrome with increased CRP, ESR, Fibrinogen, leukocytosis and thrombocytosis. Hypoalbuminemia, increased hepatic transaminases, can also be detected.

- *Serological tests* may reveal negative anti-neutrophilic cytoplasm (pANCA) perinuclear antibodies and positive anti-Saccharomyces cerevisiae (ASCA) antibodies.

- *Stool tests* are necessary to rule out an infectious cause. Thus, stool culture, testing for toxin A and B Clostridium difficile, stool examination will be performed**.** *Increased fecal calprotectin* expresses inflammation in the intestine and is also useful in monitoring treatment.

Paraclinic

- *Lower digestive endoscopy - total colonoscopy with ileoscopy* and sampling of multiple biopsies from the rectal, colonic and terminal ileum mucosa. Aphthoid lesions, deep, linear ulcers, appearance of the mucosa in "paving stone" can be detected (ulcers in the inflamed mucosa will divide it, making it look like paving stones, with the presence of areas of inflammatory stenosis). These lesions can be found in the terminal ileum, colon, but also in the esophagus or duodenum.

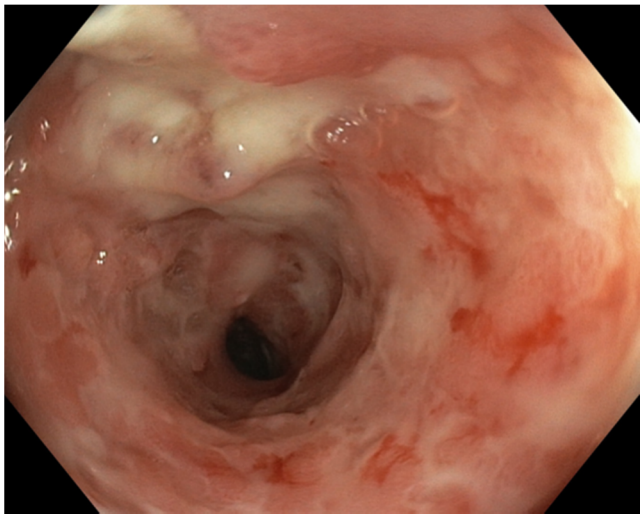


Figure 8.4. Colonic CD. Endoscopic appearance (deep ulcers, edema, stenosis).

- *Upper digestive endoscopy* is necessary to rule out esophageal or gastro-duodenal involvement.

- *The biopsy* is mandatory, revealing the transmural inflammatory aspect (especially the appearance in the UC) of the granulomatous type. The presence of deep ulcers, fibrosis, fistulas is the rule.

- *Radiological examination, less* faithful, is useful where endoscopy is not accessible. Ileal reflux irrigography, or enteroclysma (administration of barium through the duodenal probe) can be used to demonstrate lesions of the terminal ileum, or even passage barium, with follow-up at 1,2,3 and 4 hours. The pathological appearance of "paving stones" in the terminal ileum, the presence of areas of stenosis and overlying dilation, the presence of fistulas, are characteristic of CD.

- *Transabdominal ultrasound* will reveal the thickening of the intestinal wall in the area of inflammation (Fig. 8.5), thus being able to assess the extent of the affected area. The areas of stenosis and dilation, the presence of possible complications, such as perforation, fistulas, can be evaluated. It requires a dedicated examiner with experience in the field of digestive ultrasound.

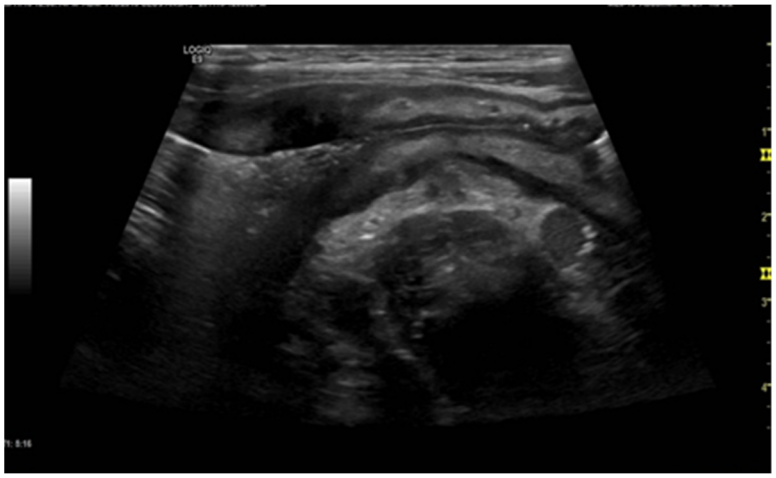


Figure 8.5. Crohn's disease. Transabdominal ultrasound - terminal ileum with thickened wall and adjacent adenopathies.

- *EnteroCT or EnteroMRI* are modern methods that highlight jejuno-ileal involvement, by demonstrating localized parietal thickening and periluminal changes.

- *Perianal MRI or transrectal ultrasound* to assess the existence and trajectory of possible perianal fistulas.

- *The endoscopic video capsule* is a non-invasive method reserved for cases in which endoscopic exploration of the stomach and duodenum, as well as the colon, are negative, but there are typical symptoms of CD or radiological changes. The use of the endoscopic capsule is not indicated in the suspicion of digestive stenosis, due to the risk of its impact. The enterocapsule can reveal small lesions in otherwise unexplored areas of the small intestine.

The positive diagnosis of CD is based on clinical, radiological (imaging), biological, endoscopic and histological criteria. Genetic or serological tests can support the diagnosis, but are not recommended in routine clinical practice. The complete diagnosis of CD must include the location of the disease, the severity of the inflammatory flare-up, the clinical-pathological form and the presence of complications.

- In relation to the *location*, the following topographic forms of CD are described*: ileo-colonic* (about 40% of cases), ileal - located strictly in the small intestine (30%), *colonic* - located strictly in the colon (25%), located in the upper digestive tract (oro-esophagogue-gastro-duodenal – about 8% of cases). Approximately 1/3 of patients have associated perianal CD.

- *The staging of the disease* takes into account several parameters, through the sum of which the disease activity score is made: CDAI (Crohn Disease Activity Index – Table 8.III). These parameters are: number of stools/day, presence of abdominal pain, general condition, extradigestive symptoms (fever, arthritis, uveitis, skin damage, fistulas/ fissures/abscesses), use of antidiarrheals, palpation of an abdominal mass, hematocrit value and weight loss in relation to ideal weight. Based on the CDAI, the severity of a flare-up is assessed, with values above 450 suggesting a severe flare-up, between 220 and 450 for moderate to severe disease, between 150 and 220 for mild disease, and below 150 for remission of the disease. For staging, the Best score can also be calculated.

Table 8. III. Crohn's Disease Activity Index (CDAI)

Variable	Description	Multiplication Factor
Number of liquid stools per 7 days	Total number of diarrheal stools in the last 7 days	x2
Abdominal pain (7-day daily average)	**0** = Painless **1** = Easy **2** = Moderate **3** = Severe	x5
Overall health (7-day daily average)	**0** = Very good **1** = Good **2** = Satisfactory **3** = Evil **4** = Very bad	x7
Complications (1 point per complication)	1. Arthritis/arthralgia 2. Uveitis/irritis 3. Erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis 4. Fistulas, fissures, perianal abscesses, other fistulas 5. Fever (over 37.8, over 7 days)	x20
Opioid treatment for diarrhea	**0** = No **1** = Yes	x30
Presence of palpable abdominal mass	**0** = No **2** = possible; **5** = defined	x10
Hematocrit (%)	Difference from the standard value of 47% for men and 42% for women	x6
Body weight	Percentage of body weight deviation from standard weight	x1
CDAI Total Score		

- *The Montreal (Vienna) classification* of Crohn's disease takes into account age of onset (age - A), location of lesions (L), and disease behavior (behaviour - B):

A (Age at diagnosis):

A1 < 16 years old
A2 17-40 years old
A3 >40 years old

L (Rental):

L1 terminal ileum
L2 colon
L3 concomitant ileocolon
L4 disease isolated in the upper digestive tract

B (Behavior):

B1 non-stenosing, non-penetrating form
B2 stenosing form
B3 penetrating, fistulizing form.
P – perianal manifestations

Differential diagnosis will be made with the following pathologies:

- *ulcerative colitis (UC)* - bloody diarrhea predominates in the clinical picture; endoscopically the inflammation necessarily affects the rectum and can extend proximally to the colon, the lesions are continuous, and histopathological the inflammation is limited to the mucosa, with the presence of cryptic abscesses, etc.

- *infectious colitis/enterocolitis* (Salmonella, Shigella, Entamoeba histolitica, Campylobacter, etc.) the diagnosis is established by stool culture, immunoenzymatic techniques, mucosal biopsy, etc. Clostridium difficile infection (pseudomembranous colitis) is frequently associated and should be excluded at any outbreak of activity. The diagnosis is made by stool examination, highlighting the Clostridium toxin. Cytomegalovirus infection (serological tests and relevant histopathological examination).

- *Colorectal cancer* is excluded by colonoscopy with biopsy and histopathological examination.

- *ischemic colitis* – endoscopic and biopsy diagnosis (segmental localization, usually in the descending colon), in an elderly patient with associated atherosclerotic pathology.

- *irradiation colitis* – history of therapeutic abdominal irradiation;

- *microscopic colitis* (collagen or lymphocyte) – watery diarrhea (but without blood emission), in which the endoscopic appearance is normal, but the biopsy will reveal the presence of a submucosal collagen band or a rich lymphocyte infiltrate;

- *indeterminate colitis* – an inflammatory bowel disease in which we cannot specify from the beginning whether it is CD or UC.

- *acute appendicitis* – clinical picture of acute abdomen, surgical emergency.

- *intestinal tuberculosis* - fever, weight loss, night sweats, positive Quantiferon TB test, positive epidemiological context, associated pulmonary or peritoneal manifestations, histopathological caseous granuloma, AFB present.

- *irritable bowel syndrome* - normal blood inflammatory samples, normal fecal calprotectin, absence of endoscopic lesions.

- *celiac disease* - positive serology (anti-gliadin needle, anti-transglutaminase needle), duodenal biopsy with villous atrophy, absence of ileocolonic inflammatory lesions.

Complications

Complications are a rule of the disease, being represented by intestinal stenosis, internal fistulas (entero-enteral, entero-colonic, entero-vesical, entero-vaginal) or external fistulas (entero-cutaneous), perforation, formation of perilesional abscesses, neoplastic – colorectal cancer, toxic megacolon (empty abdominal X-ray highlights the dilated colon over 6 cm in the context of signs of systemic toxicity – fever, tachycardia, leukocytosis, hypotension, hypotension, disorders hydro-electrolytes), bone complications - osteopenia or osteoporosis, thromboembolic complications - deep vein thrombosis, pulmonary thromboembolism.

Evolution and prognosis

The evolution of CD is characterized by periods of activity, alternating with periods of clinical remission. The localization of CD tends to remain stable, but clinical behavior changes throughout evolution, from uncomplicated inflammatory forms to stenostic, fistulizing and penetrating forms. About 50% of patients require surgery after 5 years of disease progression. Risk factors associated with an unfavorable prognosis are: ileal/ileo-colic localization, extensive involvement of the small intestine, severe forms, rectal involvement, perianal lesions, stenostic or penetrating forms at onset, young age at diagnosis (< 20 years) and smoking.

Treatment

Treatment in CD aims at rapid induction and maintenance of deep remission (clinical and endoscopic), mucosal healing, prevention of complications and hospitalization, avoiding surgery and increasing quality of life.

1. Hygienic-dietary regimen. The diet in the flare-up will be one of digestive sparing, with the avoidance of milk and dairy products, raw vegetables and fruits, concentrated sweets. In moderate-severe forms, parenteral nutrition can be used for a few days or enteral nutrition (more often in pediatric patients).

2. Drug treatment.

In ***the acute phase*** of the disease, start with *Prednisone or Prednisolone*, possibly *Hydrocortisone hemisuccinate* if necessary i.v., at a dose of approx. 30-60 mg/day. After the remission of symptoms, usually after one month, the dose is lowered by 5 mg/week, so that it reaches approx. 10-15 mg/day after 6-10 weeks of treatment. Consolidation of attack treatment with Prednisone is continued with *azathioprine* (Imuran) 2.5mg/kgbody/day for a long time. Other immunosuppressive preparations for maintenance therapy are *Mercaptopurine* at a dose of 1.5 mg/kg/day or *Methotrexate* (25 mg 1x/week until remission and then dose reduction to 15 mg/week). In colonic locations it can be associated with *Mesalazine* 2-3 g/day. ***Chronic treatment*** of CD will be performed with *Imuran* (azathioprine) 2.5mg/kg body weight/day, over a long period. Imuran is started with corticosteroid therapy, as azathioprine starts to work after 4-8 weeks.

The emergence of a new topical corticosteroid (*Budesonide*) with minimal systemic effects has brought therapeutic improvements. It is administered in ileal or ileo-colonic forms. The attack dose is 9 mg/day (Budenofalk or Entocort preparations), with the attack treatment being administered for a maximum of 2 months.

Basically, in the acute flare-up of the disease, we start therapy with an oral corticosteroid (Prednisone or Budesonide), and maintenance therapy is done with Imuran (100-150 mg/day), which is administered for years.

In ***severe forms*** of CD, especially fistulizing ones, the following may be indicated for treatment:

- *Anti-TNF medication,* the available preparations are: *Infliximab,* the induction dose being 5 mg/kgc at week 0, 2, 6, then the same dose for maintenance, but administered at 8 weeks, on a long-term *basis. Adalimumab* induction dose is 160 mg at week 0, 80 mg at week 2 and maintenance dose at 40 mg s.c. at 2 weeks.

- *Anti-integrin monoclonal antibodies: Vedolizumab* which is administered for induction 300 mg i.v. at 0, 2 and 6 weeks, then as maintenance the dose of 300 mg at an interval of 8 weeks.

- *Monoclonal antibodies directed against interleukins 12 and 23: Ustekinumab,* induction dose 260 mg - 520 mg depending on body weight, maintenance dose 90 mg s.c at 8 weeks.

Recent preliminary studies have shown promising results for new preparations in the treatment of moderate-severe active CD:

- *Monoclonal antibody directed against the p19 unit of interleukin 23 : Risankizumab*

- *Mongersen oral anti-sense oligonucleotide*

- *Janus Kinase inhibitors,* oral administration: *Upacitinib, Filgotinib*.

The control of diarrhea can be done in the short term with imodium or codeine.

3. Surgical treatment is especially aimed *at complications*, such as segmental stenosis or perforations, or forms that are not responsive to drug therapy. Interventions can be segmental resections with anastomosis or, more rarely, colectomy with ileo-rectal anastomosis or panproctocolectomy with ileostomy (in severe relapsing and disabling forms). Sometimes endoscopic procedures for recalibration of stenosis (balloon dilation, stricturoplasty) can be tried. After segmental resections, prolonged therapy with Mesalazine or Imuran can prevent relapses or reverse flare-ups. Maintenance immunosuppressive therapy is indicated in patients at high risk of relapse (previous surgery, smokers, penetrating disease at the time of the first intervention).

4. Basically, at present, there are two therapeutic strategies:

-*"Step up"* consists of starting corticosteroid therapy, followed by immunosuppression, and in case of failure (corticoresistance) or corticodependence, switching to anti-TNF therapy (Infliximab or Adalimumab). On the other hand, important clinical studies have shown that the combination of anti-TNF with Imuran has superior results compared to monotherapy. Infliximab is given as IV infusions, while adalimumab is given subcutaneously. It starts with an attack therapy and then maintenance.

-*"Step down"* consists of starting anti-TNF therapy, and maintenance can be done with anti-TNF + Imuran medication, chronically. The advantage of antiTNF therapy is "mucosal healing", which is a new standard of therapy in Crohn's disease.

Before starting antiTNF therapy, previous exposure to tuberculosis or viral hepatitis B should be sought, and there is a risk of reactivation of these conditions under therapy.

In about 5-10% of cases, the differential diagnosis between RUH and CD is difficult ("indeterminate colitis"), in which the disease has clinical and endoscopic elements of both entities.

To note

- Inflammatory bowel diseases (IBD) are chronic conditions characterized by inflammation with an autoimmune mechanism in the gastrointestinal tract. The main forms are ulcerative colitis (UC) and Crohn's disease (CD).

- UC always affects the rectum and can extend proximally to the level of the cecum. The clinical picture includes diarrhea with blood, mucus and pus. Endoscopic lesions are continuous, consisting of superficial ulcers, mucous membrane slightly bleeding to the touch. Microsocpic superficial ulcers and cryptic abscesses are typical. A severe complication is toxic megacolon.

- CD can affect any segment of the digestive tract, the most common being damage to the terminal ileum and colon. The clinical picture includes chronic diarrhea (with blood if the rectum is affected), abdominal pain. Endoscopic lesions are discontinuous and consist of aphthoid ulcers or deep longitudinal or serpiginous ulcers that achieve the appearance of paving stone. Microscopically, deep transmural ulcers are

present, with lymphoid infiltrate and in about 50% of cases with the presence of specific granulomas - non-caseifying aggregates of epitheloid cells and Langhans cells. Complications of CD are common and include stenosis and fistulas.

- In the biological picture of IBD, signs of inflammation are present (CRP, fibrinogen, increased ESR), iron deficiency anemia. Fecal calprotectin is used to highlight intestinal inflammation and to follow the evolution under treatment.

- The positive and differential diagnosis is based on the clinical, endoscopic and microscopic picture specific to each one, in up to 10% of cases it is not possible to differentiate between UC and CD.

- Treatment in IBD is done according to the location and severity of the disease and is based on corticosteroid therapy (as an attack treatment, with a decrease in doses after remission of the clinical picture) and immunomodulatory treatment as a long-term maintenance therapy, especially in CD (based on either azathioprine or biological agents).

9. COLORECTAL CANCER

Definition

Colorectal cancer (CRC) is a type of cancer that begins in the colon or rectum and is a public health problem due to its high incidence and mortality among the population. It usually develops by abnormal growth of cells in the lining of the colon or rectum, often starting from non-cancerous polyps. Over time, some polyps can degenerate malignantly if they are not detected or treated early.

Epidemiology

Colorectal cancer is the third most common cancer globally, accounting for 10% of all cancers, with approximately 1.93 million new cases and 935,000 deaths reported in 2020 according to GLOBOCAN - part of the World Health Organization that deals with cancer analysis. It disproportionately affects men (M/F ratio 2:1), with most cases being diagnosed after the age of 50. However, the incidence of "early-onset" CRC (under 50 years of age) is increasing in developed countries, which has led some countries (USA, Canada) to recommend screening from the age of 45.

In Romania, CCR accounts for 13% of all cancer cases, ranking first in the general population (12,938 cases annually). In women, it is the second most common cancer, after breast cancer, and in men, it ranks third after lung and prostate cancer. Mortality data, based on GLOBOCAN 2020, reported 6,767 deaths related to CRC, making it the second leading cause of cancer death in Romania, after lung cancer. Future projections estimate an increase of more than 1,600 new cases and 1,300 deaths annually by 2040.

Most colorectal cancers develop on the left side of the colon, in the area of the sigmoid and rectum. However, recent studies indicate a slow increase in the number of lesions located in the right colon. Synchronous tumors (occurring simultaneously) are present in 5% of patients, while 3-5% develop metachronous tumors (a second tumor appears after the resection of the initial one). The maximum incidence of colon cancers is around the age of 70. The increase in incidence begins in the fourth decade of life, and 90% of colorectal cancer cases occur after the age of 50.

The peculiarity of this type of cancer is that it is, to a large extent, preventable, because at present the polyp-tumor sequentiality is clearly established, so the active endoscopic detection of polyps and their removal will prevent the appearance of colorectal cancer. The role of the genetic factor (e.g. Lynch syndrome) in the occurrence of colon neoplasia is also known.

Pathophysiology

Most colorectal cancers (Fig. 9.1) develop sporadically, without being associated with a known genetic mutation. However, the involvement of several factors in the

pathogenesis of colon neoplasm is clearly defined, namely dietary factors, the (questionable) role of bile acids, predisposing states. Etiological theories mainly focus on the role of intraluminal chemical carcinogenesis. These theories suggest that carcinogens either originate from ingested food or result from biochemical processes that take place in the intestinal lumen.

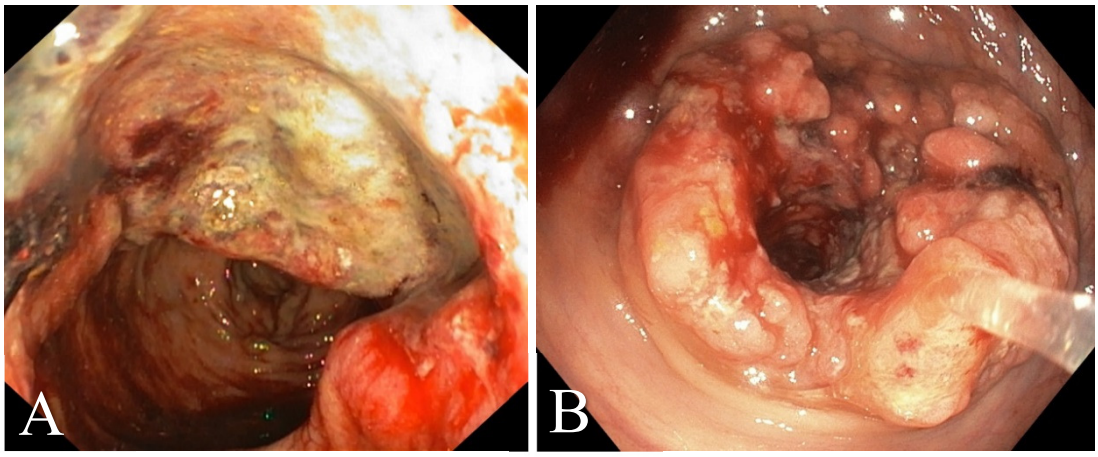


Fig. 9.1. A- *Tumor* (adenocarcinoma) of the sigmo*id colon*, with ulcer-vegetative appearance. B- Descending colon tumor, partially stenosing.

Geographical epidemiological studies indicate that certain populations have a very low incidence of colon and rectal cancer, probably due to the presence of beneficial dietary factors (e.g. high fibre and low fat). However, the influences of social habits and the lack of exposure to environmental carcinogens cannot be excluded. Public health programs often recommend a low-fat, high-fiber diet as a protective measure against colorectal cancer. There is also evidence to suggest that certain antioxidants, prostaglandin inhibitors, or some nonsteroidal anti-inflammatory drugs (NSAIDs), when taken regularly, can significantly reduce the risk of adenomatous polyps and colon cancer.

Risk factors for the occurrence of CRC are:

1. Dietary factors - epidemiological studies seem to demonstrate the involvement of dietary factors in favoring carcinogenesis: excess animal fats and proteins, red meat, alcohol, smoking and excessive caloric intake.

2. Bile acids – are considered a potential risk factor for the development of CRC. Studies have demonstrated a complex relationship between bile acids, the gut microbiota, and the colorectal epithelium, which may contribute to carcinogenesis under certain conditions.

3. Predisposing factors for CRC are considered to be colorectal polyps, familial colonic polyposis, inflammatory diseases of the colon (ulcerative colitis and Crohn's disease with long evolution and colonic involvement), family history of cancer or colonic polyps (familial predisposition), Lynch syndrome.

- Colorectal polyps are frequently encountered in gastroenterological practice, so that almost 25% of people over 50 years of age and up to 30% of people over 70 years of age have colonic polyps (Fig. 9.2, Fig. 9.3).

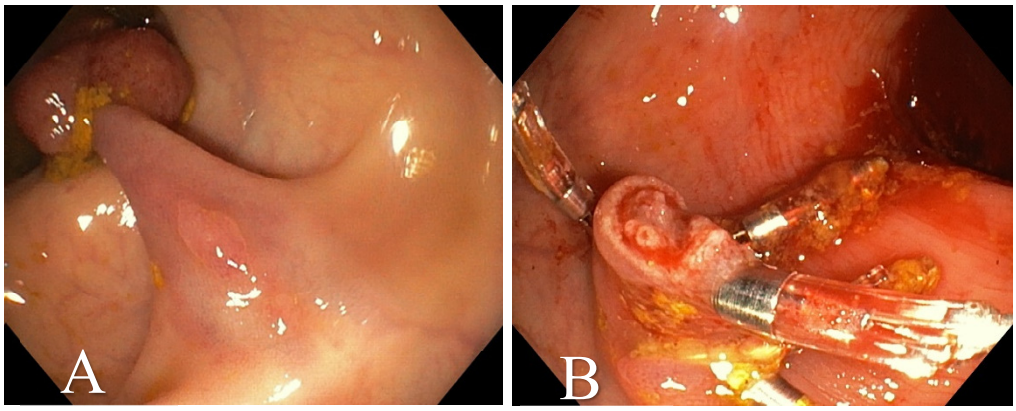


Figure 9.2. Pedunculated polyp at the level of the descending colon (A), in which polypectomy and endoscopic hemostasis with hemoclips at the level of the remaining stump (B) were performed.

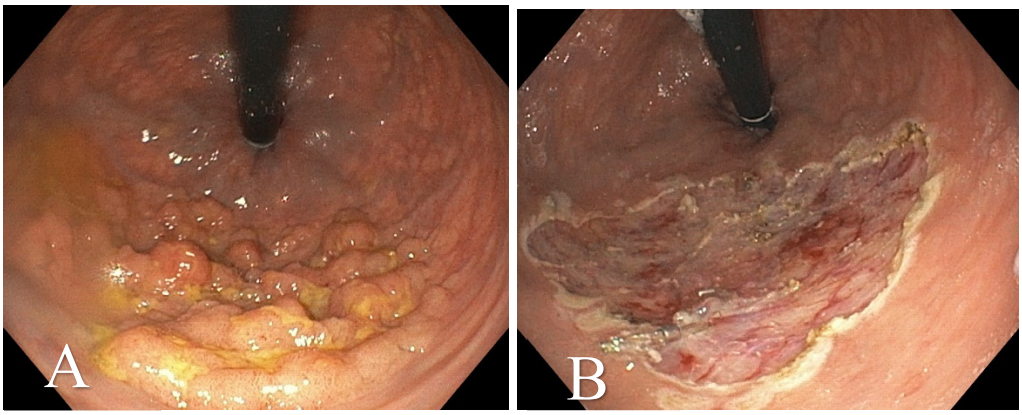


Figure 9.3. A - Sessile polyp with a granular appearance (adenoma) at the level of the rectum, visualized in retrospect. B - Post-endoscopic resection appearance.

Polyps are most commonly adenomatous (adenomas) or hyperplastic (Table 9.I). Adenomatous polyps (true polyps) are of several histological types: tubular, tubulo-villous and villous. The greatest potential for malignancy is in villous polyps, and the lowest in tubular polyps. Hyperplastic (inflammatory) polyps have no malignant potential.

The evolution of polyps towards malignancy seems to be related to genetic (familial), metabolic (the co-carcinogenic effect of bile acids) and dietary factors (the negative effect of the lack of greens and fibers). Polyps have a higher malignant risk, the larger they are (generally over 2 cm in diameter), the more numerous they are, and the more severe dysplasia they have at the biopsy. Starting from these premises regarding the polyp-neoplasm relationship, it is necessary to discover polyps by colonoscopy,

followed by endoscopic polypectomy (Fig. 2-B; Fig. 3-B), thus achieving the best prophylaxis of recto-colonic neoplasm. Polyps are usually asymptomatic, but in some cases, they can cause bleeding significant enough to prompt the patient to seek medical investigations. Most commonly, they are discovered during routine colonoscopic examination.

Table 9.I. Types of colonic polyps (IBD = Inflammatory bowel disease)

Bloke	**Frequency**	**Localization**	**Malignant potential**	**Treatment**
Tubular adenoma	25% of adults >50 years old will have an adenoma	20% in rectosigmoid	Reduced	Endoscopic excision
Villous adenomas		80% in rectosigmoid	Elevated	Endoscopic excision
Hamartoma	Rare	Small intestine	Reduced; rare	Excision in case of bleeding or obstruction
Inflammatory	Rare, except BII*	Colon and rectum	None	Follow up
Hyperplastic	Frequently	Stomach, colon and rectum	None	Follow up

- Familial polyposis syndromes. About 6% of all colorectal cancer cases are attributed to such a syndrome, caused by a known genetic mutation that can be inherited.

- FAP (Familial adenomatous polyposis) syndrome, caused by a mutation in the APC gene, is responsible for 1% of colorectal cancer cases. It is an autosomal dominant genetically inherited disease, being characterized by the presence of more than 100 polyps (adenomas) in the rectum and colon, which appear before the age of 30, the evolution of polyps to cancer being the rule. Therefore, it is necessary to evaluate the colonoscopic evaluation of the relatives of a patient diagnosed with FAP, once the diagnosed disease is recommended to perform total colectomy as early as possible, before the onset of malignancy.

- Lynch syndrome or hereditary nonpolypoidal colorectal cancer - represents 5% of colon cancers and is characterized by the presence of colorectal cancer in several members of a family, the appearance at a young age (30-40 years), more frequently in the right colon, and the frequent association with other neoplasms (most often ovary and endometrium). It is caused by mutations in the repair genes MLH1, MSH2, MSH6 and PMS2. The elements that suggest that it is a Lynch syndrome are the discovery of a colon neoplasm at a young age and family aggregation. In this syndrome, the neoplasm is often

located in the right colon and can be synchronous (neoplasm with another location existing at the same time) or metachronous.

- Inflammatory bowel diseases with colonic localization with a long evolution increase the risk of colon neoplasm. This risk is about 10% after 25 years of evolution of ulcerative colitis (the risk begins to become significant only after more than 10 years of evolution of the disease). The risk is lower in the case of Crohn's disease, and it also occurs after a long evolution.

- Family predisposition represents an increased risk for the descendants of a family with colon cancer (increasing the frequency of cancer by 2-3 times for first-degree relatives).

Colorectal cancer screening

According to specialized institutes, the survival rate of colorectal cancer at 5 years is 65%, largely due to an effective screening program. It allows early detection of cancer or prevention by removing adenomatous polyps. In colorectal cancer screening, patients are classified into average or high risk categories.

High-risk patients are those with a family history of colon cancer in a first-degree relative, a personal history of adenomatous polyps, inflammatory bowel disease (IBD), or a known familial cancer syndrome (FAP or Lynch).

Patients who do not have any of these risk factors are considered to be at *average risk*. From the age of 50, people in this category should choose one of the following options:

Screening tests for colorectal cancer are:

- *Tests that identify both polyps and cancer*
  - Flexible sigmoidoscopy every 5 years*
  - Colonoscopy every 10 years
  - CT colonography (virtual colonoscopy) every 5 years*
- *Tests that identify especially cancer*
  - Faecal occult blood test (FOBT) every year*
  - Immunochemical test (FIT) for detecting occult bleeding in feces, performed every year*
  - Faecal DNA test at variable intervals *

**Colonoscopy should be performed if test results are positive.*

Protective factors against CCR are presented in Table 9.II:

Table 9.II. Protective factors against CCR

Protective Factors	Details
Physical activity	Regular physical activity helps reduce the risk of neoplasia.
Diet rich in fiber, vegetables, fish	Eating fiber-rich foods, vegetables, and fish helps protect against colorectal cancer.
Low-calorie, low-carbohydrate diet	Diets low in calories and carbohydrates help reduce the risk of neoplasia.
Vitamin supplements	Folic acid, vitamin B6, calcium, vitamin D and magnesium have beneficial effects in cancer prevention.
Coffee	Moderate coffee consumption was associated with a lower risk of neoplasia.
Medicines	Statins, bisphosphonates, angiotensin inhibitors, aspirin (aspirin contributes not only to reducing the risk of neoplasia, but also to a better post-diagnosis evolution).

Pathology

More than half of colorectal cancers are located in the rectum and sigmoid. In the cecum and ascending colon occur about 20% of cases. Histologically, colon cancers are adenocarcinomas, and, according to their macroscopic appearance, they can be vegetating, ulcer-vegetating or stenosing.

The staging of colon neoplasm is done either in the TNM (tumor-nodule-metastasis) system or, using the Dukes classification on the surgical specimen. The Dukes classification has the following stages (A, B, C, and D):

- stage A – tumor located in the mucosa;
- stage B1 – the tumor that reaches muscularis propria;
- stage B2 – the tumor invades the entire wall of the colon (without lymph node involvement)
- stage C – tumor with involvement of loco-regional lymph nodes;
- stage D – metastases in distant organs.

Post-surgical survival depends on the Dukes stage at the time of intervention, being about 90% at 5 years in stage A and about 50% at 5 years in stage C.

Clinical Picture

The clinical picture of colon cancer is relatively suggestive in advanced forms of the disease. Typical signs are: rectorrhagia, transit disorders, rectal tenesma (continuous or recurrent sensation of defecation without eliminating a significant amount of feces), subocclusive syndrome, anemic syndrome.

- *Rectorrhagia* is an important sign and occurs especially in left-side neoplasms (it is rare in ceco-ascending neoplasm). Depending on the location of the neoplasm, the blood may be red or burgundy, it may be mixed with the stool, or just line it; It can only be

blood emission or stool with glere. An important thing is that *rectal bleeding is often painless* (unlike anal fissure or hemorrhoidal thrombosis, in which rectal bleeding is associated with a sensation of pain, or burning when defecating). Of great practical importance is the attitude of the patient and especially of the doctor in front of a rectorrhagia. Thus, rectal bleeding in adult and elderly patients should always be considered as possibly malignant and only after excluding a serious cause should the possibility of hemorrhoidal disease or anal fissure be considered. Using this strategy, we will have a greater chance of discovering a neoplasm in a timely manner and not unduly delaying the diagnosis, blaming the rectorrhagia on a hemorrhoidal disease.

- *Transit disorders* may suggest a colon neoplasm. Severe and accentuated constipation may suggest a left colon neoplasm, and diarrhea may occur in the neoplasm of the right colon. It is also important the change in the pattern of the stool, for example a patient with normal stool becomes constipated, with an increasingly rebellious constipation, or a patient who is usually constipated, begins to have softer and softer stools. Of course, not every transit disorder is associated with a neoplasm, but together with other signs, especially in an elderly patient, it can be an alarm signal. Subocclusive syndrome, with intermittent and incomplete cessation of fecal-gas transit, can raise the suspicion of stenosing neoplasm of the colon.

- *Anemic syndrome* is an important warning sign for colon neoplasm. Anemia is of the iron deficiency type (hypochromatic, microcyte) and is usually mild or moderate. It is not mandatory to be preceded by rectorrhagia, as microscopic (occult) losses are common. But, in the face of an anemic syndrome without visible blood loss, the doctor must think about a microscopic loss through the colon and therefore a neoplasm.

- Colon neoplasm is *often completely asymptomatic*, especially in the early stages. The satisfaction of the doctor's discovery of an abdominal tumor mass (advanced neoplasm) or a metastatic tumor liver is nil, because the case is therapeutically outdated. Unfortunately, there are cases in which the diagnosis of colon neoplasm is made late, during an emergency intervention for intestinal occlusion.

Diagnosis

The diagnosis of colorectal cancer can be made by the following diagnostic means: rigid rectoscopy (rectal neoplasm); flexible rectosigmoidoscopy (rectosigmoid neoplasm); Colonoscopy; CT colonography - virtual colonoscopy; double contrast irrigography (with air insufflation); the test for the detection of occult bleeding in the stool, as a screening test (or the immunochemical test for the detection of occult bleeding in the stool-FIT).

- *Rigid rectoscopy* requires a rigid, metal rectoscope and allows examination of about 20-25 cm of the rectum and sigmoid. The device is not expensive, the technique is not difficult and allows a diagnosis of rectal cancer. Together with digital anal examination and anuscopy (which diagnoses pathology of the anal canal and rectal ampulla), it can correctly assess the distal region of the digestive tract.

- *Flexible Rectosigmoidoscopy uses flexible* sigmoidoscope for diagnosis. It allows the exact evaluation of the left colon (most often up to the splenic angle of the colon), the place where 70-80% of colon neoplasms are located. The technique is relatively easy, the patient's preparation can be done only with enemas (2 enemas), and the patient's discomfort is not very high (the examination is done on an outpatient basis, without sedation).

- *Colonoscopy* is the ideal method of examining the colon, as it evaluates the entire colon, can visualize any lesion at this level, allows biopsies to be taken. It also allows therapeutic measures, such as endoscopic polypectomy (secondary prophylaxis of colon neoplasm). Colonoscopy is a medical technique with a relative degree of discomfort for the patient (painful, having to be performed under sedo-analgesia) and which requires a special preparation of the colon (purging with various preparations on the day before the examination). It is the most sensitive method of colon evaluation, including for small lesions, the only one that can highlight vascular lesions of the colon (colon angiodysplasia), and which also allows endoscopic hemostasis if needed. For these reasons, it is considered the ideal technique for diagnosing colon pathology.

- *Irrigography* highlights the colon by retrograde opacity with barium substance. The double contrast technique (also using air blowing) is useful. It does not allow biopsy of suspicious lesions and does not allow therapeutic measures (polypectomy). The technique was the most widespread method of evaluating the colon, but it has a diagnostic sensitivity much lower than colonoscopy. The method is increasingly replaced by colonoscopy, with the increase in the number of centers where quality endoscopy is performed.

- More recently, the use *of computer tomography* to perform virtual colonoscopy or CT colonography, allows the virtual reconstruction of the colon, thus highlighting the pathology of neoplasm or colonic polyps. The method is under development, has the disadvantage of irradiation of the patient, and of the lack of possibility of taking biopsies from suspicious lesions or polypectomy.

- *Transrectal ultrasound* allows the assessment of the extension of the neoplasm in the layers of the rectal wall and is used to assess the tumor extension.

- *Fecal* occult blood testing (FOBT) tests allow the assessment of microscopic bleeding in the stool. It is a test that can be used for population screening, so it is aimed at asymptomatic people, with the aim of discovering subjects with suspicion of lesions who will then undergo endoscopic examinations. *The FOBT test* is recommended to be done annually, after the age of 50. *Immunochemical occult stool hemorrhage* (FIT) tests highlight the presence of human hemoglobin in the stool, using monoclonal antibodies, and do not require a special regimen before the test.

- *Genetic tests* in the stool aim to highlight altered DNA, are modern screening tests (but more expensive) and have not yet entered current diagnostic practice.

After the detection of the colon tumor, the **disease is staged**, which, for colorectal cancer, involves performing a thoracic, abdominal and pelvic CT scan to exclude the presence of distant metastases. Common locations of metastases are the liver and lungs. Staging also includes the measurement of carcinoembryonic antigen (CEA) in the blood, which, although not specific to colorectal cancer, is useful in post-resection monitoring for the detection of disease recurrence. Rectal cancer requires further investigation, usually MRI or endorectal ultrasound, to assess the depth of tumor invasion in the intestinal wall and lymph node involvement.

Differential diagnosis of colon cancer

The problems of differential diagnosis of this condition are especially related to *the differentiation of rectorrhagia*. The main causes are:

- hemorrhoidal disease and anal fissure (in which rectal bleeding is associated with pain/discomfort when defecating);
- Crohn's disease;
- ulcerative colitis;
- colonic diverticulosis with diverticular bleeding;
- ischemic colitis and radic colitis (postradiotherapy);
- colonic angiodysplasia (predominantly bleeding in the right colon, in the elderly, through angiomatous lesions).

Another problem is *the differential diagnosis of anemic syndrome*. It will be sought if the anemia is of the iron deficiency type, and in this situation (even if rectal bleeding was not present), the most likely cause is related to the digestive tract (eso-gastric, intestine or colon).

Evolution, prognosis

The evolution of colon cancer depends on the time of discovery and surgery. In the case of a Dukes A stage, the 5-year survival is about 90%, and in Dukes C about 50%. In a neoplasm with liver metastases (Dukes D), survival is reduced.

Most recurrences occur in the first 2 years, so patient’s follow up is extremely important. Colonoscopy is routinely performed at 1 year and 4 years postoperatively, then every 5 years. CT scan of the chest, abdomen and pelvis is performed annually in patients at risk for relapse (stage 3).

Complications

The most common complications of colon neoplasm are metastasis (hepatic, pulmonary), intestinal occlusion, perforation and severe iron deficiency anemia.

Colorectal cancer treatment

1. Surgical treatment – it is considered the treatment of choice for colon neoplasm. The intervention will be done as soon as possible, and the type of intervention depends on the location: right hemicolectomy in cecoascending cancer, left hemicolectomy in descending colon cancer, segmental colectomy, etc. The preoperative evaluation will include the evaluation of lymph node extension as well as the presence of lung, liver or peritoneal metastases.

Rectal cancers for which staging by pelvic MRI or endorectal ultrasound reveals invasion of the rectal wall (T3 or T4) or lymph nodes are initially treated with chemotherapy and radiotherapy. The goal of neoadjuvant treatment is to reduce the size of the tumor and reduce the risk of local recurrence at the anastomosis level. After the completion of radiochemotherapy, which lasts 6 weeks, there is a recovery period of 8-12 weeks, during which the cancer continues to regress and respond to the treatment administered. The surgery is performed later.

2. Post-surgical chemotherapy is indicated for patients in Dukes stages B2 and C. Regimens containing 5 fluoro-uracil, combined with folinic acid or other current more potent regimens (oxaliplatin) are used. Given the increase in survival after chemotherapy, it is advisable that, after surgery, the patient be sent to the oncologist for further treatment.

Antiangiogenic therapy with Bevacizumab (Avastin) inhibits vascular endothelial growth factor (VEGF) activity. Clinical studies have shown that its combination with chemotherapy regimens improves the survival of patients with metastatic colorectal cancer.

3. Radiotherapy is especially aimed at rectal and anal cancer, which, due to its position in the small pelvis, cannot always be correctly resected (with lymph node dissection).

4. Endoscopic treatment

Endoscopic resection (by colonoscopy Fig.9.2-B; Fig.9.3-B) is indicated for Tis lesions and certain cases of T1 with superficial submucosal invasion, complying with strict histological safety criteria.

Patients may sometimes experience acute obstruction of the large intestine, caused by colon or rectal cancer. In such cases, *Metal stents for the colon* can be used and placed endoscopically or under fluoroscopic guidance. If the procedure is performed successfully, stents ensure that the patency of the obstructed colonic lumen is maintained, avoiding the need for emergency surgery and colostomy. This intervention can have a temporary role, serving as an intermediate step before an elective surgical resection, or it can be used as a palliative measure in cases of advanced metastatic disease.

To note

- Colorectal cancer is the third most common cancer globally, in Romania on the first place in the general population.

- Colorectal cancer is frequently asymptomatic, with suggestive clinical signs such as rectorrhagia, transit disorders, and iron deficiency anemia.

- Positive diagnosis involves colonoscopy with biopsy, as well as staging by sectional imaging methods, to look for distant metastases.

- The ideal treatment is surgical associated or not with chemotherapy and/or radiotherapy (in rectal cancer), depending on the stage of the disease.

- Colorectal cancer is preventable by implementing the screening program for the detection of polyps and polypectomy before malignant transformation.

- Screening is applied to the asymptomatic population over 50 years of age and is done by annual fecal occult blood test (FOBT or FIT) followed by colonoscopy in case of positivity, or by colonoscopy at 7-10 years of age.

10. IRRITABLE BOWEL SYNDROME (IBS)

Definition

Irritable bowel syndrome (IBS) is a functional disorder of the intestine, defined by recurrent abdominal pain, associated with defecation or changes in the frequency and/or consistency of the stool. Patients may also experience diarrhea, constipation or alternation between them, accompanied by bloating.

According to the current Rome IV criteria, the symptomatology must have an onset of at least 6 months and be present at least 3 days a month in the last 3 months. Due to the lack of structural damage, IBS is considered a prototype of functional digestive disorders and one of the most common functional disorders globally.

Epidemiology

Functional gastrointestinal disorders are widespread, with about 40% of the population having dysfunctions of this type. Of these, IBS occupies a central place, with an estimated global prevalence of 4.1%, in Romania it is about 3.5%. Most studies indicate a higher frequency in women (ratio 2–3:1), who more often complain of constipation and bloating, men have diarrhea more frequently. The disease is diagnosed especially in young adults and middle-aged adults (18–39 and 40–64 years), with prevalence usually decreasing in the elderly.

Etiopathogenesis

IBS has a multifactorial etiopathogenesis and is still incompletely understood. Although there are no clear organic lesions or specific biomarkers, several main mechanisms involved in the etiopathogenesis of IBS have been demonstrated (Table 10.I)

Table 10.I.IBS Pathophysiology

Mechanism	Details
Brain-gut axis dysfunction	Central mechanism, involving abnormal communication between the CNS, the enteric nervous system, and the hypothalamic-pituitary-adrenal axis.
Visceral hypersensitivity	Responsible for typical abdominal pain. Low threshold of perception of distension and pain, correlated with changes in the cingulate cortex, insular cortex, and other brain processing regions.
Serotonergic disorders	Serotonin (5-HT) regulates perception, secretion, and motility. Increased 5-HT levels in IBS with diarrhea and decreased in IBS with constipation.

Changes in intestinal motility	IBS with diarrhea: high-amplitude contractions, exaggerated response to stimuli. IBS with constipation: reduced contractions, slowed transit.
Psychosocial factors	Stress, trauma, anxiety, depression can aggravate or trigger IBS.
Low-grade inflammation	The mast cell and intestinal lymphocyte infiltrate present in some patients releases mediators that amplify pain.
Bacterial overpopulation (SIBO) and microbiota alteration	Flora imbalances can cause excess gas and bloating.
Genetic factors	Relevant family history in approximately 33–42% of cases.
Dietary factors	Certain foods can exacerbate symptoms, although the relationship is not always clear. The role of FODMAPs and gluten sensitivity in some patients is discussed.

Pathology

From a morphopathological point of view, IBS does not cause obvious structural abnormalities. Endoscopy and intestinal biopsies are generally normal. Thus, morphopathological investigations confirm the functional character of the disease and exclude other pathologies with organic substrate.

Clinical picture

The clinical picture of irritable bowel includes:

- *Abdominal pain* either diffuse or localized on the colonic pathway. They can be deaf, but often have a colic character (cramps), lasting seconds or minutes. Other times, the patient only feels abdominal discomfort or burning sensation, located subcostally, at the level of the right and/or left hypochondria, at the level of the colonic flexions. Symptoms most often disappear during periods of relaxation, vacation, etc. An essential feature is the relationship between pain and the act of defecation or transit changes.

- *Transit disorders* are frequent, characteristic being the alternation of constipation with diarrhea. The emission of the stool is often in the form of schibale (hard, fragmented stools), covered with mucus. False diarrhea can often occur, in which, after these hard stools, the continuation with liquid stool of colonic irritation follows. Diarrheal stools appear occasionally, most frequently in the form of urgency, morning, postprandial or emotional stools (before exams).

- *Bloating* is common in patients with irritable bowel, being diffusely localized, or the patient feels it especially in certain areas of the abdomen. The emission of gases can temporarily ease the patient's suffering.

Biological and paraclinical picture

The purpose of biological and paraclinical explorations is to exclude other conditions with similar symptoms. The diagnosis of IBS is fundamentally based on clinical criteria.

1. Initial investigations include *usual blood tests* (Blood count, ESR, CRP, TSH/fT4, liver tests – generally normal in IBS), *stool and stool culture* that exclude intestinal infections, *classic blood culture test with guaiac or fecal immunohistochemical test (FIT)* which, by highlighting occult hemorrhages, can point to organic diseases (e.g. neoplasia). An important test is the determination *of fecal calprotectin*, a test sensitive to intestinal inflammation, with good sensitivity for inflammatory bowel diseases such as Crohn's disease or ulcerative colitis.

2. Endoscopic explorations include: *upper digestive endoscopy, ± duodenal biopsy* - to highlight any gastric and organic duodenal suffering, to exclude gluten enteropathy; *colonoscopy with ileoscopy ± biopsies,* which are mandatory in case of the presence of warning signs (bleeding, anemia, weight loss) or in people over 50 years of age (in whom screening for colon cancer must be performed); *endoscopic capsule or enteroscopy* - for the exclusion of enteral organic pathology, usually used only when there are warning signs.

3. Imaging explorations include *abdominal ultrasound* - to highlight the suffering of the gallbladder, pancreas, genitals and *sectional CT*/MRI imaging that are used when there is clinical and endoscopic suspicion of tumors or extensive inflammation.

4. Further investigations in forms with diarrhea are carried out to exclude organic diagnostics

- Celiac disease – anti-tissue transglutaminase IgA antibodies, duodenal biopsy.
- Lactase deficiency – the clinical test of lactose tolerance, with or without the biological and radiological component
- Inflammatory bowel diseases, especially Crohn's disease – fecal calprotectin.
- Microscopic colitis – colonoscopy with layered biopsies.
- SIBO (bacterial overpopulation syndrome) – performing the respiratory test with lactulose/glucose.
- Exocrine pancreatic insufficiency – determination of fecal elastas.
- Other causes: neuroendocrine tumors, hyperthyroidism, ovarian neoplasm, etc.

Positive diagnosis

The diagnosis of IBS is based on the Rome IV clinical criteria, without being exclusively an exclusion diagnosis. There is no specific marker, and invasive investigations are done as needed, in the presence of alarm signs.

Rome IV Criteria

- *Recurrent abdominal pain*, at least 1 day/week in the last 3 months;
- Associated with *two or more* of:
    - Relationship with defecation;
    - Change in the frequency of the stool;
    - Change of the shape/appearance of the stool;
- Onset of symptoms at least 6 months before diagnosis.

Additional symptoms (tenesmus, mucus stools, bloating) may support the diagnosis, but are not included in the formal criteria. Depending on the consistency of the IBS stool, it can be subclassified into IBS with constipation, IBS with diarrhea, mixed IBS and non-specific IBS, as seen in Table 10.II. The subtypes of IBS are determined according to the consistency of the stools, not the frequency of defecation, and guide treatment options. The Bristol scale (type 1–2 hard seats, type 6–7 soft/watery seats) is a useful benchmark in classification (Table 10.III).

Table 10.II Subtypes of IBS according to the Rome IV criteria.

Subtype	Features
IBS-C (with constipation)	• >25% hard stools (type 1–2 on the Bristol scale) • <25% soft/watery stools (type 6–7)
IBS-D (with diarrhea)	• >25% soft/watery stools (type 6–7) • <25% hard stools (type 1–2)
IBS-M (mixed)	• >25% hard seats • >25% soft/watery seats
IBS-U (non-specific)	• Insufficient changes in seat consistency to fall into categories IBS-C, IBS-D or IBS-M

Table 10.III. Bristol Stool Layout Classification Scale

Type	Description	Clinical Significance	Image
1	Hard, separate grains, difficult to remove.	Severe constipation	
2	Sausage with a gnarled surface.	Mild constipation	
3	Sausage with cracks on the surface.	Normal	
4	Smooth, soft, snake-like sausage.	Normal	
5	Soft, well-defined pieces, easy to remove.	Fast transit	
6	Soft, ragged pieces with increased consistency.	Mild diarrhea	
7	Liquid, aqueous, without solid particles.	Severe diarrhea	

Differential diagnosis

To confirm IBS, the presence of organic diseases and other functional disorders as seen in Table 10.IV should be excluded,

Table 10.IV. Differential Diagnosis in Irritable Bowel Syndrome (IBS)

	Conditions
Organic disorders	• Neoplasms (anorectal cancer, colon cancer) • Inflammatory bowel diseases (Crohn's, ulcerative colitis) • Diverticulitis • Lactase deficiency • Microscopic colitis • Celiac disease and other malabsorptions • Exocrine pancreatic insufficiency • Endocrine disorders (hyper-/hypothyroidism) • Neuroendocrine tumors
Other functional disorders	• Functional constipation • Functional diarrhea • Functional bloating • Centrally mediated abdominal pain (lack of correlation with transit changes)

Complications

Being a functional disease, IBS does not cause serious organic damage (ulcers, strictures) and does not increase the risk of neoplasia or inflammatory bowel disease. However, the *psycho-social impact* (chronic discomfort limits daily activity and social relationships, which can lead to worsening anxiety and depression) and *the impairment of the quality of life* of these patients due to fears of unforeseen symptoms, dietary restrictions, etc., should not be ignored.

Evolution and prognosis

IBS evolves chronically, with alternating episodes of improvement and exacerbation. It does not cause organic complications or shorten life expectancy, but it can markedly influence the quality of life through frequent discomfort and possible anxious-depressive reactions. An effective therapeutic approach – diet, medication, stress management – helps reduce the frequency and severity of attacks, allowing for a relatively normal life.

Treatment

The approach is multimodal, adapted to the subtype (IBS-D, IBS-C, IBS-M) and the severity of the manifestations.

1. General measures include patient education, diet, and lifestyle changes

- *Patient education and counseling* consists of explaining the benign nature of IBS and the fact that there are no major organic risks.

- *The diet* consists of recommending a diet rich in fiber or with added fiber (psyllium) especially in constipation. It is recommended to restrict potentially triggering foods (dairy, alcohol, fat, FODMAPs) with gradual exclusions and reintroductions to identify individual tolerances. FODMAP is an acronym that stands for Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) nutrients potentially involved in the maintenance of IBS symptoms.

- *Lifestyle changes* involve the recommendation of regular physical exercise, stress control measures (relaxation, yoga, mindfulness).

2. Drug therapy is symptomatic, having the role of improving the symptoms and therefore the quality of life of patients. Unfortunately there is no definitive curative treatment for IBS, frequently symptoms reappear when stopping medication. The main medicinal products used in IBS are presented in Table 10.V.

Table 10.V. Drug treatment in IBS

The dominant symptom	**Treatment**		**Dose**	**Observations**
Diarrhea	Loperamide		2-4 mg/day - as needed	Useful in acute episodes
	Cholestyramine		9 g of 2-3x/day	Fixatives, bile acids, biliary malabsorption
	Colestipol		2x2 g/day	
	Probiotics		Numerous products available, duration of administration - 4 weeks	Different effects depending on the strain Relieves bloating, can regulate transit
	Rifaximin		400 mg x 3/day - 2 weeks	Temporarily relieves, possible relapses
	Antagonists 5 HT3	Allosetron	2x0.5 mg/day	Risk of ischemic colitis, indicated only in refractory forms
		Ondansetron	4-8 mg of 3x/day	
		Ramosetron	5 micrograms once/day	
Constipation	Bulking agents (psyllium)		Over 30 g/day (3x10g/day)	May accentuate bloating

The dominant symptom	Treatment		Dose	Observations
	PEG		17-34 g/day	Osmotic effect
	Lubiprostone		2x 8 micrograms/day	CI Channel Enablers increased intestinal secretion
	Linaclotide		290 micrograms - once/day	
Pain	Antispasmodic	Trimebutine	2x300 mg/day, 2x200 mg/day 3x40 mg/day	Short-term effect Relieves pain and bloating
		Mebeverina		
		Othylonium bromide		
	Peppermint oil		Capsules 250-750 mg of 2-3x/day	Peppermint oil: beware of reflux
	Tricyclic antidepressants	Amitriptyline	10-50 mg/day in the evening	Decrease motility (useful in diarrhea), Analgesic effect Adverse effects: sedation, constipation, xerostomia
		Desipramine	25-100 mg/day - evening	
	Selective inhibitors of serotonin reuptake	Paroxetine	10-40 mg/day	It is necessary to maintain dose for at least 6-8 weeks. Most common The cause of therapy failure is inadequate dose or insufficient duration.
		Fluoxetine	20-40 mg/day	
		Sertraline	50-100 mg/day	
		Citalopram	10-40 mg/day	
	Allosetron		2x0.5 mg/day	Antagonist 5 HT3
	Probiotics		Numerous products available, duration of administration - 4 weeks	
Bloating	Rifaximin		400 mg x 3/day - 2 weeks	Significantly reduces bloating Short-lasting effect

3. Psychological therapy (psychotherapy) in various forms (cognitive-behavioral therapy, hypnosis, relaxation techniques) is recommended in forms refractory to standard therapy or when there are emotional factors (anxiety, depression) evident. As a rule, it is applied after at least 12 months of drug treatment without a satisfactory response.

To note

- Irritable Bowel Syndrome (IBS) is a common condition, without organic substrate, without organic complications, but with the potential to significantly affect the quality of life through abdominal pain and transit disorders.
- The diagnosis is a clinical one, based on the Rome IV criteria, and the investigations help to exclude other diseases.
- Treatment involves general measures (diet, exercise, stress management) and medication adapted to the symptoms (antispasmodics, antidiarrheals, laxatives, etc.), sometimes complemented by psychological support.
- Through an individualized approach and an appropriate doctor-patient relationship, most patients with IBS can maintain an active life and a good degree of comfort.

11. UPPER AND LOWER DIGESTIVE HEMORRHAGES

Digestive bleeding is a potentially life-threatening medical emergency that requires rapid diagnosis and immediate intervention. Hemorrhages are classified into **upper gastrointestinal bleeding (UGIB)** and **lower gastrointestinal bleeding (LGIB)**, depending on whether the bleeding site is located above or below the ligament of Treitz.

A. Upper Gastrointestinal Hemorrhage

Definition and clinical manifestations

Upper gastrointestinal bleeding refers to hemorrhage originating from the digestive tract proximal to the ligament of Treitz.

The most common clinical manifestations include:

- **Melena** – black, shiny, soft, and foul-smelling stools resulting from the degradation of hemoglobin by intestinal flora.
- **Hematemesis** – vomiting of fresh blood or “coffee ground” material due to incomplete digestion of hemoglobin in the stomach.
- **Hematochezia** – in the context of massive bleeding (>1,000 mL), the passage of partially digested or undigested blood, often dark red and resembling rotten cherries; although more commonly associated with colonic bleeding, in this setting it may also signal a brisk upper gastrointestinal source.
- **Signs of hypovolemia** – tachycardia, hypotension, pallor, and confusion, which in severe cases may progress to hemorrhagic shock, reflecting significant blood loss.

Causes of upper gastrointestinal hemorrhage (HDS):

Upper gastrointestinal hemorrhage (UGIB) is a gastroenterological emergency, with the source of bleeding located in the esophagus, stomach, or duodenum. The etiologies are diverse and can be divided into **non-variceal causes** (the most frequent) and **variceal causes**.

1. Non-variceal causes (80–90% of cases)

These are the most common and are mainly associated with diseases of the mucosa of the upper gastrointestinal tract.

a) Peptic ulcer – Gastric and duodenal ulcers are the leading causes of UGIB, accounting for 35–50% of non-variceal cases. Risk factors include:

- *Helicobacter pylori* infection.
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin.
- Severe physiological stress, such as in critically ill patients with major burns (Cushing or Curling stress ulcers).

b) Gastro-duodenal erosions – Represent 10–20% of non-variceal causes. They are often associated with erosive gastritis or duodenitis and are commonly induced by NSAIDs, alcohol consumption, biliary reflux, or severe physiological stress.
c) Erosive esophagitis – Caused by severe gastroesophageal reflux disease (GERD), and frequently worsened by alcohol, tobacco, and NSAID use. It can progress to esophageal ulcers or strictures.
d) Mallory–Weiss syndrome – Accounts for 5–10% of non-variceal cases. It is defined as a longitudinal tear of the distal esophageal mucosa or at the gastroesophageal junction, most often due to repeated episodes of vomiting (e.g., alcoholism, pregnancy, bulimia), but may also result from severe coughing or abdominal trauma.
e) Esophagogastric neoplasms – Represent 2–5% of non-variceal causes. Malignant tumors such as gastric or esophageal cancer may bleed either chronically or acutely. Recognized risk factors include *Helicobacter pylori* infection, smoking, and diets rich in smoked or salted foods.
f) Angiodysplasia and vascular malformations – Abnormal blood vessels in the gastric or duodenal mucosa, most commonly seen in the elderly. A particular subtype is **GAVE (Gastric Antral Vascular Ectasia)**, also known as "watermelon stomach," which is associated with liver cirrhosis and autoimmune diseases.
g) Hemobilia and hemosuccus pancreaticus – Rare causes of UGIB.

- *Hemobilia* is bleeding into the biliary tract, usually secondary to liver trauma, hepatobiliary tumors, or invasive hepatobiliary procedures.
- *Hemosuccus pancreaticus* is hemorrhage into the pancreatic duct, most often caused by rupture of a pseudoaneurysm of the splenic artery.

2. Variceal causes *(*10-20% of HDS cases) Variceal hemorrhage occurs in the setting of **portal hypertension**, most commonly secondary to liver cirrhosis.

a) Esophageal varices – Dilated submucosal veins of the esophagus that develop as a consequence of portal hypertension. Risk factors for bleeding include:

- A portohepatic venous pressure gradient greater than 12 mmHg.
- Large varices (diameter >5 mm).
- The presence of red wale marks or red spots on the varices, which indicate friability and a thin vessel wall.
- Severe liver dysfunction, particularly in patients with advanced cirrhosis (Child-Pugh class C).

b) Gastric varices – Also occur as a result of portal hypertension. Although less common than esophageal varices, they tend to cause more severe bleeding when rupture occurs.

c) Portal hypertensive gastropathy – Characterized by vascular changes in the gastric mucosa secondary to portal hypertension. It typically causes diffuse oozing rather than focal bleeding.

3. Rare causes of UGIB

a) Dieulafoy lesion – Rupture of a large-caliber submucosal arteriole in the absence of an ulcer. This lesion can lead to severe, spontaneous upper gastrointestinal bleeding.

b) Aortoenteric fistula – A rare but catastrophic cause of UGIB, representing a fistulous connection between the aorta and the gastrointestinal tract. It is most often a complication of an abdominal aortic aneurysm and carries a very high risk of mortality.

c) Iatrogenic bleeding – Occurs after endoscopic procedures such as polypectomy or endoscopic submucosal dissection (ESD).

HDS Management:

a) Patient stabilization *– This is the first priority in upper gastrointestinal bleeding and includes:*

- *Continuous monitoring of vital signs and electrocardiogram (ECG).*
- *Establishment of two large-bore intravenous lines, with administration of intravenous fluids and blood transfusions when necessary.*
- *Essential laboratory tests: complete blood count, serum urea, creatinine, coagulation profile, liver function tests, and blood glucose.*

b) Prokinetic therapy *– Facilitates visualization of the gastric mucosa and decreases the need for repeat endoscopy. Agents such as erythromycin or azithromycin, which act as motilin receptor agonists in the stomach and enhance gastric motility, may be administered. The recommended dose is 250 mg intravenously, given 20–90 minutes before endoscopy, to optimize intraprocedural visualization.*

c) Risk stratification *– Performed by calculating the* ***Glasgow-Blatchford Score (GBS)*** *(Table 11.I), which is essential for guiding management decisions.*

- *A score of* ***0*** *indicates very low risk and that hospitalization is not required.*
- *A score of* ***≥8*** *suggests high risk and the need for intensive care unit (ICU) monitoring and management.*

Table 11.1 Glasgow-Blatchford Presentation Risk Score for HDS

Presentation risk marker	***Points***
Serum urea (mmol/L)	
6.5–8	*2*
8–10	*3*
10–25	*4*
>25	*6*
Hemoglobin (Hb) (g/L) – Men	
120–130	*1*
100–120	*3*
<100	*6*

Presentation risk marker	***Points***
Hemoglobin (Hb) (g/L) – Women	
100–120	*1*
<100	*6*
Systolic blood pressure (mmHg)	
100–109	*1*
90–99	*2*
<90	*3*
Pulse ≥100/minute	*1*
History / Comorbidities	
Presentation with melena	*1*
Presentation with syncope	*2*
*Liver disease**	*2*

** Liver disease*: Known history or clinical/laboratory evidence of a chronic or acute liver disease.
†*Heart failure*: Known history or clinical/echocardiographic evidence of heart failure.

d) Considerations regarding anticoagulant and antiplatelet therapy. Patients with pre-existing cardiovascular diseases require special attention:

- Aspirin for secondary prophylaxis of cardiovascular diseases should not be discontinued in HDS, as it increases mortality at 30 days;
- In patients on dual antiplatelet therapy, the European Society of Digestive Endoscopy (ESGE) recommends continuing aspirin and temporarily stopping the second agent.
- Platelet transfusion is not routinely recommended because of the thrombotic risk.

Endoscopic treatment:

Patients should undergo diagnostic and therapeutic endoscopy only once hemodynamic stability has been achieved. The recommended parameters are: systolic blood pressure (SBP) above 100 mmHg, heart rate (HR) ideally below 100 beats per minute, hemoglobin (Hb) greater than 7 g/dL (and above 8 g/dL in cardiac patients), and ideally a platelet count greater than 50,000/mm³.

Prior to endoscopy:

- *In suspected **non-variceal hemorrhage**, a proton pump inhibitor (PPI) 80 mg intravenous bolus may be administered.*
- *In suspected **variceal hemorrhage**, vasopressor therapy such as terlipressin, somatostatin, or octreotide can be initiated.*

- *In patients with **decompensated liver cirrhosis** (particularly in the presence of ascites), antibiotic prophylaxis with ceftriaxone 1 g/24 h for a maximum of 7 days is recommended.*

***Orotracheal intubation (OTI)** is indicated in comatose patients and in those with massive hematemesis, in order to protect the airway during endoscopy. Extubation should be performed as soon as clinically feasible after completion of the procedure.*

b) Endoscopy should be performed within the first 12–24 hours after hospital admission, once the patient has been stabilized and at least 6 hours after the last oral intake. Performing endoscopy too early, in a patient who remains hemodynamically unstable, carries a significant risk of complications such as cardiorespiratory arrest, arrhythmias, aspiration, or even death.

In addition, attempting endoscopy in a stomach filled with blood or food debris makes visualization of the mucosa and therapeutic intervention more difficult. For this reason, careful and patient technique is essential. The procedure must be performed systematically, with thorough inspection of all gastric and duodenal segments, and retroflexion should always be performed to evaluate the gastric fundus.

Any identified lesions should be assessed with respect to their type, anatomical location, depth, the presence or absence of active bleeding, and the potential risk of rebleeding. To stratify this risk and guide endoscopic therapy, the Forrest classification is applied (Table 11.II).

Table 11.II. Forrest's classification of endoscopic lesions in upper gastrointestinal hemorrhage (PPI – proton pump inhibitor; iv – intravenous).

Forrest	Description	Risk of rebleeding	Management
Takes	Active, pulsatile arterial bleeding		Immediate endoscopic hemostasis (thermal coagulation injection, hemoclipes), IV PPI
Ib	Active venous bleeding		Endoscopic hemostasis, IPP iv
II a	Visible vessel	50%	Obligate endoscopic hemostasis
II b	Adherent clot	25-30%	Attempt to remove the clot, then endoscopic hemostasis if necessary
IIc	Hematin in the ulcer crater	5%	Oral PPI
III	Fibrin	Below 3%	Oral PPI

Lesions classified as **Forrest Ia/Ib** represent active hemorrhage and require immediate combined hemostasis. This is achieved by perilesional injection of adrenaline, followed by thermal coagulation and/or mechanical hemostasis using hemoclips.

Lesions classified as **Forrest IIa**, characterized by a visible vessel, require endoscopic treatment even in the absence of active bleeding at the time of examination, due to the high risk of rebleeding.

Lesions classified as **Forrest IIb**, with an adherent clot (Fig. 11.1), require removal of the clot by traction with biopsy forceps and/or vigorous irrigation. The lesion is then reassessed and managed according to its new classification. If clot removal is not possible, repeat endoscopic evaluation is recommended after 12 to 24 hours.

Lesions classified as **Forrest IIc/III** carry a low risk of rebleeding and do not require endoscopic therapy; they are managed conservatively with proton pump inhibitor (PPI) therapy.

c) Endoscopic hemostasis techniques in non-variceal hemorrhage

- **Adrenaline injection** – Performed using an endoscopic injection needle. Adrenaline, diluted 1:10,000, is injected in 1–2 mL aliquots at several points around the lesion. Hemostasis is achieved through the local vasoconstrictive effect. However, because the effect is temporary (approximately 15 minutes), adrenaline injection should never be used as monotherapy; it must always be followed by mechanical or thermal hemostasis.
- **Mechanical hemostasis** – Achieved through the endoscopic application of hemoclips (Fig. 11.2), which provide direct mechanical occlusion of the bleeding vessel.
- **Thermal therapy** – Most often performed with bipolar probes, and less frequently with heated forceps, especially in cases of diffuse, low-intensity bleeding. The bipolar probe is applied directly to the lesion, gentle pressure is exerted, and then electric current is activated to heat the probe tip. Pressure and current are maintained for 5–10 seconds to achieve thermal coagulation of the bleeding vessel.
- **Hemostatic powder and PURASTAT** – Hemostatic powder (Fig. 11.3) and PURASTAT (a biocompatible synthetic peptide-based gel) can be used in cases of diffuse and persistent bleeding.
- **Argon plasma coagulation (APC)** – A technique in which electricity is delivered to the tissue via ionized argon gas, creating a focused plasma beam. APC has the advantage of limited tissue penetration (approximately 5 mm) and is mainly indicated in diffuse bleeding lesions such as angiodysplasia and gastric antral vascular ectasia (GAVE).

When standard endoscopic techniques fail, **rescue therapy** consists of interventional radiology with angiographic embolization, rather than further endoscopic attempts.

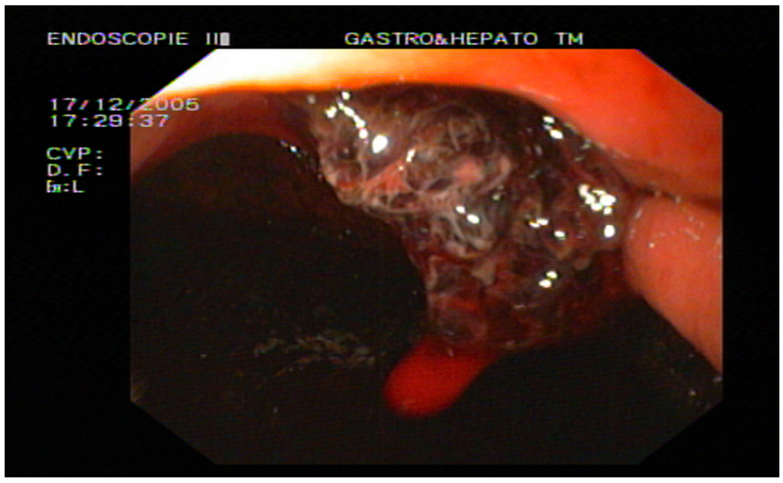


Fig. 11.1. Ulcer with adherent clot

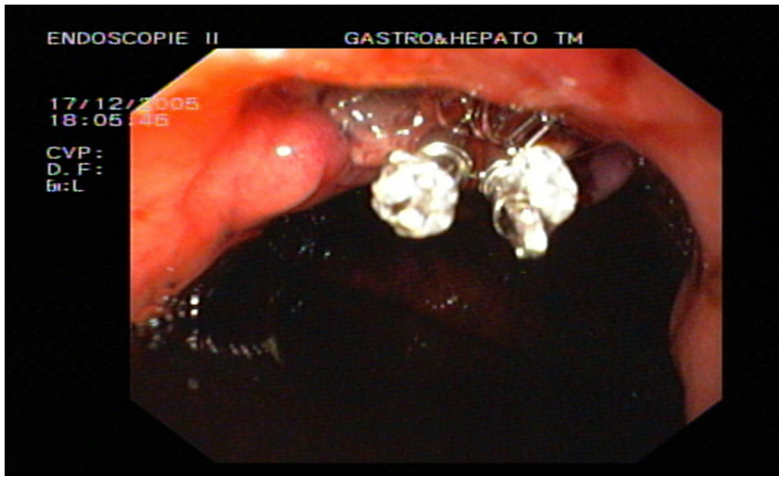


Fig. 11.2. Hemostasis with hemoclips

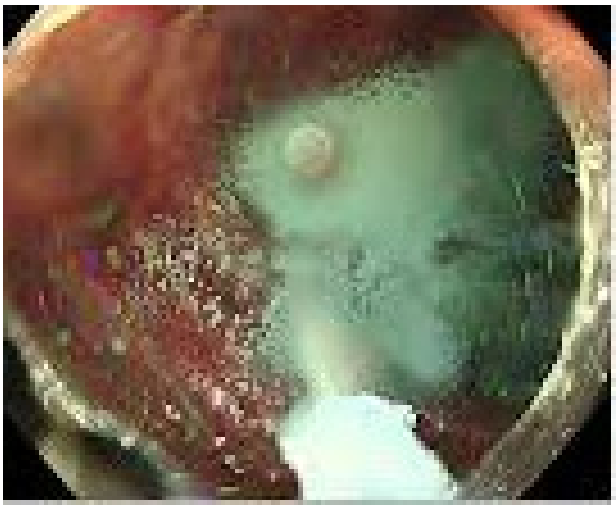


Fig. 14.3. Application of hemostatic powder

d) Endoscopic techniques of hemostasis in variceal hemorrhage. Variceal hemorrhage is a severe and life-threatening complication of portal hypertension. Several therapeutic options are available:

- **Endoscopic band ligation** – This is the standard treatment for esophageal varices. It consists of placing elastic bands around the varices (Fig. 11.4). The ligated vein undergoes necrosis, followed by fibrosis that obliterates the vessel lumen. The bands eventually detach and are eliminated naturally. At the site of ligation, post-banding ulcers may form, which carry a risk of bleeding, especially in patients with advanced liver dysfunction (Fig. 11.5).
- **Cyanoacrylate injection** – Used primarily for gastric varices (Fig. 11.6). Cyanoacrylate is a tissue adhesive that polymerizes and solidifies after injection, effectively obliterating the varix. Unlike band ligation, this technique is not associated with ulcer formation at the injection site.
- **Balloon tamponade (Sengstaken–Blakemore tube)** – A temporary measure indicated in severe hemorrhage that cannot be controlled endoscopically, or while awaiting transfer to a center capable of definitive hemostasis. The balloon provides compression of the bleeding varices, but it should be maintained for no longer than 24 hours because of the high risk of ischemia and esophageal perforation.
- **Danis stent** – A fully covered self-expandable metal stent (Fig. 11.7) designed to tamponade bleeding esophageal varices. It can be left in place for up to 7 days but must then be removed due to the risk of ischemic complications.
- **TIPS (Transjugular Intrahepatic Portosystemic Shunt)** – A salvage therapy performed percutaneously. It creates a portosystemic shunt that decompresses the portal circulation and reduces variceal pressure. TIPS is recommended for patients at high risk of rebleeding, particularly those with large gastric varices. (For details, see the chapter on liver cirrhosis.)

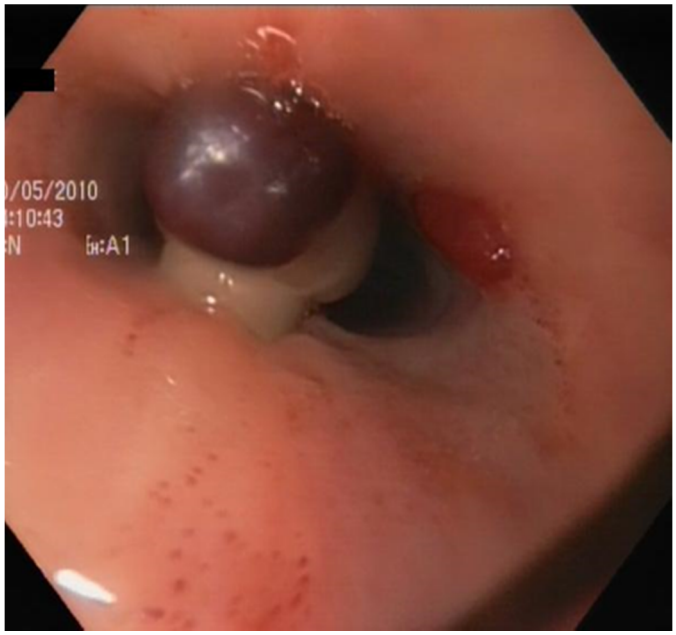


Fig. 11.4. Ligated esophageal varices

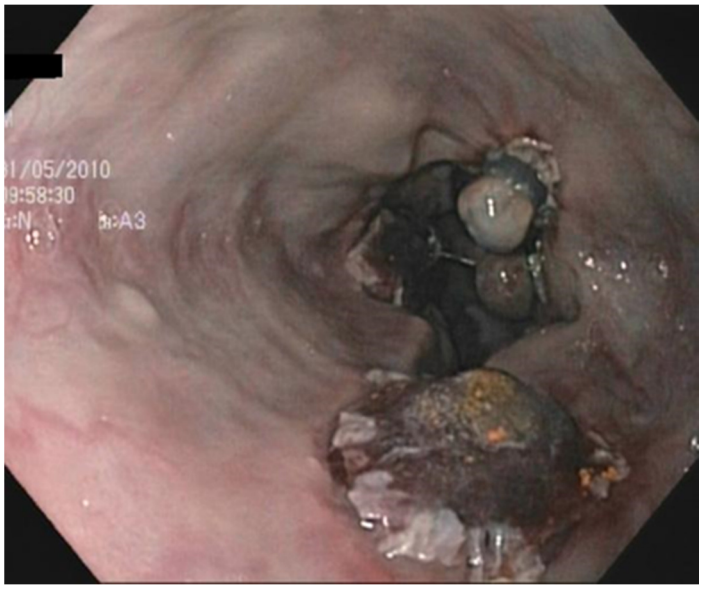


Fig. 11. 5 Post-ligation ulceration (5 o'clock), with adherent blood clot. At 2 o'clock, a ligated varicose vein with the ligation ring is visualized in place

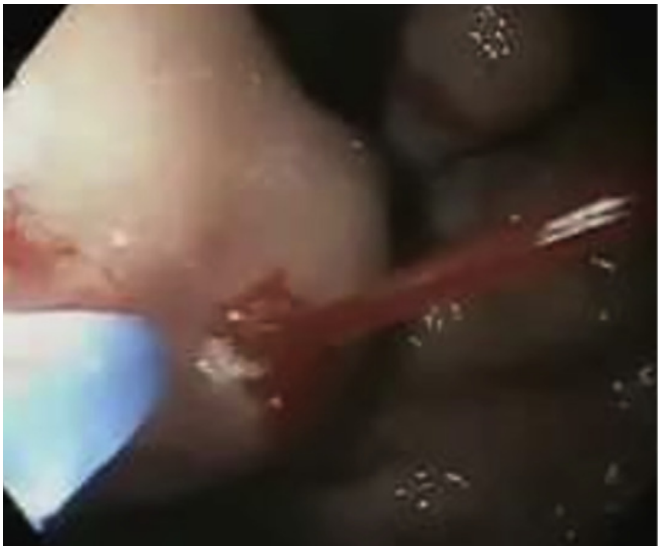


Fig. 11. 6. Cyanoacrylate injection - note the jet hemorrhage from a fundic varicose vein, and the injection needle (blue)

Fig 11.7. Stent Danis

e) Associated drug treatment.

Endoscopic therapy must always be combined with appropriate pharmacological treatment:

- **In patients with non-variceal bleeding**, intravenous proton pump inhibitor (PPI) therapy is indicated, consisting of an 80 mg bolus followed by continuous infusion at a rate of 8 mg/hour for 72 hours.
- **In patients with variceal bleeding**, vasoactive agents are administered to reduce portal pressure. Commonly used drugs include terlipressin, somatostatin, and octreotide.
- **In patients with decompensated liver cirrhosis**, particularly those with ascites, antibiotic prophylaxis is mandatory to prevent bacterial infections and spontaneous bacterial peritonitis. The recommended regimen is ceftriaxone 1 g intravenously every 24 hours, for a maximum duration of 7 days.

B. Lower digestive bleeding

Definition and clinical manifestations

Lower gastrointestinal hemorrhage (HDI) is defined as bleeding that originates from the gastrointestinal tract located below the ligament of Treitz, including the jejunum, ileum, colon, and rectum. The causes of HDI vary depending on the patient's age, comorbidities, and the exact location of the bleeding.

The clinical picture of HDI includes:

Rectoragia – elimination of fresh red blood

Hematochesis – massive bleeding (>1000 ml), with partially or not at all digested blood (color similar to rotten cherry or blood clots.

Signs of hypovolemia – tachycardia, hypotension, pallor, confusion, which can go up to shock, indicating significant blood loss.

Etiology of HDI

1. Colon causes – are the most common causes of HDI, as the colon is well vascularized and prone to bleeding from multiple sources.

a) Diverticulosis is the most common cause of HDI in elderly patients (30-50% of HDI cases). Bleeding occurs through the erosion of the arterioles that cross the diverticula. From a clinical point of view, it is characterized by massive hematochesia, suddenly installed, usually without pain. It is self-limiting in most cases, but may require endoscopic hemostasis, embolization, or surgery in case of relapse.

b) Angiodysplasia accounts for 10-20% of HDI causes. They are submucosal vascular malformations, more common in patients >60 years old. It is characterized by intermittent, self-limiting bleeding, most commonly affecting the right colon.

c) Colorectal tumors account for 5-10% of the causes of HDI. Large polyps and colorectal cancers can bleed intermittently or massively. It is characterized by occult bleeding (the only sign of which is iron deficiency anemia) or visible, usually intermittent, associated with chronic iron deficiency anemia, with or without changes in intestinal transit, with a blood culture test usually positive.

d) Ischemic colitis accounts for 5-15% of HDI causes. It occurs due to hypoperfusion of the colon, commonly in patients with atherosclerosis, heart failure or severe hypotension. It is characterized by sudden abdominal pain, associated with hematochesis. The typical location is the left colon (the border area between the upper and lower mesenteric artery). The diagnosis is made by abdominal CT/angio, colonoscopy.

e) Infectious colitis is rarer in our region. Pathogens involved are *Salmonella, Shigella, Campylobacter, Escherichia coli (EHEC), Clostridium difficile* (pseudomembranous colitis - occurs in tarrated patients, with the consumption of antibiotics and/or PPIs). It is characterized by bloody diarrhea, fever, abdominal pain.

f) Inflammatory bowel diseases (IBD) include ulcerative colitis (UHCR) (Fig. 11.8) and Crohn's disease (see dedicated chapter). It is characterized by chronic bloody diarrhea, abdominal pain and association with extraintestinal manifestations (arthritis, uveitis, erythema nodosum).

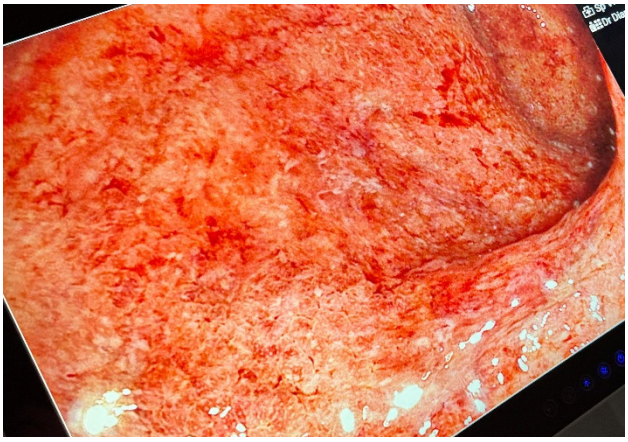


Fig. 11.8 Diffuse bleeding in UHCR

g) Hemorrhoids and anal fissures are common causes of minor bleeding. It is characterized in the case of hemorrhoids by rectal bleeding with bright red blood, at the end of defecation, without pain, and in the case of anal fissures by pain during defecation, red or pink blood on toilet paper.

2. Small bowel causes (5-10%). Hemorrhages in the small intestine are more difficult to diagnose and require investigations such as video-capsule endoscopy or enteroscopy.

a) Small bowel angiodysplasia is similar to colonic angiodysplasia. It occurs mostly in the duodenum and jejunum and can cause obscure bleeding and chronic iron deficiency anemia. If they are larger, they are most often manifested by the melena.

b) Intestinal tumors (leiomyomas, GIST, metastases, lymphomas) are rare causes of HDI, but should be suspected in patients with occult bleeding and unexplained anemia.

c) Meckel's disease (Meckel's diverticulum) is a congenital malformation that may contain ectopic gastric mucosa, leading to ulceration and bleeding. It is common in children and young adults. The diagnosis is made by technetium-99 scintigraphy (Meckel test).

d) Celiac disease and protein-wasting enteropathy can cause minor bleeding and iron deficiency anemia. The diagnosis is made by duodenal biopsy.

3. Iatrogenic causes of HDI are mainly post-polypectomy bleeding (after resection of a colorectal polyp) and postoperative complications (defective anastomoses). In these cases there is a history of medical maneuvering, and the bleeding is usually with fresh blood or hematochesis. Another cause is the overdose of anticoagulant treatment, which can precipitate diverticular, hemorrhoidal bleeding, etc.

4. Vascular causes such as aorto-enteric fistulas are rare complications of abdominal aortic aneurysm, potentially fatal.

HDI Management:

a) Patient stabilization is a priority and includes:

- Monitoring of vital signs and EKG;
- Double venous access, fluid administration and blood transfusions if necessary;
- Essential laboratory tests: blood count, urea, creatinine, coagulation tests, liver enzymes, blood glucose;

b) purgation for hemostatic purposes has been shown to be effective in diverticular hemorrhage. Half a portion of preparation solution is administered, or a whole portion if the patient's condition allows colonoscopy to be performed.

c) endoscopic treatment differs depending on the etiology of HDI

- Colon diverticulosis - hemoclips are applied if the vessel is visible bleeding, or APC is performed for diffuse bleeding. In cases where endoscopic hemostasis fails, arterial embolization by interventional radiology is recommended.
- Angiodysplasia - the treatment of choice is by APC or by applying hemoclips if there is an active vessel.
- Inflammatory Bowel Disease - Massive diffuse bleeding from UHCR can be treated with APC or hemostatic powder, associated of course with drug treatment of UHCR.
- Colorectal tumors - massive bleeding requires emergency surgical treatment if the patient's condition allows it and the tumor is operable or arterial embolization by interventional radiology.
- Post-polypectomy hemorrhages can be prevented by prophylactic application of hemoclips or endoloop in the case of large polypectomies (>2 cm). Hemostasis can be achieved by applying hemoclips or Hemospray/Purastat

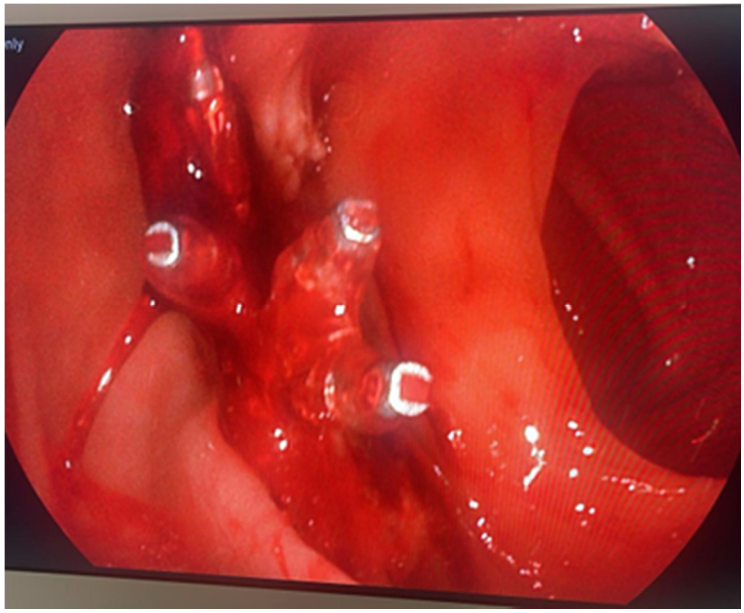


Fig. 11.9. Postpolypectomy bleeding controlled by the application of hemoclips

To note

- Digestive bleeding is a potentially fatal medical emergency, requiring rapid diagnosis and intervention. They are classified into upper digestive hemorrhages (HDS - with prigine in the esophagus, stomach, duodenum) and lower digestive hemorrhages (HDI - originating in the jejunum, ileum, colon), depending on the location of the bleeding related to the ligament of Treitz.
- The management of the patient with digestive hemorrhage primarily involves his hemodynamic rebalancing, diagnostic and therapeutic endoscopy is not done in a patient in hypovolemic shock.

- Before endoscopy, associated with rebalancing treatment, drug treatment can be started (PPI in the suspicion of non-varicella HDS, vasopressor medication in the suspicion of varicella hemorrhage).
- Purgation for hemostatic purposes is useful in diverticular HDI.
- The main techniques of endoscopic hemostasis are:

A. Injectable Therapy – commonly used as a first line for active bleeding, usually in combination with other methods.

- Substances used:
  - Adrenaline 1:10,000 – local vasoconstriction, rapid (but temporary) effect.
  - Sclerosing solutions – cyanoacrylate (for esophageal varicose veins).

B. Mechanical therapy (hemostasis with clips)

- Through-the-scope hemoclips (TTS clips) – ideal for visible vessel ulcers (Forrest IIa), Mallory-Weiss lesions, Dieulafoy lesions, diverticular hemorrhage, postpolypectomy hemorrhage
- Over-the-Scope Systems (OTSC) – for large ulcers (>2 cm) or refractory bleeding.
- Elastic ligation – the standard method for esophageal varicose veins.

C. Heat therapy

- Gold Probe/BiCOAG bipolar probe electrocoagulation – captive coagulation for hemorrhagic ulcers.
- Thermal probes:
  - Heater Probe – applies heat directly to the lesion for coagulation.
  - Argon Plasma Coagulation (APC) – for diffuse bleeding (e.g. angiodysplasia, GAVE, post-irradiation proctitis, UHCR).

D. Hemostatic substances

- Hemospray, PuraStat – used for diffuse bleeding or when classical methods are not applicable or outdated (uncontrolled acute non-variceal or variceal bleeding, diffuse bleeding after endoscopic resection).

- Combination therapy (e.g. adrenaline injection + hemoclip/thermal coagulation) is superior to monotherapy.

12. CELIAC DISEASE

Definition

Celiac disease or gluten enteropathy is a systemic autoimmune disease generated by gluten intolerance in cereals (wheat, rye, barley). The symptoms are digestive (given by damage to the intestinal mucosa and malabsorption) and extra-intestinal. The morphological element is represented by the atrophy of the jejunal mucosa, and the gluten-free diet leads to the clinical and histological improvement of the disease.

Epidemiology

The disease is widespread in temperate climate areas and has a chronic evolution, with the appearance or exacerbation of gluten-containing flours.

The prevalence of the disease worldwide is 1%, being similar in children and adults. It occurs in the first decades of life, with women being more frequently affected (female/male ratio 1.5:1).

The disease was widely described in the Netherlands after World War II, because the lack of wheat during the war led to a decrease in the frequency of the disease, and the reintroduction of wheat after the war favored the reappearance of symptoms. Over the past 15 to 20 years, in addition to the classic forms of the disease characterized by diarrhea, steatorrhea, and malabsorption, latent forms of gluten intolerance have emerged. These do not necessarily result in villous atrophy but may instead manifest as interstitial or preatrophic jejunitis, often with a more subtle clinical presentation.

The condition has a genetic basis and often displays a familial pattern. First-degree relatives of affected individuals carry a 4–17% risk of developing celiac disease, while those who are homozygous for HLA-DQ2 face an increased risk of up to 30%.

Etiopathogenesis

Celiac disease arises from the interaction of environmental, genetic, and immunological factors. In genetically susceptible individuals, exposure to gluten triggers a cascade of immune-mediated reactions that ultimately damage the intestinal mucosa.

In gluten enteropathy, a genetic deficiency of oligopeptidase in enterocytes leads to heightened sensitivity to α-gliadin (fraction III of gluten). Gliadin is present predominantly in wheat and rye, and to a lesser extent in barley and oats. The immunogenicity of gluten varies across geographical regions, which may account for differences in the prevalence of the disease.

Prolonged contact of the enterocyte (in the absence of intestinal oligopeptidase) with undigested gliadin will lead to a local immune conflict, through the formation of gliadin immune complexes - antigliadin antibodies. These immune complexes attach to the intestinal mucosa, stimulate the aggregation of natural killer (NK) T lymphocytes and the

release of pro-inflammatory mediators that will produce tissue injury, with villous atrophy and cryptic hyperplasia.

Adherence to a gluten-free diet promotes restoration of the villous epithelium and improvement of transit disturbances and malabsorption, provided the diagnosis is established within the first 3 to 6 years after clinical onset. In advanced stages of the disease, however, regeneration of the intestinal mucosa is markedly delayed or may not occur at all.

Pathology

Macroscopically the pathological intestinal mucosa appears pearlescent whitish, with the absence of villi that give the appearance of normal velvety appearance.

Microscopically, the lack of normal villi is visualized, which appear flattened, up to total villous atrophy in severe forms (Fig. 12.1); with cryptic hyperplasia and the presence of intraepithelial lymphocytes.

Histological staging of the disease is performed using the modified Marsh classification, which evaluates the degree of villous atrophy, the presence of crypt hyperplasia, and the extent of chronic inflammatory infiltrate.

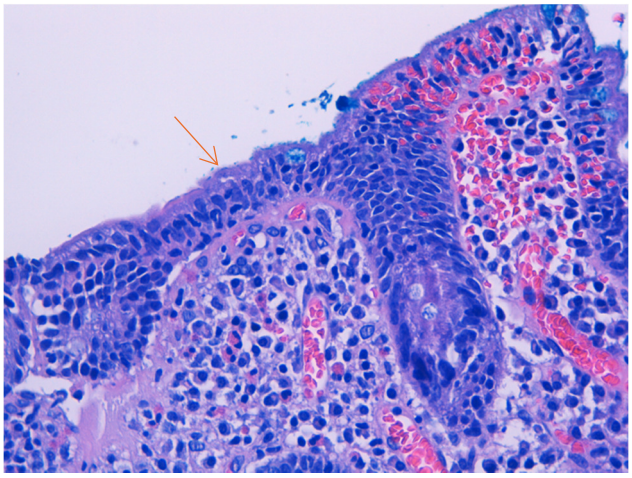


Fig. 12.1 Celiac disease – complete villous atrophy and multiple intraepithelial lymphocytes.

Clinical picture

Clinically, the manifestations of celiac disease correlate with the severity and extent of lesions in the intestinal mucosa. The disease may be *symptomatic* or *asymptomatic* and can be diagnosed at any age, often in the absence of the classic presentation. The *typical clinical picture* includes diarrhea with or without steatorrhea, edema, and weight loss. In atypical forms, however, celiac disease may present with short stature, infertility, unexplained anemia, mild hepatocytolysis of unknown origin, recurrent aphthous stomatitis, or dermatitis herpetiformis.

In celiac disease with *infantile onset*, the child develops normally until the introduction of flour into the diet. Subsequently, soft, foul-smelling stools and intestinal cramps appear, followed by anemia, hypoproteinemia, edema, and growth retardation.

In adults, celiac disease typically presents with diarrhea, steatorrhea, and, in later stages, malabsorption syndrome. Patients often experience chronic diarrhea, characterized by 3–6 stools per day over several years, accompanied by abdominal discomfort and bloating. The onset of diarrheal symptoms is usually insidious, beginning in childhood or sometimes manifesting after the age of 20–30 years. Diarrhea frequently occurs 1–2 hours after the ingestion of wheat-based foods such as bread, pasta, or noodles. As the disease progresses, multiple additional food intolerances may develop, complicating the diagnostic process. A key clinical feature is the correlation between symptoms and wheat consumption, with notable improvement typically observed within 2–3 weeks of eliminating wheat products from the diet.

Many cases of celiac disease present with *extraintestinal manifestations*, including secondary iron-deficiency anemia, weight loss, hypocalcemia, dermatological conditions such as dermatitis herpetiformis, osteoporosis, infertility, recurrent aphthous stomatitis, enamel hypoplasia, vitamin deficiencies, psychiatric disorders, and arthritis, etc.

Biological picture

Biochemical and hematological tests may reveal microcytic, hypochromic, iron-deficiency anemia and mild hepatocytolysis. In advanced cases, features of malabsorption syndrome, including hypoproteinemia, hypoalbuminemia, and vitamin deficiencies, are often present.

Serological tests involve the determination of antibodies specific to celiac disease:

- anti-tissue transglutaminase IgA antibodies (sensitivity and specificity ≥ 95%) and dosage of total serum IgA level (IgA deficiency is more common in patients with celiac disease);
- anti-gliadin IgA antibodies;
- anti-gliadin deamidate IgA antibodies;
- anti-endomysium antibodies.

Overall, these antibodies have a sensitivity and specificity > 90% for the diagnosis of celiac disease, and their quantitative titers correlate with the extent of intestinal inflammation and the degree of villous atrophy. The titers of celiac disease–related antibodies typically normalize within several months to a year of strict adherence to a gluten-free diet, serving as a useful indicator of the patient's compliance with dietary restrictions.

Paraclinic

Upper digestive endoscopy with multiple biopsies from duodenum I (in 10% of cases only the duodenal bulb is affected) and *duodenum II*. Endoscopic findings suggestive of

celiac disease include mucosal fissures, nodular mucosa, mucosal atrophy, and loss of duodenal folds, often giving the duodenal mucosa the characteristic appearance described as “cracked-earth”. (Fig. 12.2). Histological lesions are most pronounced in the proximal small intestine, although in severe cases they may extend to the ileum.

Serological tests for celiac disease are positive in 90–100% of advanced cases, but may be less reliable in the early stages. Therefore, an intestinal biopsy, with sampling of at least four fragments, is recommended in all suspected cases.

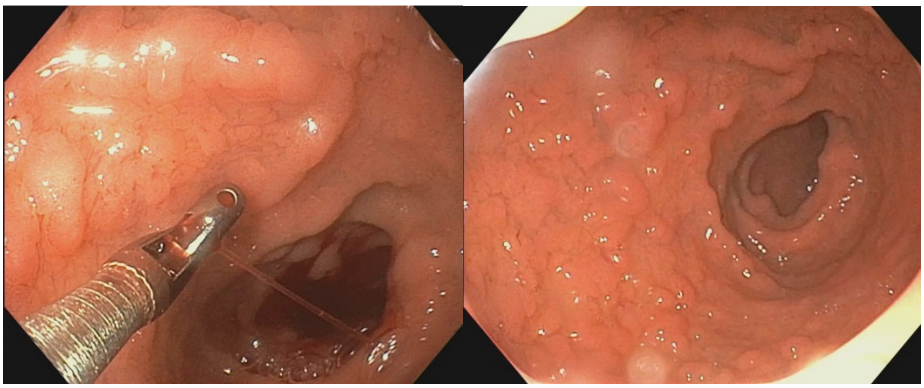


Fig. 12.2 Biopsies taken from the duodenum II in a patient with celiac disease. Endoscopically, a duodenal mucosa with a nodular appearance and the deletion of the duodenal folds are highlighted.

Additional paraclinical tests that may be performed in celiac disease include:

- genetic testing to identify HLA-DQ2 and HLA-DQ8 alleles.
- quantification of steatorrhea, which in severe cases typically ranges from 7 to 50 g/day.
- assessment of intestinal absorption, such as the D-xylose test.
- barium radiological examination of the intestine, which will usually reveal dilated loops;
- evaluation for malabsorption syndrome– either selective (iron, folic acid, calcium) or global;
- endoscopic video capsule (may be useful in refractory celiac disease and suspected complications).

The positive diagnosis is made on the basis of diarrheal syndrome, steatorea and malabsorption appearing later in the evolution. Food history, as well as family history, can suggest the diagnosis. The association of the intestinal biopsy with the presence of positive serology for celiac disease is the "gold standard" in terms of the diagnosis of the disease.

Celiac disease should be considered in cases of unexplained iron-deficiency anemia, early-onset osteoporosis (before age 50 in women), growth retardation or

delayed puberty in children, and in patients with autoimmune conditions such as type 1 diabetes or Hashimoto's thyroiditis (with an estimated prevalence of 1 in 30). Additional clinical clues include recurrent aphthous stomatitis and dermatitis herpetiformis.

The differential diagnosis should include other conditions that present with chronic diarrhea:

- lactase deficiency, in which diarrhea is associated with the consumption of milk and dairy products, positive lactose intolerance test;
- Crohn's disease characterized by the presence of an inflammatory syndrome, elevated fecal calprotectin, and typical endoscopic findings.
- Intestinal TB associated with inflammatory markers, altered endoscopic appearance, positive Quantiferon test, and potentially positive cultures for Mycobacterium tuberculosis.
- chronic pancreatitis - often linked to a history of alcoholism and supported by characteristic imaging findings, etc.

Possible complications are malabsorption with malnutrition, lactose intolerance, bowel cancer, coronary artery disease, being more common in undiagnosed patients or those noncompliant with a gluten-free diet.

The evolution and prognosis depend on the time of diagnosis.

In undiagnosed cases, malabsorption will progressively occur, which will lead, in severe cases, to death. The risk of developing intestinal lymphoma increases in symptomatic patients and with prolonged exposure to foods containing gluten. Other cancers favored by celiac disease are esophageal cancer and small intestine cancer.

For patients that are diagnosed early and adhere strictly to a gluten-free diet, the prognosis is favorable, with resolution of diarrhea, steatorrhea, and malabsorption, and a significantly reduced risk of intestinal lymphoma.

Treatment

Hygienic-dietary regimen. *A strict, lifelong gluten-free diet is essential,* excluding wheat, barley, rye, and oats, with careful attention to potential cross-contamination during processing.

Gluten-free food groups include vegetables, fruits, dairy products, meat, fish, legumes, nuts, and peanuts. Gluten-free cereals and grains suitable for consumption include rice, corn, soy, lentils, millet, quinoa, and cassava. These products can be consumed by patients with celiac disease.

Following initiation of a gluten-free diet, clinical symptoms typically improve within days to weeks, preceding normalization of antibody titers, which may take several months

up to one year. Histological recovery of the intestinal mucosa generally occurs within 3–5 years of strict dietary adherence.

Compliance with the diet can be monitored by measuring anti–tissue transglutaminase IgA antibodies. Current guidelines also recommend a follow-up intestinal biopsy at 24 months, as histological improvement or normalization closely correlates with adherence to the gluten-free regimen.

A wide variety of gluten-free products are available on the market, but it is essential to carefully check labels to ensure they are truly gluten-free. Patient support organizations and online forums provide valuable resources, including discussions on disease management, nutrition, and gluten-free recipes.

Medications. In celiac disease, the necessary medication addresses complications and correction of nutritional deficiencies. In refractory forms of celiac disease, when there is no clear response to the elimination of dietary gluten (possibly advanced phases), treatment with oral corticosteroids in low doses can be administered for a period of 4 to 8 weeks, which can improve the clinical symptoms.

Key Points on Celiac Disease

- Celiac disease or gluten enteropathy is a systemic autoimmune disease generated by intolerance to cereal gluten.

- The typical presentation includes diarrhea, with or without steatorrhea, edema, and weight loss. The disease can also be asymptomatic, with iron-deficiency anemia often serving as a clue.

- The most important extraintestinal manifestations are: secondary iron deficiency anemia, weight deficit, dermatitis herpetiformis, osteoporosis, infertility, aphthous stomatitis, vitamin deficiencies.

- Serological tests specific to celiac disease include anti-tissue transglutaminase IgA antibodies; anti-gliadin IgA antibodies; anti-gliadin deamide IgA antibodies; anti-endomysium antibodies.

- The histopathological examination visualizes the lack of normal villicities, which appear flattened, up to total villous atrophy in severe forms, with cryptic hyperplasia and the presence of intraepithelial lymphocytes.

- The endoscopic findings include mucosal fissures, nodular mucosa, mucosal atrophy, loss of duodenal folds, and a “cracked-earth” appearance of the duodenal mucosa.

- If undiagnosed, celiac disease may progress to severe malabsorption, leading to steatorrhea, underweight, hypoproteinemia with edema and ascites, and, in extreme cases, death.

- The cornerstone of therapy is a strict gluten-free diet, which leads to clinical improvement within weeks, normalization of serological markers within months, and histological recovery over several years.

13. DISACCHARIDASE DEFICIENCY (LACTASE DEFICIENCY)

Definition

Disaccharidase deficiency is a relatively common clinical condition resulting from the absence or insufficient secretion of disaccharidases in the small intestine. The condition is frequently underrecognized, which can lead to chronic gastrointestinal discomfort and persistent digestive symptoms.

Pathophysiology

Dietary carbohydrates are ingested in the form of monosaccharides (glucose, fructose, galactose), disaccharides (lactose, sucrose, maltose and trehalose) and digestible (starch, glycogen) and indigestible oligosaccharides (cellulose vegetable fibers and hemicellulose).

Disaccharides are broken down by intestinal glycosidases—lactase, maltase, sucrase, and trehalase—which are secreted at the brush border of enterocytes. These enzymes hydrolyze disaccharides into monosaccharides within the intestinal lumen. The distribution and activity of disaccharidases vary along the small intestine, with the highest activity in the proximal jejunum. Genetic programming governs disaccharidase secretion, and the loss of enzymatic activity may reflect this intrinsic regulation.

Disaccharidase deficiency can be:

- *congenital:* present at birth, e.g., congenital lactase deficiency (newborn intolerance to milk), sucrase, maltase, or trehalase deficiencies
- Acquired: can develop later in life and may be transient or permanent. The most common form is lactase deficiency, leading to adult-onset lactose intolerance.

The absence or reduced activity of disaccharidases in the intestinal epithelium impairs the hydrolysis of disaccharides into monosaccharides, preventing their absorption. Initially, this leads to an increase in intraluminal osmolarity, resulting in water retention within the lumen and an increased volume of intestinal contents. This distension stimulates intestinal osmo- and chemoreceptors, triggering the release of prokinetic chemical mediators, such as serotonin and bradykinin. Undigested disaccharides that reach the colon are metabolized by bacterial flora, producing short-chain fatty acids (butyrate, lactate, propionate, acetate) and gases (carbon dioxide, hydrogen, methane) through fermentation. Clinically, these processes manifest as acidic, watery stools, abdominal bloating, distension, and flatulence following ingestion of disaccharides.

The severity of symptoms in disaccharidase deficiency depends on both the degree of enzyme deficiency (partial or total) and the amount of disaccharide ingested.

Since lactase deficiency is the most commonly encountered form in clinical practice, it will be discussed in detail. Lactase deficiency also serves as a model for understanding other disaccharidase deficiencies.

LACTASE DEFICIENCY

Definition

Lactase deficiency is characterized by a reduction or complete absence of lactase enzyme secretion in the intestinal mucosal epithelium.

Epidemiology

The prevalence of lactase deficiency varies significantly across geographical regions. Populations with historically low dairy consumption—such as Australian Aborigines, Eskimos, American Indians, and Chinese—exhibit lactase deficiency in 40–90% of adults. In contrast, populations with a long history of animal husbandry, such as Europeans and their descendants, have a much lower prevalence, ranging from 5–15% in northern Europe.

Lactase deficiency can also be **congenital**, manifesting immediately after birth with the onset of diarrhea.

Late-onset primary lactase deficiency is a relatively normal situation. Thus, after the infant has stopped breastfeeding, there is a repression of lactase activity. An adult still has about 5-10% of the newborn's lactase secretion. This primary form is genetically determined and varies among ethnic groups, independent of geographical location, environmental factors, or current milk consumption. The persistence of lactase activity into adulthood is considered an adaptive genetic mutation in populations with a long history of dairy consumption, while lactase deficiency is viewed as a normal condition in most humans.

Acquired lactase deficiency (secondary) results from reduced lactase secretion due to intestinal injury or inflammation. Common causes include acute gastroenteritis, Crohn’s disease, microscopic colitis, giardiasis, radiation enteritis, short bowel syndrome, and temporarily in celiac disease until villous atrophy resolves with a gluten-free diet. Acquired lactase deficiency may be transient, with lactase activity returning to normal after resolution of the underlying intestinal pathology.

Pathophysiology

Lactase deficiency will cause lactose malabsorption in the small intestine. Thus, lactose will go through the bacterial fermentation process in the colon with the production of gases and short-chain fatty acids. Clinically, this process will lead to abdominal pain, bloating and diarrhea after taking lactose. Lactase activity decreases physiologically after ablactation of the infant and is slower to recover after enterocyte damage compared to other disaccharides.

Pathology

Microscopically, the intestinal mucosa appears normal, including the villi and the brush border. Immunohistochemical techniques can demonstrate a reduction or absence of lactase activity at the brush border. Structural changes are typically observed only in cases of secondary (acquired) lactase deficiency, reflecting the underlying intestinal disease.

Clinical picture

The clinical signs of the disease are relatively typical, however they are often ignored by the sufferer for years. The signs of the disease differ depending on the intensity of the lactase deficiency and the amount of lactose consumed. Typically, after consuming milk or milk derivatives, the patient with lactase deficiency appears, after a few tens of minutes, bloating, bloating, explosive watery stools, flatulence.

The symptomatology is more pronounced in patients with functional gastrointestinal diseases or psychiatric conditions due to their visceral hypersensitivity.

The tolerance of dairy products varies among individuals with lactase deficiency. Sweet milk is generally the least well tolerated, followed by yogurt and kefir, while fermented or unfermented cheeses are usually better tolerated. Symptom severity also depends on the quantity and frequency of lactose intake, as repeated consumption can further deplete enterocyte lactase reserves.

Biological picture

Patients with lactose intolerance have a normal biological profile. In secondary lactase deficiency, changes related to the underlying pathology (anemia, inflammatory syndrome, etc.) may occur.

Paraclinic

Respiratory tests use C14 lactose labeling, with the determination of CO2 labeled in exhaled air (it is a marker of reabsorbed lactose), or only with lactose, with the determination of H2 in exhaled air (an increase in exhaled H2 > 20 ppm 3-6 hours after ingestion suggests a lactase deficiency, being a marker of unexorbed lactose).

Hydrogen testing in exhaled air is a simple test that requires minimal prior preparation: fasting for 12 hours and avoiding foods that digest slowly such as beans, peas, lentils 24 hours before testing.

The actual testing is done in the morning, the patient is asked to blow into a device that will measure the basal amount of H2, then drink a solution containing lactose. Subsequently, the patient is asked to blow again into the machine at approx. 30 min, testing takes 2-3 hours. The significant increase in H2 in the breath confirms lactose intolerance.

Genetic test – by determining the C/T genotype, genetic predisposition can be established and the differential diagnosis can be made between primary or secondary deficiency.

The lactose tolerance test (TTL) consists of 3 phases: clinical, biological, and radiological. The patient is determined to have fasting blood glucose, after which 50 g of lactose in 400 ml of water and a packet of barium sulfate are administered. Blood glucose is taken every 30, 60, 90 and 120 minutes (simplified, only every 1 and 2 hours) and an empty abdominal X-ray is performed every hour.

Interpretation of the results:

- clinical - the appearance of typical symptoms indicates a positive clinical test (possibilities of error after gastrectomy, when, no longer having the pyloric frenulum, osmotic diarrhea due to milk appears);

- biological - the absence of an increase in blood glucose by more than 25% of the fasting value is a positive test (if lactose does not break down into glucose and galactose, blood glucose will remain in the plateau);

- radiological: dilution of the baritate mass (by hypersecretion), aeroenteria with distension of the loops and a very accelerated intestinal transit will occur; Usually, the barium column reaches the colon within an hour.

Intestinal biopsy with lactase determination - ideally requires a jejunal biopsy or possibly a duodenal biopsy at upper digestive endoscopy, with determination of the lactase value (allows a quantitative assessment of the deficiency). The method is laborious, expensive, requires biopsy.

Diagnosis

Anamnesis is the first step in diagnosing lactase deficiency. Patients typically report gastrointestinal symptoms following the ingestion of lactose-containing foods.

Based on clinical suspicion, a simple outpatient assessment can be performed: the patient ingests 250–300 ml of milk on an empty stomach, without other foods, and symptoms are observed over 2–3 hours. The appearance of characteristic symptoms strongly supports the diagnosis.

A **definitive diagnosis** is established by combining clinical findings with one of the objective tests described previously. Mild forms of lactase deficiency may be more challenging to diagnose.

Differential diagnosis should be made with:

- milk allergy (sometimes in children), other food allergies,

- osmotic intolerance to milk (upset stomach),

- psychogenic intolerance to milk (patients experience aversion toward milk without a physiological cause).

The evolution of the disease in adults is favorable, because most patients balance and modify their diet by avoiding milk products until the discomfort disappears. In some cases, especially undiagnosed, multiple conditioning may occur, with prolonged diarrhea, sometimes even malabsorption.

Treatment

Hygiene-dietetic. The treatment aims to reduce the patient's symptoms and involves limiting the intake or completely removing milk and related products from the diet (depending on the existing lactase reserve).

In primary lactase deficiency, it is recommended to eliminate milk and milk products from the diet.

In adults, a strictly lactose-free diet is generally unnecessary, as most individuals with lactase deficiency can tolerate 5–10 g of lactose per day (approximately 100–250 ml of milk) without developing symptoms. Patient education regarding the lactose content of various foods is essential, as lactose may also be present in processed products such as puddings, chocolate, candies, and some soups or creams.

Lactose content varies by dairy product: a cup of milk contains roughly 12 g of lactose, with yogurt, fresh cheese, and fermented cheeses containing progressively lower amounts.

Lactose-free milk is particularly useful in cases of congenital lactase deficiency, where dietary restrictions begin from birth. In Table 13.I the indicative lactose content of different products is presented, the lactose content may vary depending on the brand and processing method.

Table 13.I Indicative lactose content found in various foods or food products.

Food	Lactose content (*g lactose/100g*)
Condensed milk	9
Ice cream	5
Cow's milk	4,8
Goat's milk	4,1
Yogurt	4
Milk chocolate	3,7
Cream	3
Cottage cheese	2,7
Mozzarella cheese	0,5
Butter	0,5
Cheddar cheese	0,1

Drug treatment. It consists of taking dietary supplements containing lactase (of bacterial origin), such as lactase preparations, Laluk, Lact-Aid, Digex plus. Administering 2–3 tablets of lactase-containing preparations concurrently with meals can facilitate lactose digestion and prevent the onset of clinical symptoms. These products are widely available in pharmacies and do not require a prescription.

A low-FODMAP diet is effective in 50–80% of cases. Additionally, supplementation with probiotics, such as Lactobacillus and Bifidobacterium, may provide symptomatic relief. During acute gastroenteritis episodes, temporary restriction of lactose intake is recommended.

The other disaccharide deficiencies are very rare. In **the sucrase deficiency**, sugar will be excluded, in **the maltase deficiency** starch-containing foods will be excluded, and in **the trehalase deficiency,** avoidance of foods containing trehalose, such as fresh mushrooms.

Key Points on Disaccharidase Deficiency

- Disaccharidase deficiency is a relatively common clinical entity, caused by the absence or insufficient secretion of disaccharidades at the enteral level.
- Disaccharidases—including lactase, maltase, sucrase, and trehalase—are secreted at the brush border of enterocytes and hydrolyze disaccharides into absorbable monosaccharides.
- Symptom intensity depends on the degree of enzyme deficiency (partial or total) and the amount of disaccharide ingested.
- The most common disaccharidase deficiency is lactase deficiency and refers to the reduction or lack of lactase secretion in the epithelium of the intestinal mucosa.
- Symptoms are generally typical, including abdominal bloating, distension, watery diarrhea, and flatulence within tens of minutes after ingestion of milk or dairy products. Symptom severity depends on the amount of lactose consumed.
- Sweet milk is least tolerated, followed by yogurt and kefir, while cheeses are usually better tolerated.
- The diagnosis is based on clinical history (often sufficient) and can be confirmed by the lactose tolerance test, respiratory tests, genetic test (in the absence of the clinical picture, the latter is not sufficient for diagnosis).
- Hygienic-dietary treatment involves limiting the intake or completely removing milk and dairy products from the diet.
- Drug treatment consists of taking dietary supplements containing lactase (of bacterial origin) to facilitate lactose digestion.
- The other disaccharide deficiencies are very rare. In the sucrase deficiency, sugar will be excluded, in the maltase deficiency starch will be excluded, and in the trehalase deficiency, young mushrooms will be excluded.

14. MALABSORPTION SYNDROME

Definitions

Malabsorption syndrome (MS) is a pathological situation in which the assimilation of nutrients is difficult or impossible due to disorders in their digestion, transport or absorption, with systemic repercussions. It can affect macronutrients (proteins, carbohydrates, fats) and/or micronutrients (vitamins, electrolytes) resulting in their excessive fecal elimination, gastrointestinal symptoms, and nutritional deficiencies.

The term "malabsorption syndrome" includes maldigestion and malabsorption itself.

Maldigestion is caused by damage to the intraluminal digestive processes (e.g. in pancreatic insufficiency) or at the level of the intestinal mucosa (e.g. in lactase deficiency), responsible for the breakdown of food into absorbable food principles

Malabsorption is due to disturbances in the mechanisms of transparietal transport of the final products of digestion to the intestinal mucosa as well as through the lymphatic and blood pathways. Malabsorption is found in intestinal diseases with destruction of the mucosa (for example in Crohn's disease) where digestion has been carried out properly.

Malabsorption syndrome can be global or selective. In ***global malabsorption*** , all dietary principles are affected, which occurs in diseases associated with extensive damage to the mucosa, or when the absorption surface is reduced, thus producing disorders of absorption of all food components (for example in celiac disease or short bowel syndrome). ***Selective malabsorption*** is caused by diseases that interfere with the absorption of a single nutrient or a limited range of nutrients. An example is Biermer's anemia associated with atrophic gastritis, a disease that leads to the malabsorption of cobalamin (vitamin B12).

Notions of digestion physiology

Protein digestion. In the stomach, under the action of pepsin and hydrochloric acid, food proteins are converted into peptones. Subsequently, at the level of the duodenum, pancreatic proteases (chymotrypsin, trypsin) cleave peptones to amino acids, bipeptides and oligopeptides. At the level of the brush edge of the intestinal mucosa, under the action of oligopeptidases, bi- and oligopeptides are broken down into amino acids.

Digestion of carbohydrates. Dietary carbohydrates are influenced very little by salivary amylase because it is quickly inactivated by acidic gastric pH. In the intestine, under the action of pancreatic amylase, carbohydrates will be broken down into disaccharides, which, under the action of disaccharides at the edge of the intestinal brush, will be transformed into monosaccharides (glucose, fructose, galactose).

Digestion of lipids. Food lipids are emulsified and mycelized in the small intestine under the action of bile salts. Subsequently, under the action of pancreatic lipase, triglycerides will be broken down into monoglycerides and free fatty acids. A condition for lipase to be able to act is a neutral pH, achieved by neutralizing gastric HCl by bicarbonate in pancreatic juice.

Notions of absorption physiology

The absorption of proteins is done actively (with energy consumption) in the form of amino acids, predominantly at the level of the proximal jejunum.

The absorption of carbohydrates is done in the form of monosaccharides, at the level of the proximal jejunum, actively for glucose and galactose, and passively for fructose. Xylose, a pentosic monosaccharide, is actively absorbed at low concentrations and passively, by diffusion, at high concentrations.

The absorption of lipids, broken down into monoglycerides and free fatty acids, occurs mainly in the first 100 cm of the jejunum, and to a lesser extent in the ileum. Initially, the mechanism is passive for crossing the cell membrane, later requiring energy consumption.

The absorption of iron takes place in the duodenum and in the first intestinal loops, in reduced form. Transport inside the enterocyte is done with the help of ferritin, and in circulation the iron is taken up by siderophylline.

Vitamin B 12, extrinsic factor, binds to intrinsic factor secreted in the stomach. Vitamin B12 is absorbed in the terminal ileum, where there are receptors that recognize the intrinsic factor-extrinsic factor complex.

Fat-soluble vitamins (A, D, E, K) are absorbed in the proximal half of the small intestine.

Electrolytes and water are absorbed both passively and actively, in the duodenum and ileum, while Na and K are also absorbed in the colon.

Etiology of malabsorption syndrome

Malabsorption syndrome is caused by the varying interpenetration of maldigestion with malabsorption itself, the main causes of which are presented in Tables 14.I and 14.II

Table 14.I. Causes of maldigestion

Gastric	***Bile ducts***	***Pancreatic***	***Intestinal***
- gastrectomy Billroth II, - gastroenteroanastomosis (GEP), - Zollinger Ellison syndrome	- chronic liver disease, - chronic biliary obstructions	- chronic pancreatitis, - pancreatic cystic fibrosis	- disaccharidase deficiency (lactase, maltase, sucrace, trehalase), - Blind loop syndrome - by bacterial overpopulation (SIBO)

Table 14.II. Causes of intestinal malabsorption

Abnormal absorption intestinal epithelium	***Short bowel syndrome***	***Abnormal intestinal transport***	***Increased intestinal transit speed***
- celiac disease (Fig.13.1), - Whipple's disease, - intestinal amyloidosis, - chronic intestinal ischemia, - intestinal Crohn's disease, - tropical sprue, - Intestinal TB	- post-surgical, - enterocolic fistula, - Surgical bowel bypass	- intestinal lymphoma, - idiopathic intestinal lymphangiiectasia, - congenital cystic pneumatosis	- Hyperthyroidism - chronic diarrhea (ulcerative colitis, Crohn's disease, Verner-Morrison syndrome = pancreatic cholera)

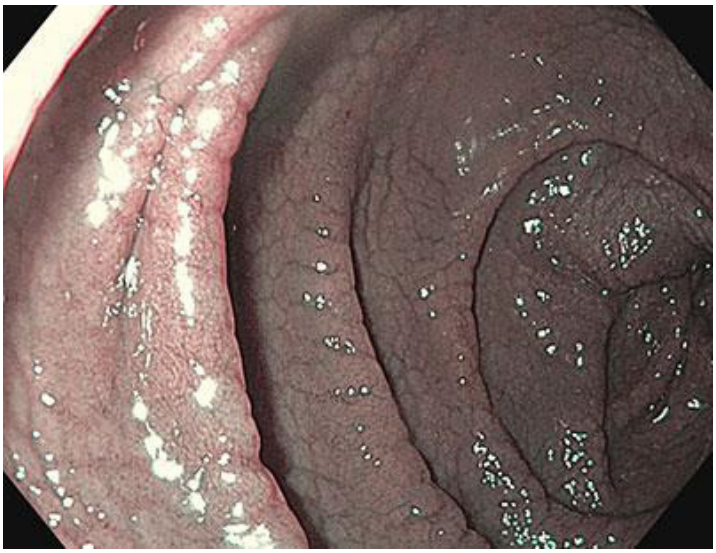


Figure 13.1. Endoscopic image of the duodenum in celiac disease – nodular appearance of the mucosa, disappearance of folds and presence of cracks in the mucosa, "cracked earth" appearance.

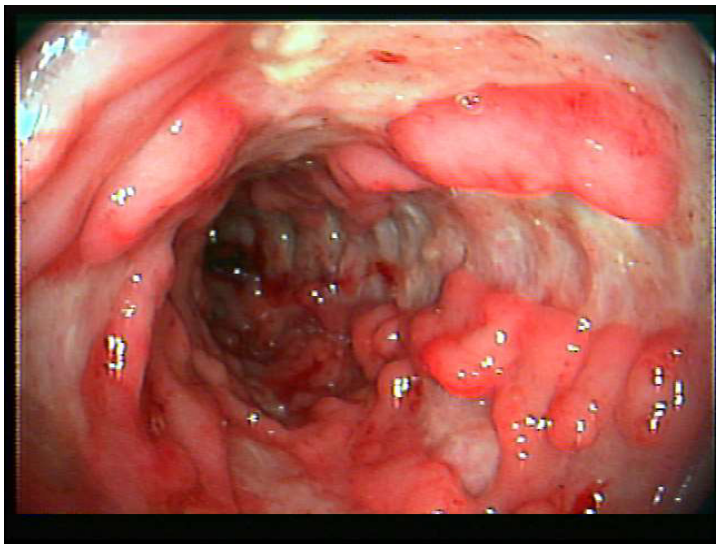


Figure 13.2. Endoscopic image of the colon in Crohn's disease – aphthoid lesions and linear deep ulcers

Clinical picture

Malabsorption syndrome should be suspected in patients with chronic diarrhea, weight loss, or nutritional deficiencies without an obvious cause. In severe cases, *steatorea* (soft, light-colored stools, with a rancid smell, adherent to the toilet) appears, defined as a loss of more than 5 g of fat/24 hours through the stool. The clinical symptomatology varies depending on the type of malabsorption.

Thus, in *lipid malabsorption*, the patient will present diarrhea with voluminous, yellowish stools and in severe forms, steatorrhea. Lipid malabsorption will cause a deficiency of fat-soluble vitamins and excessive fecal loss of calcium and magnesium.

In *carbohydrate malabsorption*, the patient will present bloating, flatulence, acidic stools, watery diarrhea, phenomena that occur about 1 hour after carbohydrate ingestion.

In *protein malabsorption*, the predominant clinical signs are edema and ascites (secondary to hypoalbuminemia), muscle atrophy, amenorrhea.

In *the malabsorption of vitamin B12 and folic acid*, the patient will present neurological signs (paresthesias, ataxia, balance disorders, loss of vibrating sense), as well as skin pallor caused by anemia.

Deficiency *of iron absorption* will produce skin pallor (due to anemia), glossitis, pagophagia.

Disorders in the *absorption of B vitamins can* generate chelosis, painless glossitis, angular stomatitis, pellagra, beri-beri neuritis, peripheral neuropathy, acroderma.

Disorders *absorption of calcium, vitamin D and magnesium* can generate paresthesias, tetany, osteopenia, osteomalacia, fractures on pathological bone. The sign of Chvostek and Trousseau may be present, as well as pain in the lower and upper limbs.

The deficiency of *vitamin K absorption* generates coagulation disorders, materialized by gingivorrhagia, hematomas, epistaxis.

Endocrine diseases are common and are due to the malabsorption of proteins and/or lipids, which are substrates for hormones. Thus, pituitary insufficiency (with growth disorder in children), cortico-adrenal insufficiency (Addison's disease) and gonadal insufficiency (impotence, amenorrhea, infertility) can occur.

In addition to the clinical symptoms associated with malabsorption syndromes, there are also *signs of the disease that caused malabsorption*. Abdominal pain is constantly present in patients where malabsorption is caused by Crohn's disease, chronic pancreatitis, limited in intestinal lymphoma, persistent ulcerative pain in Zollinger-Ellison syndrome, etc.

Paraclinical investigations

When the anamnesis and objective clinical examination raise the suspicion of malabsorption syndrome, the initial evaluation should include usual tests to support the diagnosis and assess the extent of the deficits that need to be corrected. These will include: blood count, peripheral smear, albumin, folate, ferritin, total iron binding capacity, serum vitamin B12, vitamin D, serum ionogram (calcium, phosphorus, magnesium).

These usual tests must be supplemented with specific tests for the diagnosis of malabsorption

1. Lipid malabsorption assessment tests:
   - *The measurement of fecal fat* over a period of 72 hours is the gold standard method and certifies the presence of steatorrhea. At an ingestion of 100 g of lipids for 72 hours, the elimination of more than 7 g/day is pathological. The normal value of fecal fats is between 1-5% of the amount ingested.
   - *Sudan III staining of the stool* – it's a semi-quantitative test, the lipids eliminated in the stool will be colored red
   - *Stool examination* - which allows the counting of fat globules eliminated through the stool
   - Acid steatocrit - detects steatorrhea in a stool sample - with a sensitivity of 100% and specificity of 95%
   - *Near-infrared reflectance analysis (NIRA)* – accuracy comparable to 72-hour fecal fat measurement, but faster; it also measures nitrogen and carbohydrates.

2. *Tests to assess protein malabsorption:*
   - *Coprologic exam* – with the highlight of undigested or partially digested muscle fibers in the stool exam
   - *Determination of fecal nitrogen* **–** after ingestion of 100-120 g of protein/day, a value below 2.5g/24h is considered pathological.

3. *Exploring carb malabsorption:*
   - *Hydrogen breath test* - limited accuracy
   - *Lactose tolerance test*
   - *The D-xylose test* differentiates pancreatogenic MS (the test is normal) from intestinal MS (where the test is altered). The test consists of oral administration of 25 g of D-xylose and then collecting urine for 5 hours. A urinary discharge below 5 g signifies a disturbance of intestinal absorption.

4. Pancreatic Functionality Assessment Tests

Patients who are heavy consumers of alcohol and have an abdominal pain syndrome, in addition to the general clinical signs of malabsorption, should be investigated by abdominal ultrasound, echoendoscopy, computed tomography or magnetic resonance imaging, thus highlighting the alterations of the pancreatic parenchyma.

Fecal elastase test I it is useful in the diagnosis of incipient pancreatic insufficiency; *VIP level dosage* (vasoactive intestinal polypeptide) can make the diagnosis of VIP-human or pancreatic cholera (severe, watery diarrhea) with severe hypokalemia.

5. Other paraclinical investigations depending on clinical suspicion:

- *Abdominal and pelvic ultrasound* allows the diagnosis of biliary and pancreatic pathologies, highlighting adenopathies, ascites fluid and changes in the walls of the colon.
- *Gastroscopy* can highlight the presence of multiple ulcers of Zollinger-Ellison syndrome (associated with increased gastrinemia); gastroscopy with duodenal biopsy evaluates the severity of histological lesions in celiac disease; gastroscopy with biopsy of the gastric body makes the diagnosis of gastric atrophy in Biermer's anemia.
- *Total colonoscopy* with intubation of the terminal ileum and sampling of biospies for the diagnosis of inflammatory bowel diseases, root enteritis, intestinal tuberculosis.
- *Endoscopic capsule* for the evaluation of the small intestine in case of Crohn's disease, intestinal lymphoma.
- *Entero CT/ Entero MRI* in the pathology of the small intestine (Crohn's disease, intestinal lymphoma).
- *Abdomino-pelvic CT/ pancreatic MRI with secretin/ Cholangio-MRI* in hepato-biliary, pancreatic, intestinal pathologies.
- *CT* angiography - in suspicion of mesenteric ischemia
- *Intestinal barium transit* **-** low value but can highlight the presence of fistulas, short intestine, diverticulosis and tumors.
- *Respiratory test for the diagnosis of intestinal overpopulation (SIBO)* **–** after administering a carbohydrate substrate (lactulose or glucose), it will be metabolized

by the colonic microbiota, with the excess production of gas (hydrogen, methane), which is absorbed excreted through respiration, where it can be detected and dosed.
- *Jejunal aspirate* through the Quinton probe for culture is the gold standard for SIBO diagnosis
- *Laboratory tests for the diagnosis of infectious pathologies*: dosage of adenosine deaminase from ascites fluid in case of suspicion of intestinal TB, stool culture, stool testing, PCR for the detection of Tropheryma whipplei in Whipple's disease.

Diagnosis

The diagnosis of malabsorption syndrome should be suspected in patients with chronic diarrheal syndrome, weight loss despite adequate nutrient intake, anemia and light-colored, bulky, foul-smelling stools. In these patients, a thorough anamnesis, objective clinical examination and specific paraclinical examinations should be performed, detailed in advance, depending on the clinical suspicion.

Differential diagnosis

You should consider other causes of chronic diarrhea in which malabsorption has not yet occurred. For example, colon neoplasm (ceco-ascending) where chronic diarrhea, anemia, weight loss occurs, but hypoproteinemia or hypoalbuminemia does not occur.

Paraneoplastic syndromes cause cachexia, hypoproteinemia and hypoalbuminemia, but without diarrhea.

Complications

When a malabsorption syndrome is severe enough, uncontrolled or long-lasting, complications may include cachexia, mixed anemia (iron deficiency and macrocyte), which can be severe, deficiencies of vitamins, minerals, trace elements (e.g. vitamin D, B12, magnesium), coagulopathy, visual disturbances, osteoporosis, electrolyte disorders that can lead to cardiac arrhythmias, neurological symptoms such as peripheral neuropathy, ataxia .

Evolution

The evolution of MS is chronic, progressive if the etiology is not discovered and treated, and can evolve to death. Malnutrition progresses to cachexia, and uncorrected biological disorders worsen.

Prognosis

The prognosis of MS depends on the underlying disease. If it is recognized, diagnosed and medically or surgically solvable, the evolution is favorable (as is the case in celiac disease), otherwise when the disease is not diagnosed or if we do not have a therapeutic response, the prognosis is reserved.

Treatment

Treatment in malabsorption syndromes aims to identify and treat the underlying disease, treat symptoms (e.g. diarrhoea), correct deficiencies and avoid triggers (usually dietary).

1. Hygienic-dietary treatment is essential in certain conditions. For example, the gluten-free diet in celiac disease will lead to clinical and biological remission. Wheat, barley, oats and rye will be mandatorily removed from the diet, but rice and rice flour, cornmeal flour, potatoes will be allowed. In lactase deficiency, milk and milk derivatives will be completely removed or dietary supplements containing lactase will be associated. In chronic pancreatitis, the regimen will completely avoid alcohol consumption and will be low in fat. In chronic diarrheal diseases, foods rich in hard vegetable fibers (radishes, cabbage, cabbage, etc.) should be avoided.

2. Drug treatment – addresses the underlying disease

In inflammatory bowel diseases can be used depending on the severity derivatives of 5-ASA, corticosteroids, immunosuppressants, biological therapy.

In case of Verner-Morisson syndrome (VIP-human), the treatment of choice is octreotide (Sandostatin) at a dose of 200 – 300 mg/day.

In patients diagnosed with Whipple's disease, treatment is with antibiotics (Tetracycline, Ampicillin, Trimethoprim/Sulfamethoxazole – Biseptol). The treatment is long-lasting 10 – 12 months, and the doses will be, in the case of Tetracycline, 4 x 250 mg/day. Clinical symptoms resolve relatively quickly under treatment, but histological recovery may take up to 2 years.

In chronic pancreatitis, enzyme replacement is important because it will reduce pain and steatorrhea. It is very important that the dose of enzyme administered is high enough (the lipase content should be at least 20,000 IU lipase/mass).

The treatment of intestinal bacterial overpopulation syndrome (SIBO) will consist of the administration of intestinal pre/probiotics.

3. Surgical treatment **-** recommended in selected cases

In Zollinger-Ellison syndrome, the therapy of choice is resecting the gastrinoma (the tissue that produces excessive gastrin). If the origin of this tissue is not discovered, a prolonged and intense blockage of acid secretion will be made, with H+/K+ ATP-ase proton pump blockers (Esomeprazole, Pantoprazole, etc.) in double dose.

Surgical treatment may be necessary in complicated inflammatory bowel diseases such as stenosis in Crohn's disease, megacolon in ulcerative colitis, or total colectomy in ulcerative colitis that is not responsive to treatment.

Surgical treatment may also be indicated in intestinal lymphomas, pancreatic tumors, carcinoid tumors.

4. Correction of nutritional and vitamin deficiencies is mandatory in all MS.

Administration of iron preparations (oral or i.v.) in case of iron deficiency anemia, vitamin B12/folic acid in macrocytic anemia. Electrolyte deficiencies (Na, K) will be corrected parenterally, and Ca and Mg deficiencies usually orally. Vitamin deficiencies (B, D and K complex) as well as hormonal deficiencies will be corrected.

To note

- Malabsorption syndrome occurs due to the interpenetration of two entities: maldigestion (deterioration of intraluminal digestive processes) and malabsorption itself (disturbances of the mechanisms of transparietal transport of the final products of digestion at the level of the intestinal mucosa as well as through the lymphatic and blood pathways)

- The most common etiologies are chronic pancreatitis, undiagnosed celiac disease, undiagnosed and untreated inflammatory bowel diseases, short bowel syndrome.

- The clinical picture includes diarrhea with steatorrhea, weight loss, in advanced forms hypoprotein edema and ascites.

- The biological picture highlights deficits on all lines.

- In the absence of etiological treatment, the prognosis is severe, the supplementation treatment having limited efficacy.

15. ACUTE PANCREATITIS

Definition

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas that can be associated with a local and/or systemic inflammatory response. The disease can vary in severity from mild and self-limiting forms (edematous) to severe, life-threatening (necrotic) forms.

Epidemiology

There are limited data on the incidence of acute pancreatitis, mainly from the USA, Western Europe and Japan, which indicate an increasing trend, between 13-45 cases/100,000 people. The risk of getting acute pancreatitis is equal for men and women and increases in parallel with age.

It is a relatively common pathology, accounting for 2% to 3% of acute abdominal pathology. The evolution is unpredictable, the overall mortality being about 5%, different depending on the severity of the disease. While in mild forms mortality is around 3%, it can reach up to 17% in severe forms (and up to 30% in forms with superinfected necrosis). Most commonly, mild forms are encountered (severe, necrotic-hemorrhagic forms only in 20%).

Pathophysiology

Acute pancreatitis occurs through damage to the acinar cells, which allows the activation of pancreatic enzymes outside the pancreatic ducts and digestive tract. This results in the destruction of pancreatic and peripancreatic tissue. Premature, intracellular activation of trypsinogen will lead to damage to pancreatic cells ("autodigestion of the pancreas"), with the release of chemokines, cytokines and the attraction of neutrophils and macrophages, triggering an inflammatory cascade. Histological changes may include interstitial edema, inflammation, hemorrhage, and necrosis. Even if necrosis is not detectable by imaging, glandular destruction occurs at the microscopic level.

Premature enzymatic activation is determined under the following conditions:

- *Alcohol* can cause high protein secretions to precipitate, leading to blockage of small pancreatic ducts. In patients with ethanolic pancreatitis, the first episode occurs after about 6-8 years of excessive alcohol consumption. These patients often develop recurrent episodes of pancreatitis, frequently associated with persistent alcohol consumption.

- In acute *biliary pancreatitis*, choledocic lithiasis causes blockage of the Wirsung duct and bile reflux into the Wirsung duct. The mechanism is not fully elucidated, but it is assumed to involve the reflux of bile into the pancreatic ducts or an excessive increase in pressure in them.

- *Mechanical causes* of acute pancreatitis include any factor that can obstruct pancreatic ducts, such as gallstones, tumors, trauma, and parasitic diseases. Of these, gallstones are the most common mechanical cause, being present in about 60% of patients with acute pancreatitis who do not consume alcohol.

- *Post-ERCP pancreatitis* can occur in 1-5% of patients and can be caused by a sudden increase in intraductal pressure during the injection of the contrast agent.

Severe cases of acute pancreatitis can trigger *systemic inflammatory response syndrome (SIRS),* by activating mediators of inflammation, such as cytokines, lymphocytes, and complement cascade. SIRS can simulate severe sepsis and affect organs other than the pancreas, leading to complications such as acute kidney injury, acute respiratory distress syndrome (ARDS), and cardiovascular instability. Also, in addition to hyperglycemia and hypocalcemia, increased serum levels of urea and creatinine are observed, as well as hypoxia, as a result of impaired liver, lung and kidney functions.

Etiology

Alcohol consumption and gallstones are responsible for about 85% of cases of acute pancreatitis. Other etiologies of pancreatitis are metabolic, mechanical, postoperative, traumatic, vascular, infectious, genetic and autoimmune.

- *Metabolic factors*: alcohol, hyperlipidemia, hypertriglyceridemia (Tgl>1000 mg%), hypercalcemia (hyperparathyroidism), uremia, pregnancy, scorpion venom

- *Mechanical*: gallstones, pancreas divisum, ductal obstruction (roundworms, tumors, etc.), ERCP (iatrogenic), ductal hemorrhage, duodenal obstruction, ductal obstruction by fibrosis due to previous episodes of pancreatitis, Oddi sphincter dysfunction

- *Postoperative*: gastric procedures or biliary procedures, direct pancreatic damage due to trauma, impaired pancreatic vascular flow, obstruction of the pancreatic duct at the duodenal level, cardiopulmonary bypass (ischemia)

- *Vascular*: periarteritis nodosum, lupus erythematosus, embolism

- *Infectious*: Urlian virus, Coxsackie B virus, Cytomegalovirus, Cryptococcus, Enterovirus, hepatitis A, B or C, Epstein-Barr virus, Herpex simplex virus, Echovirus, Ascaris infection,

- *Hereditary and genetic:* hereditary, autosomal dominant forms, genetics - cystic fibrosis, pancreas divisum, familial pancreatitis, tropical pancreatitis

- *Autoimmune:* autoimmune pancreatitis

- *Medications:* Many medications can cause acute pancreatitis. Among the drugs with a certain association, we list: furosemide, metronidazole, tetracycline, azathioprine, 6-mercaptopurine, salicylates, estrogens, sulfonamides.

However, about 8-10% of cases of acute pancreatitis are of unknown etiology (idiopathic pancreatitis), but most can be associated with biliary sludge (microlithiasis), congenital abnormalities such as pancreasum divisum or autoimmune pancreatitis with IgG4.

Clinical picture

The onset is marked by *severe epigastric pain* or in the entire upper abdominal floor, sometimes with the character of constant, non-colic "bar pain", which usually radiates on both right and left sides and also posteriorly. The pain can be alleviated by sitting or standing position. It is usually accompanied by *nausea* and *vomiting*.

Generalized abdominal pain and pain on decompression of the abdomen, suggestive of an acute abdomen, may be present in patients with severe acute pancreatitis. Sometimes *abdominal distention* by gas is significant, and intestinal noises and transit may be absent (*ileus*). Some patients also present with *obstructive jaundice*, secondary to choledocolithiasis or compression of the common bile duct by the edematous head of the pancreas.

Clinical examination may detect *fever, tachycardia, and tenderness* in the upper abdominal floor, including *muscle defenses*.

Signs and symptoms related to other systems that denote severe *pancreatitis* are:

- hypotension and tachycardia, oliguria, altered state of consciousness (signs of dehydration or shock)

- dyspnea and tachypnea, may be due to pleural effusion or respiratory distress syndrome

- periumbilical ecchymosis (Cullen's sign) or flanks (Turner's sign) reflect the presence of retroperitoneal bleeding and is considered a sign of AP severity

- fever: in the first days it reflects the sterile inflammatory process; Starting from the second week of evolution, it can be the consequence of infection

The biological picture

Laboratory tests usually detect *leukocytosis* and increased ***serum lipase ≥ 3 x VN*** (which, in addition to pathognomonic pain "in the bar", are the most common diagnostic criteria of AP). Increases in *amylaemia* and *amylazeuria* (not so specific compared to lipase) may also occur.

Acute phase reactants grow early and are also useful as markers of poor prognosis. C-reactive protein ***values CRP>150 mg/l***, 48 hours after onset, is a valuable prognostic sign for a moderately severe AP.

Liver tests can be altered as a result of a pre-existing disease (alcohol related liver disease) or, especially, due to biliary obstruction (choledocian stone or edema of the pancreatic head). The increase in ALT >3 times normal 24-48 hours after onset suggests biliary etiology.

Hemodynamic disorders in AP can be reflected in abnormalities of *urea, creatinine and electrolytes*. In the initial phases of AP, patients may have *hyper or hypoglycemia*, *hypertriglyceridemia or hypercalcemia* (suggesting the etiology) or *hypocalcemia* (by saponification of fats).

Astrup gasometry is important in any dyspneic patient. The blood count may show *hemoconcentration*, as a result of extravasation of intravascular fluid; *Leukocytosis and thrombocytosis* appear as markers of the acute inflammatory reaction.

Imaging and other paraclinical explorations in AP

Patients in whom acute pancreatitis is suspected should be explored by:

- *chest X-ray* to highlight intrathoracic complications and exclude pneumoperitoneum;

- *simple abdominal X-ray* to identify possible calcifications (indicating chronic pancreatitis) or intestinal obstruction or pneumoperitoneum;

- *abdominal ultrasonography* to identify gallstones, dilation of the common bile duct, increase in size of the pancreas and peripancreatic fluid collections. Ultrasound is a cheap, non-irradiating, repetitive, accessible, easy-to-use method for dynamic monitoring of patients, but with limitations in acute pancreatitis, especially since the pancreas cannot always be visualized in these cases. On the other hand, however, it can bring elements suggestive of etiology (gallstones, wide common bile duct, elements suggestive of chronic pancreatitis), elements of severity (presence of ascites fluid or of some collections, hyperreflectogenicity of the omental bursa). That is why it is the imaging method that must be performed initially (first-line) on all patients suspected of having acute pancreatitis, as soon as they are referred to the emergency department. In mild forms (Fig. 15.1) only the increase in size of the pancreas may occur, with a hypoechoic, homogeneous appearance, while in severe forms the pancreas may have an inhomogeneous appearance, with hyperreflectogenicity of the omental bursa, pancreatic and peripancreatic collections, vascular complications (splenic thrombosis).

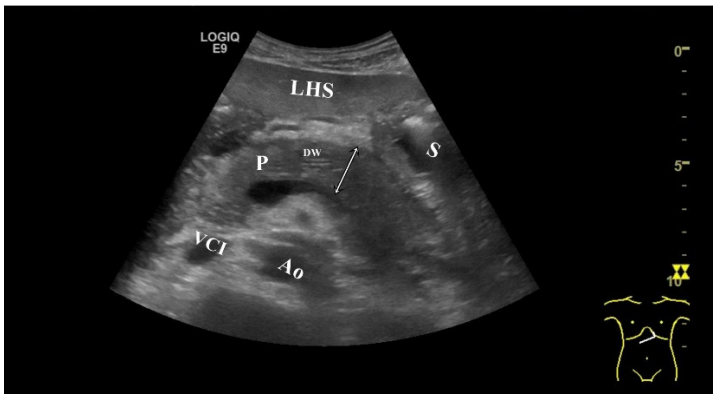


Figure 15.1. Acute pancreatitis edematous form (arrow). LHS - left hepatic lobe; P - Pancreas; S - stomach; DW - duct Wirsung; IVC - inferior vena cava; Ao - Aorta;

- Most of the time, *computed tomography* (with contrast agent) is not necessary to establish the diagnosis of acute pancreatitis. When the diagnosis remains uncertain, CT examination can establish the diagnosis, especially if the presentation is late, several

days after onset, when lipase levels return to normal or near normal values. CT with contrast allows the assessment of severity by using the Balthazar score - Table 15.I). Typical radiological aspects of CT examination range from peripancreatic collections and pancreatic edema (present in almost all patients at the time of presentation), to pancreatic necrosis, which is most commonly highlighted days or weeks after initial presentation, when dealing with severe pancreatitis. Pancreatic necrosis is identified by the absence of capture of the contrast substance by the pancreatic tissue.

Table 15.I – Balthazar (radiological) severity assessment score in AP

Degree	CT Layout
A	Normal pancreas
B	Increase in size of the pancreas
C	Inflammation of the pancreas and/or peripancreatic fat
D	Unique peripancreatic fluid collection
Is	Two or more fluid collections and/or retroperitoneal air

- In selected cases, additional investigations, such as *magnetic resonance cholangio-pancreatography* (MRCP), which provides a non-invasive visualization of the bile ducts and pancreas, may be useful.

- *Endoscopic ultrasound (EUS)* is the method of choice, non-invasive, for the evaluation of the distal common bile duct and the highlighting of choledocian stones, being also useful for highlighting chronic pancreatitis lesions

Diagnosis

The diagnosis of acute pancreatitis is confirmed when at least two of the following three criteria are met: the presence of signs and symptoms suggestive of AP (typical upper abdominal pain), increased serum amylase levels or serum lipase levels (≥ 3 x VN), and identification of characteristic radiological changes on CT/ultrasound examination. Its severity is determined according to the Atlanta classification (Table 15.II).

Table 15.II. Atlanta classification of AP severity.

Term	Definition
Mild acute pancreatitis	No local complications No systemic complications
Moderate acute pancreatitis	Moderate local complications that remit (fluid collections causing pain, fever, impossibility of feeding) Transient organ failure, less than 48 h
Severe acute pancreatitis	Serious local complications (necrosis, infected necrosis, pseudocysts) Persistent multiple organ failure (MSOF) over 48 hours

Local peripancreatic complications that may occur and that must be considered in determining severity are:

- *Acute fluid collections* (Fig.15.2.) are imprecisely delineated accumulations of sterile fluid without its own wall, located in or around the pancreas, which appear early in the evolution of AP. Usually in evolution spontaneous resorption occurs, if it persists, it can lead to the appearance of pancreatic pseudocyst that can become infected, thus becoming a peripancreatic abscess.

- *Pancreatic necrosis* – defined as diffuse or focal areas of non-viable pancreatic parenchyma, usually associated with peripancreatic fat necrosis. It can be sterile or *infected pancreatic necrosis.*

- *Pancreatic pseudocyst* (Fig. 15.3) is a collection of fluid rich in pancreatic enzymes surrounded by a wall of fibrous granulation tissue, which occurs as a result of acute pancreatitis, pancreatic trauma or chronic pancreatitis. It is built up over time, by organizing a collection, at least 4 weeks after the onset of symptoms. The appearance is round or ovoid and the contents are most often sterile, when pus is present, by superinfection, the lesion is called a pancreatic abscess.

- *Pancreatic abscess* is a circumscribed intra-abdominal purulent collection, usually in the vicinity of the pancreas, with minimal or absent pancreatic necrosis, which occurs as a consequence of AP or pancreatic trauma, often 4 or more weeks after onset. Pancreatic abscess and infected pancreatic necrosis differ in clinical expression and extent of associated necrosis.

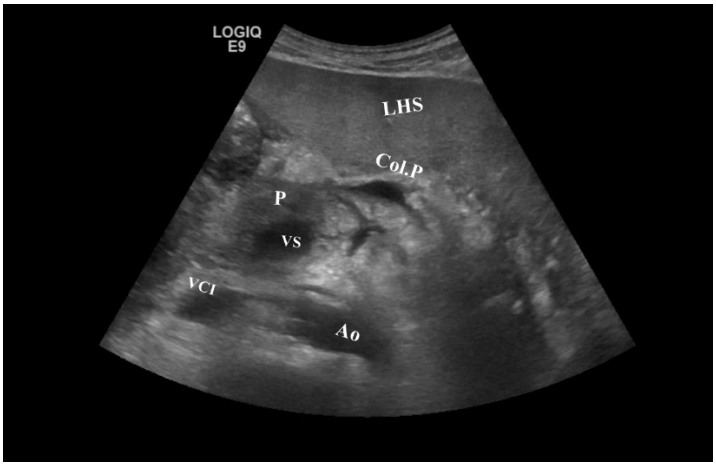


Figure 15.2. Acute suprapancreatic fluid collection – ultrasound appearance.
LHS - Left hepatic lobe; Col.P - Acute post-pancreatitis collection; P - Pancreas; VS - Splenic Vein; IVC - inferior vena cava; Ao - Abdominal aorta;

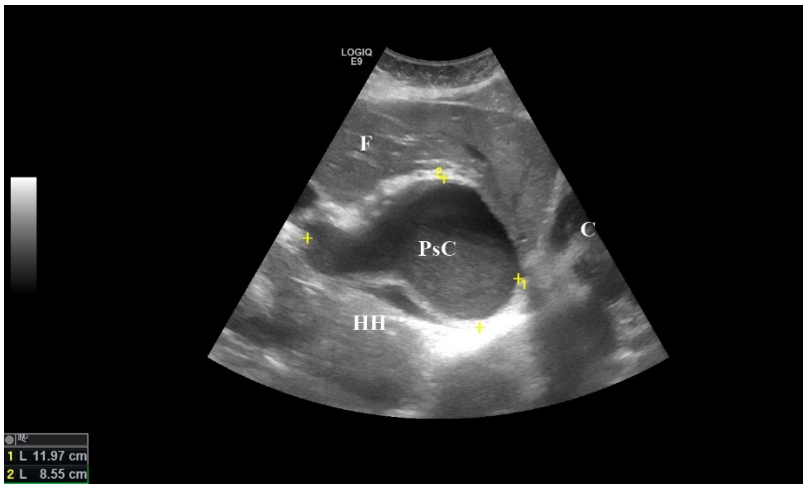


Figure 15.3. Large pancreatic pseudocyst involving the hepatic hilum. F - Liver; Psc - Pancreatic pseudocyst; C - Cord; HH - Hepatic Death;

Differential diagnosis

The differential diagnosis of AP includes other conditions with epigastric pain (biliary/choledocian colic or cholangitis, perforated ulcer, acute appendicitis, peritonitis, abscessed diverticulitis, renal colic, upper intestinal occlusion, lower myocardial infarction, entero-mesenteric infarction, aortic aneurysm, basal pneumonia), which can sometimes be accompanied by increased lipase or amylase. These conditions have specific signs, pancreatic enzymes rarely increase significantly, and imaging does not support the diagnosis of AP, being suggestive for other diagnoses.

Prognosis

Acute pancreatitis is a disease with an unpredictable evolution. Approximately 80% of the cases are mild forms of the disease in which the clinical condition of the patients will improve in 48-72 h, the evolution being favorable, with restitutio ad integrum. On the other hand, about 20% of cases are severe forms with frequent complications, forms associated with organ failure and/or local complications: necrosis, abscesses, pseudocysts. Ideally, severity stratification should be done in all patients within 48 hours of diagnosis. To assess severity, we can use several scores, such as Apache or Ranson scores.

- *Ranson's clinical classification criteria* for acute pancreatitis (Table 15.III) are based on clinical and laboratory variables that are easy to assess. They are applied at the time of the patient's admission to the hospital and include five initial variables, to which six more are added in the next 48 hours. The identification of three or more criteria suggests severe pancreatitis and is associated with an increased risk of local and systemic complications.

Table 15.III. Ranson criteria - prognostic factors for major complications or death in BP

	Non-biliary	Biliary
At the hospital		
Age	> 55 years old	> 70 years old
Leukocyte count	> 16,000/mmc	>18,000/mmc
Glucose	> 200 mg/dl	> 220 mg/dl
LDH	> 350 U/l	> 400 U/l
ASAT	> 250 U/l	> 250 U/l
In the first 48 hours		
Decreased hematocrit	>10%	>10%
BUN Growth	> 5 mg/dl	> 2 mg/dl
Calcium	< 8mg/dl	< 8mg/dl
Arterial PO2	< 60mm Hg	-
Shortage of bases	> 4 mEq/l	> 5 mEq/l
Seizure of fluids	> 6L	> 4L

- *C-reactive protein >150 mg/dl 48 hours after onset* has a good predictive value for severe forms of the disease, being an easy, fast method of assessing the patient's prognosis.

Complications

Acute pancreatitis is burdened by the possibility of multiple complications.

- *Local:* necrosis, pseudocyst, abscess, sterile or superinfected retroperitoneal collections, thrombosis of neighboring vessels, paralytic ileus, intestinal infarction

- *Systemic:* shock, respiratory failure (by pleurisy, pneumonia, mediastinal abscess), acute kidney injury, encephalopathy, retinopathy, fatty tissue necrosis, disseminated intravascular coagulation (CID), digestive hemorrhage, severe metabolic disorders.

Treatment

1. Hygienic-dietary treatment. The reduction of pancreatic secretion is achieved through fasting, but if in the past it was considered that fasting was mandatory for the recovery of the pancreas, today it is recommended that, in mild AP, oral feeding should be resumed as soon as pain, nausea and vomiting are controlled (24 hours after the pain disappears). The diet should be low in fat.

In severe AP, total parenteral nutrition should not be preferred to oral or enteral feeding (on a nasogastric or nasojejunal tube), which have the advantage of maintaining the functionality of the intestinal mucosal barrier and reducing the risk of complications.

2. Supportive measures include:

- monitoring vital functions,
- *aggressive hydro-electrolytic resuscitation* with Ringer's solutions or saline solution 250-300 ml/h, in the first 24-48 hours, considered to be the most important therapy, as it has been shown to reduce complications and increase survival in severe forms
- *Pain therapy* escalating from common analgesics to major analgesics or even epidural anesthesia.
- correction of electrolyte and metabolic disorders
- symptomatic treatment of nausea, vomiting

3. Specific therapies:

- In case of acute biliary pancreatitis *with obstructive jaundice ± cholangitis*, biliary clearance by ERCP is necessary as early as possible, preferably within the first 72 hours.
- *Asymptomatic pancreatic pseudocysts* are treated conservatively, while *symptomatic ones* (> 6 cm in general) require percutaneous or endoscopic drainage.
- In *sterile pancreatic necrosis* , conservative treatment is preferred.
- In *superinfected pancreatic necrosis* , endoscopic, percutaneous or surgical evacuation is required (preferably surgical after at least 4 weeks) along with antibiotic therapy. Numerous studies have shown that antibiotic prophylaxis is not indicated in mild and moderate forms of pancreatitis. Antibiotic prophylaxis is also not indicated in patients with sterile necrosis. Antibiotics are important once the infection has been identified.

3. Surgical treatment. Patients with mild or moderate forms of pancreatitis, secondary to gallstones, should be cholecystectomized during the current hospitalization, after remission of symptoms. Cholecystectomy for biliary pancreatitis reduces the risk of developing a new episode of pancreatitis, from about 50% to about 5%, but does not influence the pancreatitis episode itself.

To note

- AP is an acute inflammatory process of the pancreas with or without peripancreatic and systemic involvement, with unpredictable evolution, being a frequent medical emergency.

- The most common etiologies are biliary and ethanolic, followed by severe hypertriglyceridemia.

- The positive diagnosis is based on the clinical picture (severe upper abdominal pain "in the bar") associated with increases in serum lipase greater than 3 x the upper value of normal and specific imaging changes (pancreatic edema / necrosis and/or pancreatic and peripancreatic collections).

- The severity assessment must be made as early as possible, the C-reactive protein ≥ 150 mg/dl 48 hours after onset being predictive for severe forms.

- The acute phase treatment includes the cessation of food intake, with the resumption of nutrition 24 hours after the disappearance of the pain; aggressive rehydration; symptomatic treatment of pain; rebalancing metabolic imbalances. In biliary AP with obstructive jaundice, biliary deobstruction must be done within a maximum of 72 hours from the onset.

- In patients with biliary AP, cholecystectomy is indicated, if possible in the same hospitalization, to reduce the risk of recurrence.

16. CHRONIC PANCREATITIS

Definition

Chronic pancreatitis (CP) is a chronic inflammatory condition of the pancreas with a progressive evolution towards exocrine and endocrine pancreatic destruction, leading to pancreatic insufficiency. It is a disease that sets in slowly, progressively, with a long evolution (generally more than 10 years) until the appearance of the clinical picture. CP is a different condition from acute pancreatitis (AP) and not a consequence of it. AP usually evolves into complications or "restitutio ad integrum". On the other hand, a CP can present episodes of exacerbation, especially in the conditions of alcohol consumption.

Epidemiology

Morphological changes specific to this condition are identified in 5% of autopsies. Determining the exact incidence is difficult because many patients are asymptomatic, and advancing age can cause histological changes similar to those found in chronic pancreatitis.

Pathophysiology

In the conditions of chronic alcoholism, the pancreas secretes a pancreatic juice with a higher protein concentration than normal. These proteins can precipitate, forming protein plugs, which will generate ductal obstruction (obstruction of small ducts), with retrograde activation of pancreatic enzymes. Some protein plugs calcify by impregnation with calcium carbonate. The formation of stones is favored by the alteration by alcohol of the pancreatic synthesis of "lithostatin" (originally called "PSP-pancreatic stone protein"), which prevents the nucleation and precipitation of calcium carbonate crystals in pancreatic juice. As a result of the obstructions, some ducts rupture, with activation of enzymes, other ducts dilate and periductal fibrosis appears, with new stenosis. This leads to tissue destruction and calcium deposits.

Pathology

Macroscopic - The pancreas is hard at palpation, most often small, less often it can be hypertrophic, and sometimes even pseudotumoral (generating intraoperative diagnostic errors in the absence of biopsy).

Microscopically, fibrosis appears, lymphoplasmacytic infiltrate around the acines. The ducts are unevenly dilated, with protein plugs and wirsungian stones of a few mm.

Etiology

Alcohol consumption is responsible for about 70% of cases of chronic pancreatitis. It differs from acute pancreatitis in that the glandular destruction is no longer reversible, but is progressive. Each recurrent episode of pancreatitis contributes to the formation of fibrotic, scarred tissue with an abnormal ductal system, which does not drain properly and which easily clogs with the protein plugs mentioned above.

Smoking is common in patients with chronic pancreatitis of alcoholic etiology and contributes to the increased risk of intrapancreatic calcifications. It also has a direct effect on the pancreas, causing independent lesions and increasing mortality among patients with chronic pancreatitis.

Chronic pancreatitis associated *with hyperparathyroidism* occurs in 10-15% of cases of hyperparathyroidism. It causes calcium to precipitate and stimulate the secretion of pancreatic proteins and enzymes.

Ductal obstructions caused by: pancreatic trauma, pancreatic tumors, Oddian stenosis, Wirsung stones, congenital ductal anomalies of the "pancreas divisum" type (a congenital anomaly given by insufficient fusion of the ventral and dorsal embryonic ducts). In this case, much of the pancreatic juice is drained by the Santorini accessor channel into the accessory papilla, which in case it is stenotic, will lead to hypertension and CP.

Hereditary pancreatitis involves an autosomal dominant gene. In this case, the family history is important.

Various conditions such as *malnutrition* (tropical CP in India, Africa, S-E Asia), *hemochromatosis* (tanned diabetes – the cause is iron deposition in the liver, pancreas, myocardium).

In conclusion, the most common cause of CP is chronic alcoholism and smoking.

Clinical picture

The most common symptom of chronic pancreatitis is chronic *pain.* The pain is usually dull, with epigastric localization, irradiating posteriorly and can sometimes be triggered by abundant meals. Analgesic self-medication through increased alcohol intake and/or use of narcotics, with the development of addiction, is frequently encountered. When 90% of the gland has been destroyed or replaced by scar tissue, endocrine and exocrine insufficiency occur, manifested by malabsorption, diabetes and deficiency of fat-soluble vitamins, causing malnutrition. The presence of steatorea (bulky, pasty, rancid stools) is a late sign, when malabsorption already appears, and is always accompanied by weight loss.

Biological picture

The blood count is usually unchanged. Macrocytic anemia may occur due to chronic alcoholism or leukocytosis in the presence of an infected pseudocyst. Assessment *of blood glucose* and glycosylated hemoglobin, possibly glucose tolerance

test are useful. In the advanced stages of the disease, diabetes mellitus occurs secondary to diffuse pancreatic lesions. The dosage *of serum lipase* (during periods of exacerbation) is a more accurate indicator of pancreatic suffering than amylazemia, but the increases are not as large as in an AP on an unhealthy pancreas. *Liver function tests* tend to be normal, if CP has not caused biliary obstruction, in which case cytolysis, cholestasis, possibly even increases in bilirubin occur.

Pancreatic secretory tests allow the evaluation of pancreatic functional reserve, are laborious and are relatively rarely used in practice. These include the Lundh test, the secretin test, the PABA test, the pancreolauril test.

The fecal elastase-1 test is the standard test currently used to assess pancreatic functional reserve, being a useful and sensitive test for highlighting early pancreatic insufficiency.

Imaging evaluation

It is currently the most common way to diagnose CP. Often random imaging evaluations can diagnose asymptomatic CP or discover the cause of atypical abdominal pain, which has been evolving for a long time.

- *Abdominal X-ray* can reveal the presence of pancreatic calcifications in about 30% of the CP. The centering of the radiological image will be done on the epigastric (pancreatic) region, and in case of doubt a profile X-ray can demonstrate the location of calcifications anterior to the spine.

- *Ultrasound* is the most common method of diagnosing chronic advanced pancreatitis (Fig. 16.1, Fig.16.2). Ultrasonography can reveal diffuse pancreatic calcifications, pancreatic heterogeneity (inhomogeneous appearance of the pancreas), dilation of the Wirsung duct over 3 mm (it can have even 7-10 mm in pathological conditions), with the presence of Wirsung stones (hyperechoic images in the duct, with posterior acoustic shadow), the presence of pancreatic pseudocysts (transsonic images with variable sizes, generally from 1 to 10 cm, but other times they can have giant dimensions), located in the head, body or pancreatic tail. Not all cases of CP have all these ultrasound signs, but they can often be associated. The experience of the sonographer is important for the ultrasound diagnosis of CP.

- *Endoscopic ultrasound (EUS)* combines endoscopy with ultrasound and is a useful and reliable method of CP diagnosis, revealing the inhomogeneity of pancreatic tissue, dilation of the Wirsung duct, the presence of calcifications in the pancreatic parenchyma and possible Wirsung stones. It is the most accurate method of diagnosing chronic pancreatitis, even in its early stages (Fig. 16.3)

- *Computed tomography* is a useful and reliable method of diagnosing morphological changes in the CP, as well as of monitoring its evolution over time. It is indicated in all cases of initial evaluation or in cases where the ultrasound is not clear. The visualization of minor calcifications, the possibility of evaluating even obese or

bloated patients, make it superior to ultrasound (the disadvantages are related to exposure to ionizing radiation and price).

- *Endoscopic retrograde pancreatography* (ERCP) highlights the altered appearance of the pancreatic duct, irregular, with stenosis and dilations (Fig. 16.4). It is a useful method even in the fairly early stages, but it is followed by complications in about 5% of cases. It is not used strictly for diagnosis, but only if therapeutic intervention is needed.

The appearance of the pancreatic duct can also be evaluated by *MRI pancreatography*.

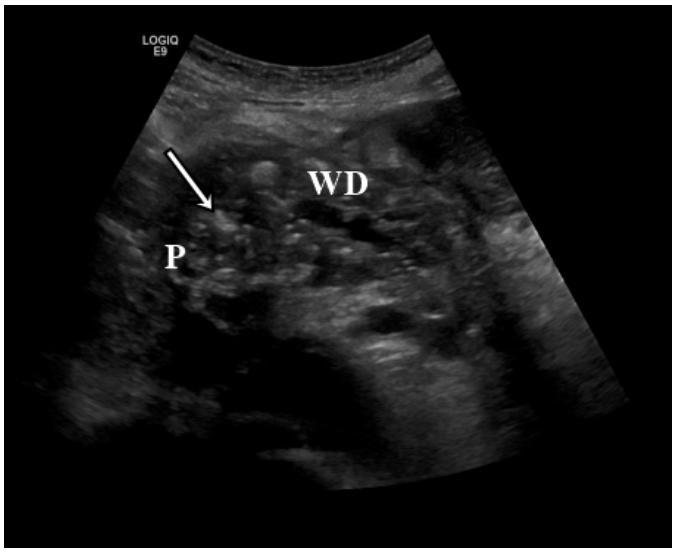


Fig. 16.1. Chronic pancreatitis - mixed form (Wirsung Duct – WD - dilated), presence of intraparenchymal calcifications (arrow); P- Pancreas.

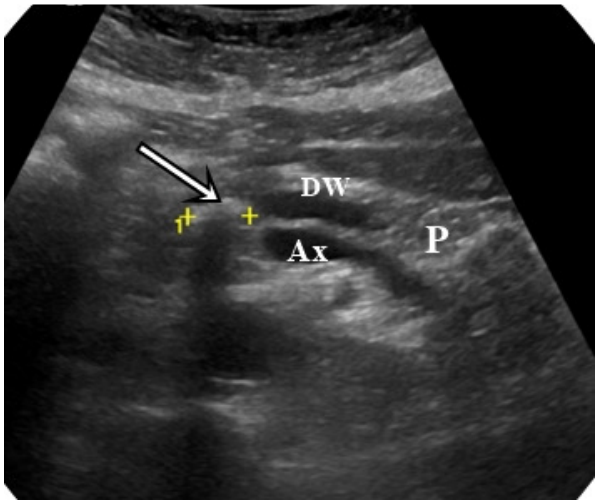


Fig. 16.2. Chronic pancreatitis - obstructive form (dilated DW-Wirsung Duct, Wirsung lithiasis with posterior-arrow shadow cone); Ax - Spleno-portal axis; P - Pancreas.

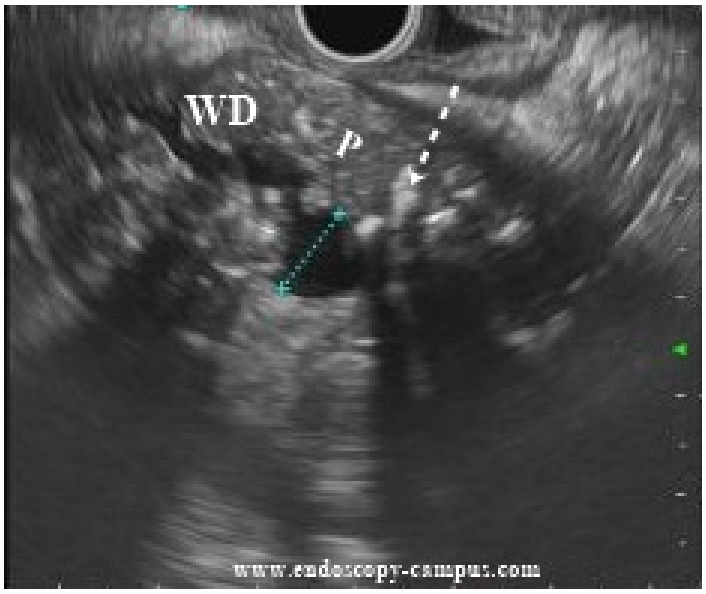


Fig. 16.3. The main pancreatic duct (WD) is dilated (see blue arrow), with an irregular contour and hyperechoic wall. The pancreatic parenchyma presents hyperechoic foci (arrow), with posterior shadows, suggestive for the diagnosis of CP.

Fig.16.4. Wirsungography during the ERCP procedure; D- Duodenoscope; DW- Duct Wirsung dilated, with an irregular appearance and expansions at this level, suggestive modifications for the PC.

Classification

Clinical forms of CP are CP with pain (intermittent or continuous) and asymptomatic CP.

Anatomopathological forms of CP are *obstructive CP* - with significant dilation of the Wirsung duct (Fig. 16.2); *Calcifying CP* where calcifications in the pancreatic parenchyma predominate; *CP mixed form* with calcifications and ductal dilations (Fig. 16.1)

Evolution

The evolution of the disease is chronic, with exacerbation flare-ups. At first, it may be asymptomatic, but over time it becomes symptomatic, and the most important element, most often, is pain. Stopping alcohol consumption altogether can have a beneficial effect on pain, but not always. Over time, maldigestion and malabsorption will occur, with secondary malnutrition. Patients with CP are also at increased risk of developing pancreatic adenocarcinoma.

Complications

The most common complications of CP are *pancreatic pseudocyst*, sometimes compressive; *pancreatic abscess*, which is caused by infection of a pancreatic pseudocyst; recurrent *ascites* rich in amylases, usually not very abundant, which may have a sero-citrine or possibly hemorrhagic appearance (therefore, in patients with ascites of unknown cause, the amylases in the ascites fluid should always be determined); *obstructive jaundice*, by compression of the common bile duct by the hypertrophic pancreatic head (difficult diagnostic differentiation with pancreatic cephalic neoplasm); *thrombosis of the splenic vein* or portal vein, due to inflammation of the vicinity.

Treatment

1. Dietetic

It will start with dietary measures, among which the most important is *the complete and definitive cessasion of alcohol intake. Avoid large meals* , rich in fats, but also in proteins, which stimulate pancreatic secretion, which can exacerbate pain. Acute episodes of AP against the background of a CP will be treated by hospitalization, fasting, parenteral feeding, possibly nasogastric tube, analgesic medication, acid antisecretory medication (duodenal acidity can stimulate pancreatic secretion).

2. The drug treatment of CP consists of:

- *analgesics* for painful episodes (Algocalmin, Piafen, Tramadol, Fortral). To combat pain, regular painkillers or even opiates are used if the intensity is high.

- *pancreatic enzyme substitutes*, which can relieve symptoms by reducing pancreatic secretion, having a negative bio-feedback effect. Doses of lipase should be high, even in the absence of malabsorption. Medication with a high lipase content should be used: Kreon, Mezym forte, Panzytrat, Festal, Cotazym, Nutryzym, Digestal forte, etc. Gastroprotected (enterosoluble) drugs are preferred, due to the neutralization of lipase by the action of acidic gastric juice. In the presence of maldigestion with malabsorption, the dose of substitute ferments should be high, at least 20,000 U lipase/mass. If the medication is not gastroprotected, an antisecretory agent (Ranitidine, Famotidine) should be administered 30 min before a meal. If maldigestion cannot be combated in this way,

medium-chain triglycerides can be added at a dose of 40 g/day (coconut oil that is more easily absorbed, partially preventing malabsorption).

The medical treatment of chronic pancreatitis also includes *the treatment of alcoholism,* narcotic addiction.

3. Surgical treatment of chronic pancreatitis*:* the therapeutic options are divided into two main categories: *drainage procedures* and *resection* procedures. Drainage procedures are more effective in patients with dilated pancreatic duct (>4 mm), while resection is recommended in cases with non-dilated ducts and localized pancreatic involvement. In patients with ductal dilation, an internal ductal decompression procedure can be performed by lateral pancreaticojejunostomy (Puestow procedure), which provides long-term pain relief in about 70% of patients. In situations where the pancreatic duct is not dilated and there is no clear focal involvement, resection procedures such as cephalic duodenopancreatectomy, distal pancreatectomy or resection of the pancreatic head with preservation of the duodenum are indicated, especially in pseudotumor forms, in which neoplasia is suspected.

4. Endoscopic alternative therapy is currently gaining more and more ground in solving these patients symptoms. In order to obtain appropriate results, a careful selection of patients must be carried out regarding the type of endoscopic intervention. The techniques practiced are represented by:

- *sphincterotomy with biliary or Wirsung duct stenting*, in case of benign strictures (which are due to inflammation or necrosis around the Wirsung duct). Technically, the sphincterotomy is performed using the papillary approach, and then the stents are placed using a guidewire that passes the stenosis (sometimes in the case of tight stenosis they require dilation). The evolution after stent placement is favorable in 85-100% of cases .

- *extraction of stones* from the Wirsung duct: the presence of stones increases the intraductal pressure, thus accentuating pain and causing pancreatic ischemia. Before the actual extraction, the sphincterotomy is performed to allow papillary access. For the extraction of stones, devices such as extraction "balloons" or "baskets" are used. In the case of large stones, lithotripsy can be attempted to allow the extraction of stone fragments. Percutaneous lithotripsy (ESWL) is the most commonly used adjuvant technique in this regard, as it allows the fragmentation of larger stones and then the extraction of smaller fragments.

- *echoendoscopic drainage* of pancreatic pseudocysts. They occur as a complication of CP in 20-40% of cases. The use of echoendoscopically guided drainage of pseudocysts is a non-surgical alternative in these patients. The purpose of transmural drainage is to create a communication between the pseudocyst cavity and the digestive lumen (cysto-gastrostomy or cysto-duodenostomy), allowing the drainage of the cyst contents into the intestinal lumen.

- *neurolysis* of the celiac plexus under endoscopic guidance - This involves the injection of absolute alcohol and anesthetic substances (bupivacaine 0.25%) at the level of the nerve fibers, with their destruction and secondary fibrosis in order to interrupt the pain transmission pathways, the injection being minimally invasive, under endoscopic guidance.

To note

- The most common cause of chronic pancreatitis is excessive alcohol consumption.
- The symptoms that can occur in chronic pacreatitis are: pain; manifestations of malabsorption – steatorea, creatorea; weight loss, association of diabetes.
- The diagnosis of chronic pancreatitis is based on imaging, ultrasound being the first-line method used, and echoendoscopy is the most sensitive diagnostic method.
- the main diagnostic imaging elements in chronic pancreatitis are: diffuse pancreatic calcifications, dilation of the Wirsung duct over 3 mm, presence of Wirsung stones.
- Pancreatic enzyme substitutes can relieve symptoms and prevent malnutrition.

17. GALLSTONES

Definition

Gallstones are defined by the presence of stones in the biliary tree. Gallstones form in the gallbladder or any other segment of the bile ducts. Depending on the composition, there are two major types of gallstones: *cholesterolotic stones* (resulting from the metabolism of cholesterol and bile acids) and *pigment stones* (resulting from the metabolism of bilirubin). In most cases, gallstones remain asymptomatic. This chapter is dedicated to gallstones.

Epidemiology

Gallstones are a relatively common entity, with over 10% of the adult population of European countries having this morbid condition. In Banat, a prospective study showed that 13% of adults over 20 years of age had gallstones. Cholesterol stones predominate (over 80%) in countries with a high socio-economic standard and are located mainly in the gallbladder.

Etiopathogenesis

The main etiological factors incriminated in the occurrence of cholesterolotic gallstones are: genetic predisposition, female sex (ratio of women to men with gallstones 2-3/1), obesity, age, hyperlipoproteinemias, metabolic syndrome, diabetes mellitus, bariatric surgery, etc.

Bila is an aqueous solution that contains 95% water and small amounts of organic substances. Gallstones are the consequence of metabolic events resulting in the secretion of a bile containing either cholesterol or bilirubin, both substances insoluble in water.

The pathogenesis *of cholesterol gallstones* consists of a disruption of the existing balance in the bile, where cholesterol, bile acids and lecithin are in a balance that ensures the solubilization of cholesterol. An increase in cholesterol elimination (in hyperlipoproteinemia, sudden weight loss, diabetes, obesity) or, on the contrary, a decrease in bile acid elimination will lead to the disruption of the balance that ensures the solubilization of cholesterol, its precipitation and the nucleation of cholesterol crystals. Biliary stasis (for example, in pregnancy) is another factor that favors the formation of stones.

In the case *of calcium bilirubinate lithiasis*, the mechanism of formation is different and consists of an increased elimination of bilirubinate, as occurs in chronic hemolysis, liver cirrhosis, Clonorsis infections (in Asian countries, where, classically, calcium bilirubinate lithiasis predominates).

Clinical picture

Most frequently, gallstones are asymptomatic and are detected by chance in patients without biliary symptoms or who present for complaints unrelated to this pathology. *Biliary colic* is the cardinal symptom that manifests itself as a sharp pain, located in the epigastrium or right hypochondrium, sometimes paroxysmal, usually lasting more than 15-30 minutes, triggered by a lunch rich in fats or cholecystokinetic foods, which can radiate interscapulo-vertebral, in the right shoulder blade or epigastrium. Patients with biliary colic may associate nausea, vomiting of food or bile, sweating, subfebrility, or fever.

Biological picture

Biochemical and hematological tests in uncomplicated gallstones are often normal, changes in the lipid profile can be detected.

Paraclinic

- *Abdominal ultrasonography* is the method *of choice* for the diagnosis of gallstones, the accuracy of the method exceeding 95%. Ultrasound examination will detect the presence of one or more hyperechoic images located in the gallbladder, mobile with a change in the patient's position and generating "acoustic shadow" (Fig. 17.1).

Ultrasound diagnosis can be more difficult when the stones are very small (less than 2-3 mm), the stones are located infundibular, or when the gallbladder is filled with stones ("shell sign"), which is easy to confuse with air in the digestive tract for a less experienced examiner. The complete examination of the gallbladder involves mobilizing the patient from the supine position to the left lateral decubitus, a maneuver that can highlight previously unvisualized stones (the "rolling" sign or the "rolling stone" sign).

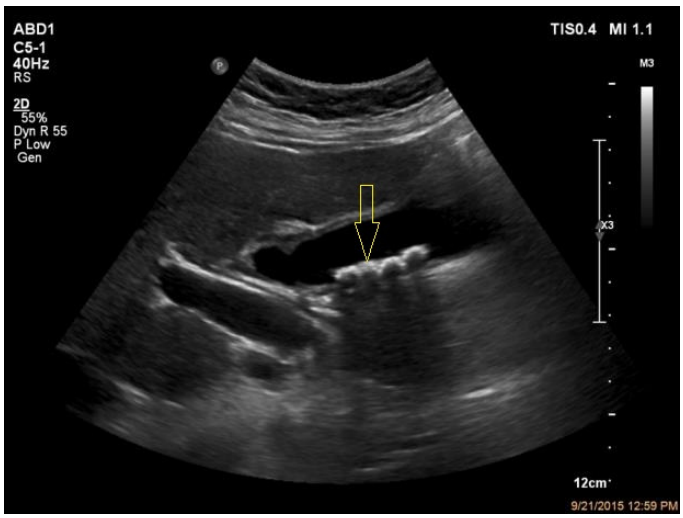


Figure 17.1 Abdominal ultrasound – gallbladder with multiple hypercogenic images with posterior shadow cone.

- *Echoendoscopy* can be used to diagnose gallstones in cases with uncertain diagnosis.

- *Abdominal computed tomography* for non-surgical therapy (drug litholysis) assesses the presence of calcifications at the level of gallstones.

Positive diagnosis

The presence of typical biliary colic raises the suspicion of the diagnosis of gallstones, but in order to establish a positive diagnosis, it is necessary to perform abdominal ultrasound, which is the method of choice for confirming the diagnosis.

A modern concept of gallstones is that of dividing gallstones into:

- *symptomatic gallstones* (which generates biliary colic); nausea or vomiting (as well as headache or migraine), occurring outside of colic pain, does not classify a lithiasis as symptomatic.

- *asymptomatic gallstones* (which do not generate biliary colic).

Differential diagnosis

From a clinical point of view, it is done with ulcerative pain, renal colic, pain from chronic pancreatitis, dyspepsia of dysmotility type, etc.

The differential ultrasound diagnosis of gallstones includes gallbladder polyps, gallbladder neoplasms, and biliary sludge. In this sense, standard ultrasound can be completed with contrast ultrasound (CEUS), which can help decide the diagnosis (for example, the tumor captures contrast, but the biliary sludge does not) (Fig. 17.2).

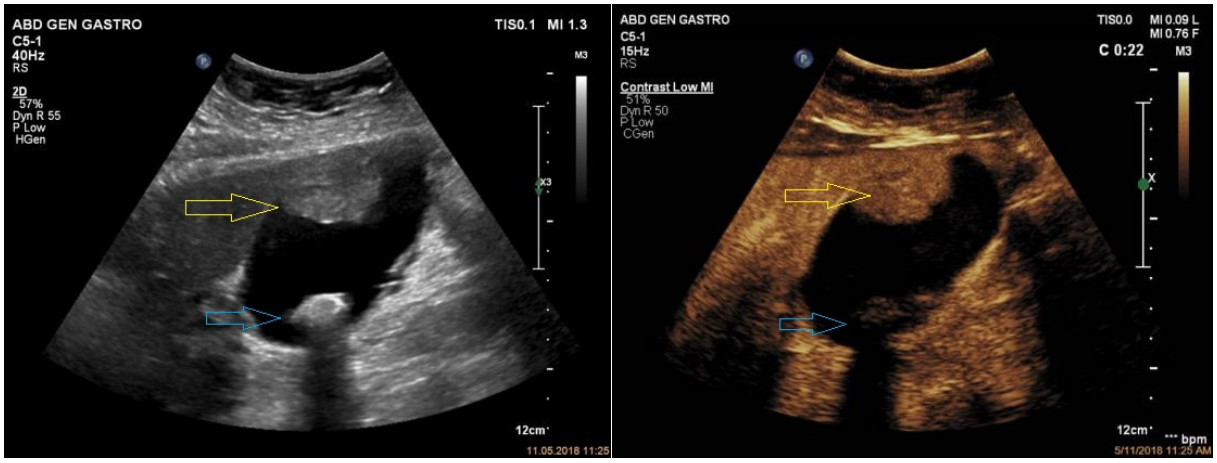


Figure 17.2. Gallbladder tumor and gallstones. Standard ultrasound (left) and CEUS (right) to examine the hyperechoic formation (yellow arrow) located at the level of the gallbladder wall. The formation captures the ultrasound contrast in the arterial phase, unlike the calculus (blue arrow), located on a slope, which is not capturing.

Complications

The most common complications of gallstones are:

1. *Biliary colic* - strong epigastric pain, sometimes with posterior irradiation and generally lasting more than 30 minutes, often triggered by cholecystokinetic foods; the diagnosis is confirmed by ultrasound. In simple biliary colic, the biological picture may be normal. Biliary colic may resolve spontaneously or with the administration of antispasmodics.

2. *Vesicular hydrodips* occur by blocking a stone at the infundibulocistic level, being a surgical emergency. The diagnosis is made by ultrasound, which reveals an enlarged gallbladder, shaft over 9 centimeters long, the vesicular wall is thin and regular, anechogenic content, and infundibular enclaved stone. The treatment is surgical.

3. *Acute cholecystitis* is characterized by epigastric pain in the right or diffuse hypochondrium, fever, leukocytosis, and Murphy's sign (clinical and ultrasound) positive, and, in some cases, local muscular defenses. In the context of the typical clinical and biological picture, ultrasound establishes the diagnosis in more than 90% of cases. Ultrasound detects thickening and splitting of the vesicular wall, a blade of hypoechoic inflammatory fluid around the gallbladder, the presence of intravesicular stones, Murphy's sign positive (Fig. 17.3). Laparoscopic cholecystectomy is the surgical treatment of choice for patients with acute cholecystitis.

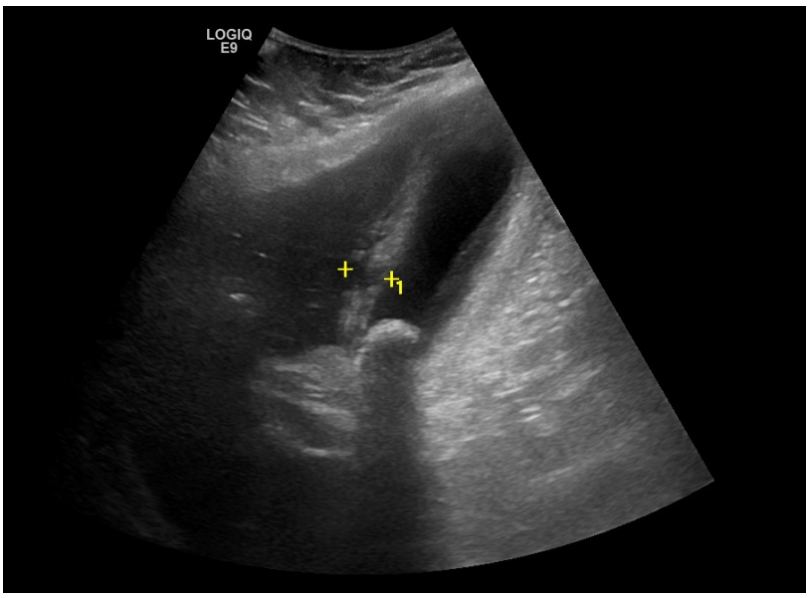


Figure 17.3. Acute cholecystitis. Gallbladder with thickened and split wall (markers), presence of infundibular calculus

4. *Coledocian lithiasis and acute cholangitis*. Mechanical jaundice caused by choledochal lithiasis occurs as a consequence of the migration of stones from the gallbladder through the cystic duct into the common bile duct. Acute cholangitis (cholangitis) is the acute infection and inflammation of the bile ducts that occurs in the presence of biliary obstruction.

Imaging explorations (transabdominal ultrasound, echoendoscopy, magnetic resonance cholangiopancreatography [cholangio-MRI]) have the role of highlighting the presence, location and cause of biliary obstruction. The *first-line imaging exploration* in a jaundiced patient is *abdominal ultrasound*, which will allow the differentiation of intrahepatic cholestasis (absence of bile duct dilations) from extrahepatic cholestasis (presence of bile duct dilations). In obstructive jaundice, intra- and/or extrahepatic bile duct dilations (common bile duct over 6 mm) and possible visualization of the obstruction will be highlighted (Fig. 17.4 -17.6).

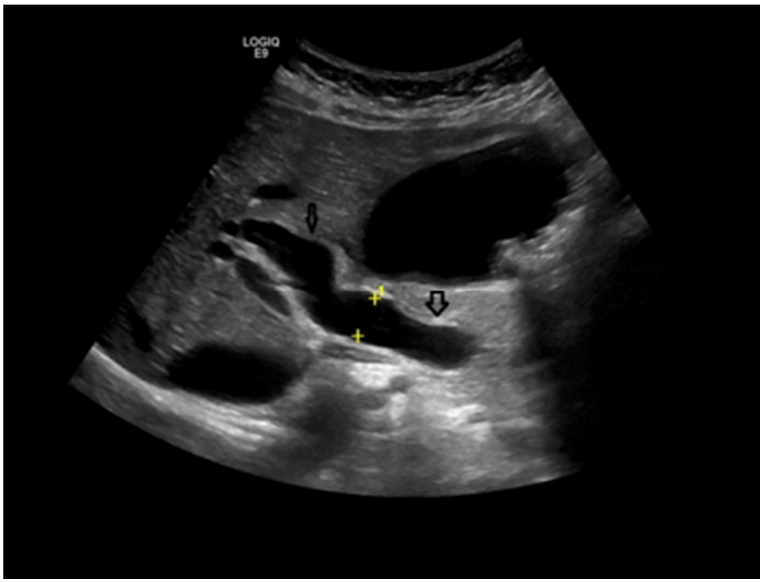


Figure 17.4. Standard ultrasound – obstructive jaundice. Wide choledocus-12 mm, thin-walled gallbladder, lithiasis with multiple small hyperechoic images with acoustic shadow cone

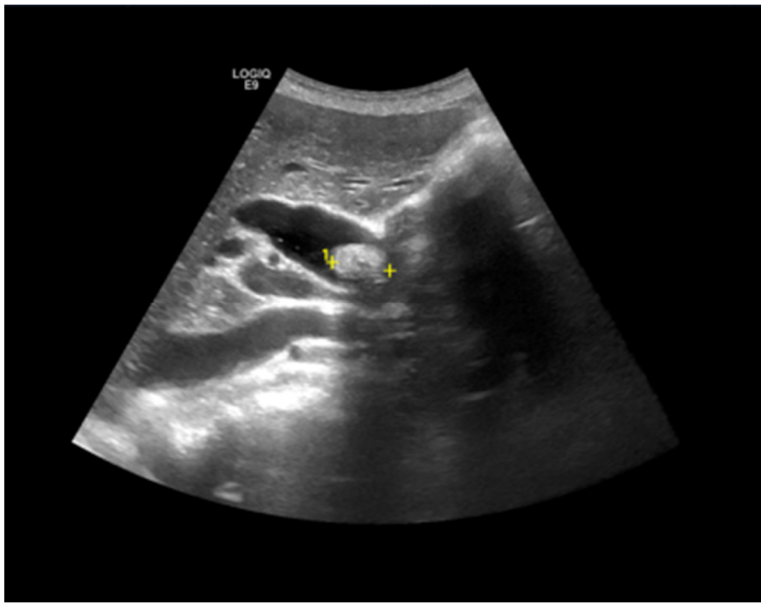


Figure 17.5. Standard ultrasound – obstructive jaundice. Large common bile duct stone of about 19 mm, common bile duct much dilated upstream (right).

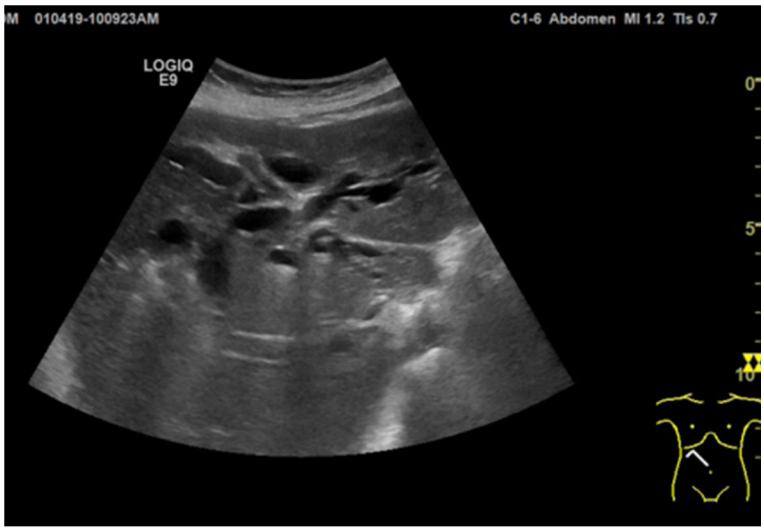


Figure 17.6. Standard ultrasound – intrahepatic bile duct dilations.

Echoendoscopy has a diagnostic sensitivity superior to transabdominal ultrasound (83-100%) for highlighting choledocian lithiasis. *Magnetic resonance cholangiopancreatogarphy (cholangio-MRI)* is another noninvasive method that allows visualization of the bile ducts (Fig 17.7).

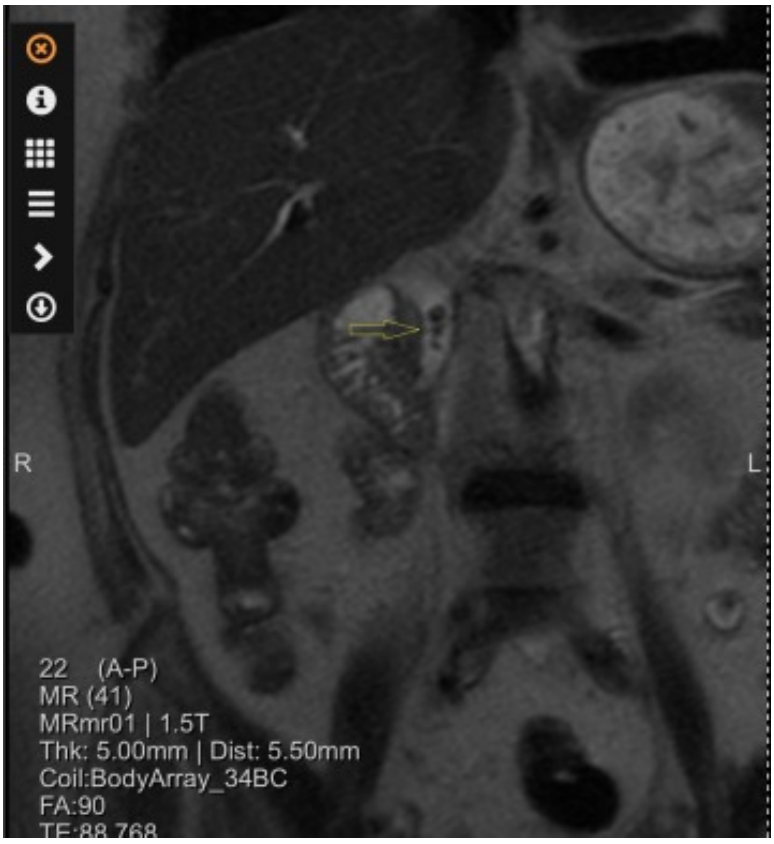


Figure 17.7. Cholangio-MRI – multiple choledocic lithiasis (yellow arrow).

In cases of choledocic lithiasis complicated with angiocolitis, the positive diagnosis is established on the basis of clinical data (Charcot triad - pain in the right hypochondrium, fever with chills, jaundice), biological data (cholestasis and inflammatory syndrome) and imaging data (intra- and extrahepatic bile duct dilations, choledocian stones).

The treatment of choice for obstructive jaundice by choledocic lithiasis is endoscopic drainage (by endoscopic retrograde cholangiopancreatography - ERCP) and consists of endoscopic sphincterotomy followed by balloon stone extraction or Dormia probe. In the case of patients with angiocolitis, hydroelectrolyte rebalancing, analgesics, antipyretics, empirical antibiotic therapy and endoscopic drainage are necessary (the timing of biliary drainage depends on the severity of cholangitis, which is appreciated by the Tokyo classification).

5. *Biliary ileus* – is a rare complication that occurs following the perforation of the gallbladder wall by a large stone (>25 mm) with its passage into the digestive tract. The most common stone is found at the level of the distal ileum (90%). The diagnosis is confirmed by abdominal ultrasound and CT of the abdomen and pelvis with SDC.

6. *Gallbladder neoplasm* is a rare complication that generally occurs in elderly patients with old gallstones (risk of about 0.3% after 30 years after the onset of gallstones), often with stones as large > 3 cm. The diagnosis is imaging by standard ultrasound followed by CEUS, CT or abdominal MRI with CDS. Often, at the time of diagnosis, the neoplasm is advanced with locoregional invasion or liver metastases.

Evolution and prognosis

The majority of patients with gallstones (70-80%) are asymptomatic, with a 2-5% annual risk of becoming symptomatic in the first 5 years of follow-up and a <1% per year risk of complications. The risk of complications is higher in patients with symptomatic gallstones, being at least 2-3% per year.

The prognosis of gallstones is good, because symptomatic cases are most often resolved surgically, and asymptomatic cases are kept under surveillance.

Treatment

1. Hygienic-dietary diet - balanced diet, rich in nutrients, fruits and vegetables, avoiding cholecystokinetic foods (fats, fried foods, refined sweets, etc.) is recommended both for the prevention of cholesterolotic gallstones and for the prevention of colic

2. Surgical treatment. At present, there is a consensus that *asymptomatic gallstones* can only be kept under observation and should not be operated on (WTO - World Gastroenterology Organization guide). Considering that only 1-2% of asymptomatic cases become symptomatic annually, expectation seems to be the most logical and economical solution, and if symptoms appear, it remains to decide on therapy. We must remember that cholecystectomy, although it is a relatively simple surgical procedure, is also sometimes burdened by the appearance of complications.

Symptomatic gallstones will be treated. Most often, this treatment is surgical (cholecystectomy) and less often by non-surgical techniques. With the introduction of laparoscopic cholecystectomy, the patient's acceptability of the intervention increased. It ensures a safe intervention, a short hospitalization, and minimal postoperative sequelae. This technique mainly treats uncomplicated gallstones, but also acute cholecystitis or vesicular hydrops. In scleroatrophic lithiasis or in suspected choledodic lithiasis, the classic technique of open cholecystectomy is most often preferred. In the suspicion of choledochal lithiasis, the exploration of the common bile duct by echoendoscopy (or by MRI cholangiography) is mandatory, and the discovery of stones allows their extraction by endoscopy.

3. Non-surgical techniques for treating gallstones are drug-induced litholysis and extracorporeal lithotripsy (less used lately).

- *Drug-induced litholysis* addresses cholesterol stones, preferably small, which fill less than half of the gallbladder volume in a gallbladder with a permeable infundibulocystic area. Treatment consists of taking ursodeoxycholic acid (10 mg/kg body/day) Ursofalk or combining it with chenodeoxycholic acid (10-15 mg/kg body/day), Litofalk preparation, for an interval of 6-24 months, until the stones are completely dissolved. The chance of success is 50% and there is a risk of recurrence of about 10%/year in the first 5 years. The results are monitored by ultrasound. The method of drug dissolution of stones has become less and less used in recent years.

- *Extracorporeal lithotripsy (ESWL)* consists of bombarding cholesterol stones with shock wave lithotripsy. It is aimed at single or a few stones, preferably under 15 mm. The fragments resulting from lithotripsy will then be dissolved by administering bile acids (especially ursodeoxycholic acid), until all stone fragments in the bladder are completely gone. Both non-surgical techniques (drug litholysis and ESWL) are relatively expensive and are increasingly used at present.

To note

- Gallstones are a common condition in the general population, affecting more than 10% of the adult population. In older adults, the prevalence is even higher, reaching 30-40%.

- In most cases, gallstones remain asymptomatic and do not require specific therapeutic intervention.

- Headache, discomfort in the right hypochondrium, are not considered to be symptoms related to gallstones.

- Symptomatic gallstones means the presence of biliary colic, defined as an intense epigastric pain or pain in the right hypochondrium, lasting from 30 minutes to 1-2 hours, which occurs after eating cholecystokinetic foods.

- Transabdominal ultrasound is considered to be the first-line imaging method for the diagnosis of complicated or uncomplicated gallstones, with an excellent diagnostic performance of over 90-95%.

- Complications of gallstones include gallstones, acute cholecystitis, and obstructive jaundice caused by choledocic lithiasis with or without angiocolitis.

- Gallbladder neoplasm is a rare complication that occurs in older adults with a long history of gallstones.

- Symptomatic gallstones (history of colic or complications) have a surgical indication.

18. CHRONIC VIRAL HEPATITIS

Chronic viral hepatitis is a public health problem, both due to the high prevalence of hepatitis viruses and due to the evolutionary potential towards severe fibrosis and cirrhosis of the liver and its complications. Taking into account the fact that not all viruses with hepatic tropism have a chronic evolution, we will discuss in this chapter only the chronic liver diseases induced by the hepatitis B, C and Delta viruses. Hepatitis A and E viruses, even if they can induce acute hepatitis, do not become chronic except under special conditions, in patients with immunological deficiencies.

To begin with, we will discuss the common elements of chronic viral liver diseases. By **definition** , chronic liver diseases are necro-inflammatory and fibrotic diseases of the liver with a duration of more than 6 months. Basically, this translates into the presence of markers of viral infection and cytolysis for a duration of more than 6 months.

The morphopathological picture has some common elements in all chronic liver diseases, as well as elements characteristic of each type of liver disease. The common elements are inflammation, hepatocytic necrosis and fibrosis, which must be quantified. The severity of fibrosis is what gives the prognosis of the disease. Semi-quantitative scores are used to quantify the severity of histopathological liver lesions , the simplest of which is the METAVIR score, which has two components: necro-inflammatory activity A (A0 – no necroinflammation, A1 – minimal necroinflammation, A2 - moderate necroinflammation, A3 – severe necro-inflammatory activity) and fibrosis (F0 - no fibrosis, F1 – mild perisinusoidal fibrosis, F2 – moderate periportal fibrosis, F3 – severe fibrosis, in bridges, F4 – liver cirrhosis, pseudonodulation of the hepatic parenchyma) (Fig.18.1).

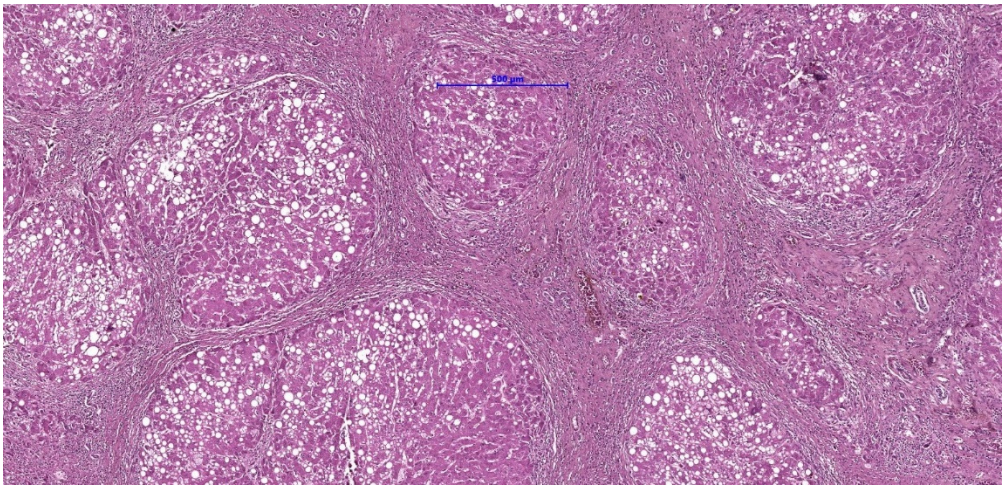


Figure 18.1. Histopathological appearance of liver cirrhosis. It is worth noting the fibrosis bands that perform the pseudonodulation of the hepatic parenchyma (courtesy of Assoc. Prof. Sorina Tăban).

The diagnosis is made starting from the clinical picture, usually poor, continuing with the biological picture - the documentation of cytolytic syndrome and viral infection older than 6 months, as well as the evaluation of liver function by determining clotting factors, albumin, bilirubin.

The diagnosis is mandatory to ***determine the severity of liver damage,*** either by liver biopsy (less commonly used today) or by non-invasive methods (biological and elastographic).

- The histological examination is done on a liver fragment obtained by ***liver biopsy*** (PBH). PBH is a minimally invasive procedure, it can be done transparietal or transjugular (preferred approach in patients at high risk of bleeding). The risk of complications (intrahepatic hematoma, intraperitoneal haemorrhage, haemobilia, biliary complications, pneumothorax), although present, is low (1–3%).

Transparietal PBH is performed ultrasound-guided (the puncture needle is followed all the time by ultrasound) or echo-assisted (ultrasound chooses the puncture site, which is performed using the "hands-free" technique). Automatic needles, such as Tru-cut, or suction needles, such as vises, can be used. PBH is done with local anesthesia and minimal sedation, by administering Midazolam. The fragment obtained is stained with hematoxylin-eosin or with specific stains to highlight fibrosis, and interpreted according to specific scores, the most used being the METAVIR score.

- Biological Tests are either simple tests (such as APRI score or FIB4 score), with a predictive value of over 90% for the exclusion of severe fibrosis/cirrhosis, or patented, more expensive tests, such as FibroTest-ActiTest or FibroMax (Fig.18.2), the latter assessing not only activity and fibrosis, but also fat load (S - Steatosis), as well as liver damage induced by it (N) or alcohol abuse (H). Patented tests take into account a series of demographic data and biological tests, included in a patented formula, resulting in a prognostic score.

Demographics	
Sex	Male
Birthdate	16/09/1955

Analysis		
Sample Date	25/10/2008	
Main Clinical background	Unkown	
Alpha2 Macroglobulin (g/l)	3.83	
Haptoglobin (g/l)	0.30	
Apolipoprotein A1 (g/l)	1.43	
Bilirubin (microMol/l)	14.53	
Gamma GT (IU/l)	81	
ALT (IU/l)	65	
AST (IU/l)	34	
Fasting glucose (mmol/l)	4.88	
Triglycerides (mmol/l)	1.79	
Total cholesterol (mmol/l)	4.27	
Weight (kg)	94.00	
Height (meters)	1.80	

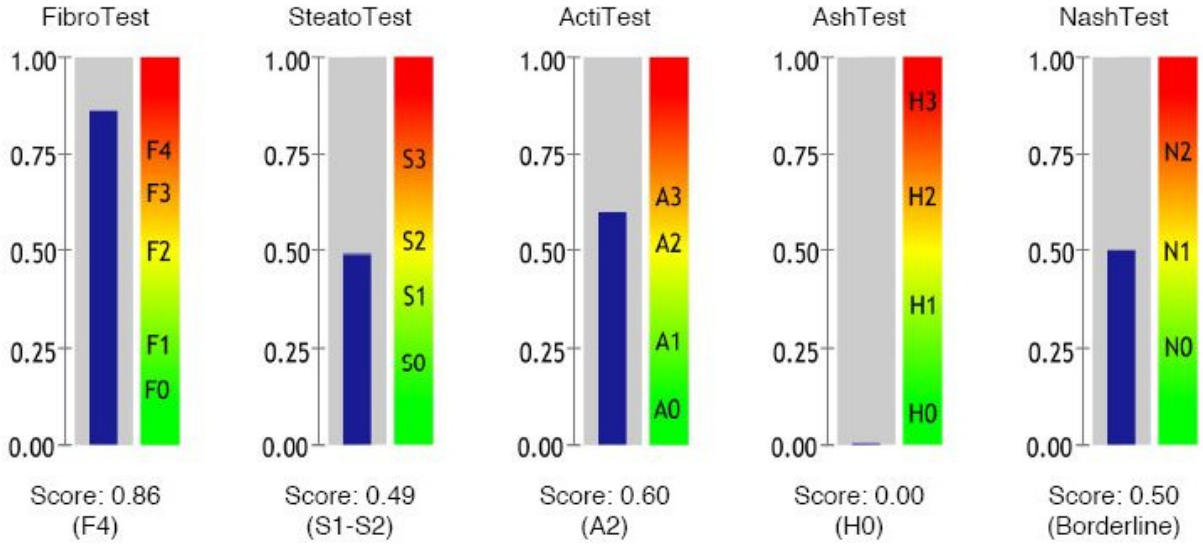


Fig. 18.2. Example of Fibromax test. In the upper table parameters take into account, in the lower chart the result

- Elastographic methods for evaluating liver fibrosis have developed a lot in recent years. They use stimulation of liver tissue with a mechanical impulse or with an ultrasound pulse of a certain frequency. Following the stimulation, the liver tissue becomes deformed, this deformity can be measured by ultrasonography, thus assessing liver rigidity. The more severe the fibrosis, the greater the liver rigidity. Although the method may have some difficulties in differentiating stages close to fibrosis, it performs well for the diagnosis of severe fibrosis (F=3) and cirrhosis (F4).

The first elastographic technique introduced was *Impulse Elastography* (performed with a device called FibroScan) (Fig. 18.3). The method is painless, is done in less than 5 minutes and is reproducible. Values below 5 kPa are considered normal, above 10 kPa for severe fibrosis, and above 13-15 kPa for liver cirrhosis. It cannot be used in case of ascites.

Figure 18.3. The FibroScan machine, used for impulse elastography, a non-invasive technique that measures liver stiffness.

Subsequently, other ultrasound-based elastographic techniques have appeared, which can be *"point" using the ARFI* - VTQ technique from Siemens (Fig.18.4) or ElastPQ from Philips, or *2D SWE (real-time)* - SuperSonic Image - Aixplorer (Fig.18.5) or 2D SWE-General Electric (have the advantage of real-time evaluation, the result being both color coded, as well as numerically). The fibrosis cut-off values are similar (but not identical) to that of FibroScan. Values below 5 kPa are considered normal, above 9 kPa for severe fibrosis, and above 13-14 kPa for liver cirrhosis. It can also be used in case of ascites.

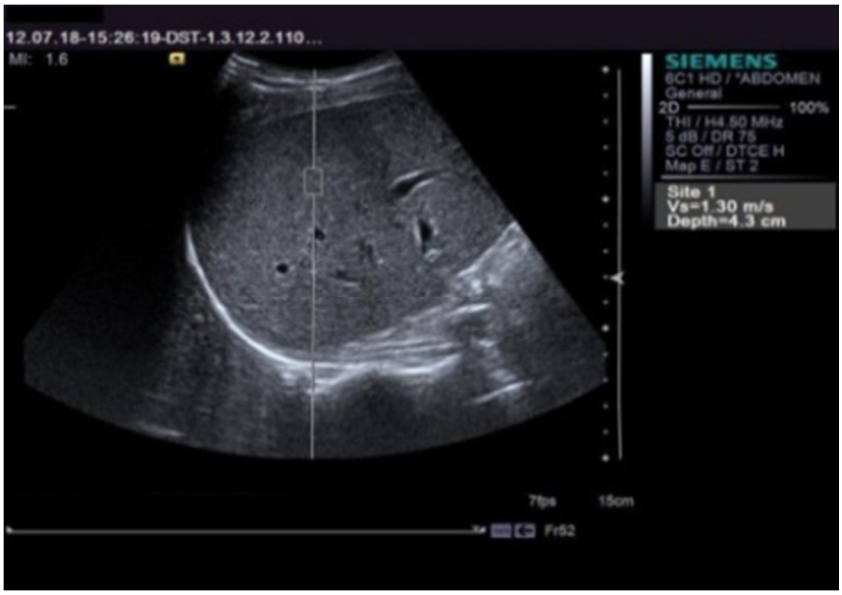


Figure 18.4. Hepatic point elastography (Siemens VTQ). Liver stiffness is measured at one point.

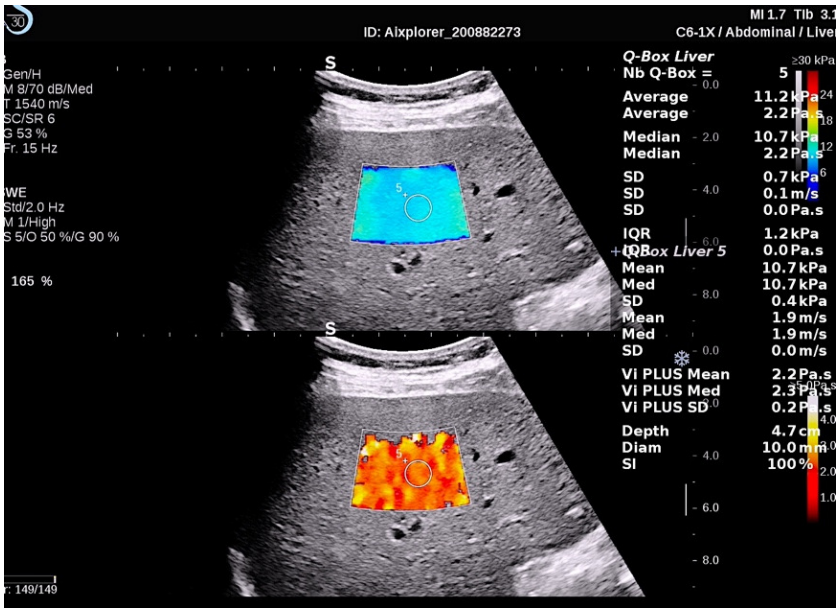


Figure 18.5. 2D-SWE (Shear Wave Elastography) elastography, which provides a real-time assessment of liver stiffness, in addition to the numerical value, a color elastogram is also obtained.

The differential diagnosis involves the confirmation or exclusion of other causes of chronic liver disease and is made by determining the pathognomonic markers for other liver diseases, discussed in the respective chapters.

The treatment aims to suppress viral replication and will be detailed in each subchapter. By suppressing viral replication, the progression of the disease to liver cirrhosis and its complications is stopped.

CHRONIC HEPATITIS WITH HEPATITIS B VIRUS (HBV)

Definition and history

Chronic hepatitis induced by the hepatitis B virus (HBV) is defined by the presence of persistent liver inflammation that lasts for at least 6 months from exposure to HBV or from the initial diagnosis. The hepatitis B virus, of a hepatotropic nature, is responsible for a wide spectrum of diseases – from asymptomatic or pauci-symptomatic forms to the progressive evolution, characterized by fibrosis, cirrhosis, liver failure and the development of hepatocarcinoma (HCC). The essential serological marker in diagnosis is HBV surface antigen (HBsAg).

From a historical perspective, HBV was first identified in 1965 by Blumberg, in the serum of Australian aborigines (being called the "Australia antigen"), and this discovery was recognized by the awarding of the Nobel Prize in Medicine in 1976, together with Alter.

Epidemiology

HBV infection is a major global problem. According to the WHO (2019), there are approximately 296 million people with chronic infection (HBsAg positive), 1.5 million new cases and 820,000 deaths annually, and approximately 2 billion people have been exposed (presenting anti-HBc antibodies). Without intervention, deaths from chronic HBV liver diseases could reach 1.14 million by 2035.

The global prevalence of chronic infection is estimated at 3.5%, with regional variations: low prevalence, **<2%** in Western Europe, USA, Australia, New Zealand; medium prevalence **2–7%** in Eastern Europe, Mediterranean region, Middle East, Central Asia, India, Singapore, Japan, Central and South America; and high prevalence **≥8%,** in China, Hong Kong, sub-Saharan Africa.

Over the past two decades, hyperendemic countries (e.g. Taiwan, China, Hong Kong) have seen significant decreases in HBV prevalence due to universal vaccination, improved socio-economic conditions and access to antiviral treatment. In some hypoendemic countries in Europe, prevalence has increased due to migration from areas with higher prevalence, and in the US, the epidemic of intravenous drug use and low vaccination rates have contributed to the increase in the number of cases.

In Romania, studies have shown a seroprevalence of HBsAg of 4.4% in adults and an exposure of 27% (estimated by the presence of anti-HBc antibodies), but recent data indicate a decrease in chronic infection to about 1.5%, due to universal vaccination at birth instituted in 1996 and prevention measures.

Pathophysiology

HBV is a hepatotropic DNA virus of the Hepadnaviride family, and its main reservoir is humans. The complete viral particle (Dane virion) is composed of:

- Viral genome - a partially double-stranded, circular DNA, including about 3200 base-pairs, which replicates with the help of a DNA polymerase. The genome is organized into four regions encoding seven proteins: surface proteins (S, preS1 and preS2), capsid proteins (precore/core – HBcAg and HBeAg), X proteins (with a transcriptional role) and DNA polymerase.

- Nucleocapsid - formed by the core antigen of HBV (HBcAg), which envelops the genome;

- Viral envelope: consisting of surface antigen (HBsAg) produced in excess and present in the form of non-infectious spherical or tubular particles.

Replication of the virus occurs exclusively in hepatocytes: the virus enters the cell through the NTCP receptor, the nucleocapsid releases the viral genome that is transported to the nucleus, where closed circular covalent DNA (cccDNA) is formed. It acts as a template for mRNA transcription and is the permanent reservoir of infection. The integration of viral DNA into the host genome can contribute to the development of HCC.

Genetic variability. HBV is classified into at least 10 genotypes (A–J), which exhibit more than 8% variability in nucleotide sequence and distinct geographic distributions. Genotype A is common in northern Europe, North America, India, and Africa, B and C predominate in eastern Asia, D in the Mediterranean regions, Eastern Europe, the Middle East, India, and Africa, E in West Africa, and F and H in South America. Genotypes C and D are associated with severe and rapid forms of disease progression, while A and B respond better to treatment with peginterferon.

Immunopathogenesis. HBV is not directly cytopathic. Liver damage occurs as a result of the host's immune response. Cytotoxic T lymphocytes recognize and destroy infected hepatocytes (by presenting HBcAg), and cytokines (e.g. TNF-α and IFN-γ) contribute to liver inflammation and viral clearance. In acute infection, a robust immune response leads to the elimination of the virus, while in chronic infection, the phenomenon of immunological depletion allows the virus to persist. B lymphocytes produce anti-HBs antibodies, which are important in achieving an immune cure.

Methods of transmission *(Table 18.I)*

HBV is found in the blood, seminal fluid, cervico-vaginal secretions, saliva and other body fluids. It is transmitted through contact with infected fluids. It is highly contagious, even more contagious than HIV, with HBV infection being considered a sexually transmitted disease.

HBV survives in the environment for up to 7 days and is more infectious than HIV; It is not transmitted through the fecal-oral route, and although it is found in breast milk, there is no evidence of transmission through breastfeeding.

Table 18.I. Routes of transmission of HBV

Main paths		Details
Vertical (perinatal)		From mother to newborn, with a significant risk if the maternal viremia is >200,000 IU/mL.
Horizontal		
	Blood	Through transfusions, contaminated blood products, hemodialysis or transplants.
	Percutaneous/per mucosal	Through the use of needles or contaminated instruments, intravenous drug administration, accidents with medical instruments, acupuncture, tattoos, body-piercing, etc.
	Sexual	Through unprotected sexual intercourse.
	Intra-family	In hyperendemic communities, through close contact and the use of personal objects (e.g., razor blades, toothbrushes) that can produce small skin or mucous lesions.

Natural history of HBV infection *(Table 18.II).* After the moment of infection, after an incubation period of several weeks, acute *hepatitis* occurs (with positive HBsAg, cytolysis in the order of hundreds and high viremia. Acute hepatitis can progress to *cure* (in more than 80% of cases if the infection occurs in an immunocompetent adult), with the disappearance of HBsAg and the appearance of anti-HBs antibodies, with normal cytolysis and undetectable viremia (Fig. 18.6).

If immunity is not enough to eradicate the infection, it becomes chronic. *Chronic hepatitis* B virus is defined as persistence of HBs Ag over 6 months with viral replication (viremia above 2000 IU/ml), moderate cytolytic syndrome and inflammatory and fibrotic lesions in the liver. Requires antiviral treatment. *Chronic infection* is defined as the persistence of HBsAg for more than 6 months, when the virus has low replication or does not replicate (viremia below 2000 IU/ml or undetectable), normal persistent cytolysis and negative HBeAg. It does not require antiviral treatment.

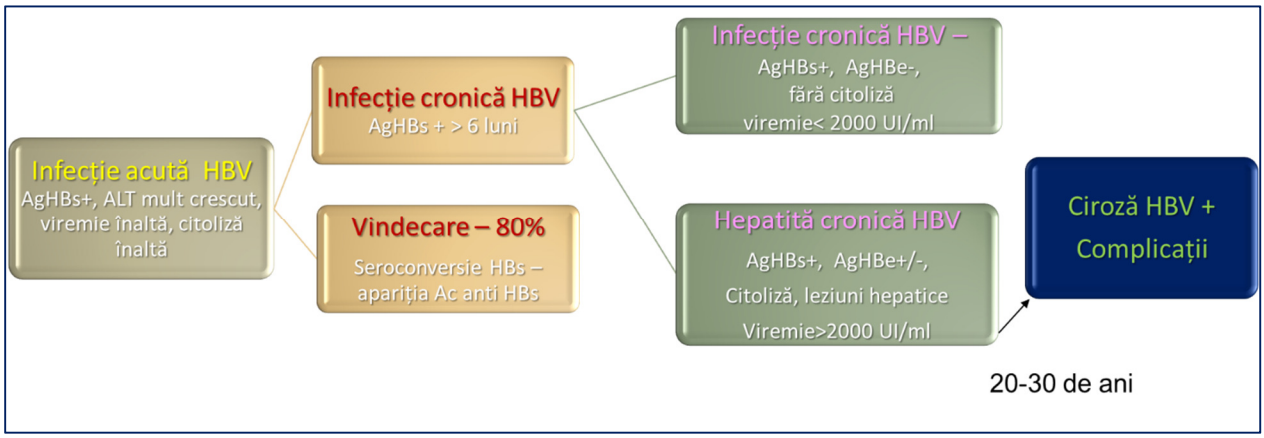


Figure 18.6. Natural course of HBV infection

The risk of developing chronic infection decreases with increasing age at infection, being over 90% in infected newborns in the first year of life, 20–50% in children under 4–5 years and 1–5% in immunocompetent adults, a risk that exceeds 50% in immunocompromised adults.

Without treatment, about 40% of patients with chronic hepatitis will develop cirrhosis of the liver, liver failure, and hepatocellular carcinoma. Viral co-infections are common: hepatitis D virus infects only HBsAg-positive patients (≈5%), and co-infection with HCV and HIV occurs in 1–15% and 1–2% of HBsAg-positive cases, respectively.

Table 18.II. Natural history of HBV infection

Markers/Phase	**Chronic HBeAg positive infection**	**Chronic hepatitis HBeAg positive**	**Chronic HBeAg negative infection**	**Chronic hepatitis HBeAg negative**	**Chronic HBsAg negative infection**
AgHBs	High Titer	High/Intermediate Titer	Low titer	Intermediate Titer	HBsAg negative, anti-HBc presence with/without anti-HBs
AgHBe	Positive	Positive	Negative, anti-HBe presence	Negative, anti-HBe presence	Negative
HBV DNA	Increased replication (>10□ IU/ml)	Increased replication (10□ - 10□ IU/ml)	Low replication <2000 IU/ml	Moderate replication/ high, persistent	Absent
OTHER	Persistently normal (<40 IU/L)	Increased	Normal	Increased	Normal
Liver disease/injury	Absent/minimal	Moderate or severe necro-inflammation, accelerated fibrosis	Absent necro-inflammation/ minimal, absent/mild fibrosis	Necro-inflammation and moderate fibrosis/ Severe	Liver damage present in various stages but inactive
Risk of progression to cirrhosis of the liver or HCC*	Reduced, but present	Moderate/ Accelerated	Reduced	Increased	Pre-cirrhotic HBsAg loss associated with minimal risk of progression to cirrhosis and HCC

Treatment	Not indicated	Shown	Not indicated	Shown	Not indicated
Epidemiological characteristics	Frequently found in young people, correlated with perinatal infection, increased contagiousness	Most patients achieve HBeAg seroconversion and HBV DNA suppression	Disappearance/ HBsAg seroconversion is found in 1-3% of patients annually	Most patients have mutant HBV infection	Immunosuppression can cause the disease to reactivate
Old nomenclature	Immunotolerance phase	Immune clearance phase or HBeAg-positive chronic hepatitis	Inactive carrier phase	Reactivation phase or chronic HBeAg-negative hepatitis	Occult HBV infection

Pathology

Histopathological examination is the standard method for evaluating necroinflammation and fibrosis. Liver biopsy is also important for differential diagnosis from other liver diseases. In cases with clinical, biological, or imaging signs are clear, biopsy is not mandatory.

Semi-quantitative scores are used to assess inflammation and the stage of liver fibrosis, the simplest of which is the METAVIR score. In cases of chronic hepatitis B, areas of interface hepatitis (lymphoplasmacytic infiltrations in the portal and periportal area) and necrosis or apoptosis of hepatocytes can be observed. Severe forms of the disease present necrosis in the bridge, which indicates progression to cirrhosis.

Histopathological examination may highlight features suggestive of the diagnosis of viral etiology B, such as *hepatocytes with* "matte glass" cytoplasm. These cells exhibit a granular and eosinophilic cytoplasm upon hematoxylin–eosin staining, due to the increased content of HBsAg. Immunohistochemical stains highlight the presence of HBsAg in the cytoplasm or on the membrane of infected hepatocytes, and HBcAg can be detected in the nucleus in patients with active HBV replication.

Clinical picture

The clinical manifestations of chronic hepatitis HBV range from *asymptomatic* or pauci-symptomatic forms (with non-specific symptoms such as asthenia and persistent pain in the right hypochondrium) to *complications* of cirrhosis (e.g. ascites, digestive hemorrhage, encephalopathy). In phases with high viral replication, the symptomatology

may mimic acute hepatitis, presenting fatigue, subfebrile state, anorexia, nausea, vomiting and jaundice.

Physical examination may be normal or show signs of advanced liver disease, such as jaundice, palmar erythema, stellate angiomas, hepatosplenomegaly, ascites, and encephalopathy.

Approximately 20% of patients have extrahepatic manifestations (e.g. arthralgia, mixed cryoglobulinemia, vasculitis, glomerulonephritis, acrodermatitis, polyarteritis nodosa), mediated by circulating immune complexes.

Diagnosis and initial evaluation

1. Anamnesis and clinical examination - have the role of identifying risk factors, family history of infection with the B virus, the presence of cirrhosis or HCC, associated conditions and clinical signs (such as splenomegaly, jaundice and stellate angiomas) that indicate the severity of the disease and its evolution to cirrhosis.

2. Evaluation of disease activity - aims to identify patients who require antiviral treatment. The most important biochemical change consists in the increase in transaminases – usually values 2–5 times above the upper limit of normal (with a characteristic ALT > AST profile). In intensive replication phases, these values can increase 10–50-fold, but fluctuations between repeated serum determinations are common.

3. Assessment of disease severity **–** aims to identify patients with advanced liver damage or cirrhosis and initiate screening for HCC. Thus, biochemical changes – abnormal values of bilirubin, albumin, GGT, alkaline phosphatase, prothrombin time/INR and platelet count – may signal progression to cirrhosis, and the increase in alpha-fetoprotein possibly suggests the appearance of HCC.

All patients should be evaluated by abdominal ultrasound, supplemented by non-invasive liver fibrosis assessment tests or, in inconclusive situations, liver biopsy.

4. The serological and virological markers of chronic HBV infection and their significance are presented in Table 18.III.

Table 18.III. Serological markers in HBV infection and their significance.

Serological marker	Meaning
AgHBs	It signifies HBV infection. Persistence over 6 months means chronic infection
AgHBe	Replication antigen, usually associated with high viremias, in wild virus infection
Anti HBc	HBV Contact Marker IgM anti-HBc – associated with acute HBV infection Anti-HBc IgG – associated with chronic HBV infection, remain present even after cure of HBV infection in combination with AntiHBs. Does not confer immunity

Ac anti HBs	Their appearance means the cure of HBV infection (in association with the disappearance of HBsAg) They also occur after HBV vaccination
Anti-HBe	They occur after seroconversion of wild virus infection, signify mutant virus infection
Viremia determined by the PCR technique	PCR-DNA-HBV ≥ 2000 IU/ml - defining element of chronic hepatitis HBV, signifies the need for antiviral treatment PCR-DNA-HBV ≤ 2000 IU/ml – associated with chronic HBe Ag-negative infection – does not require antiviral treatment.

Positive and differential diagnosis

A positive diagnosis is established by detecting HBsAg for more than 6 months in the presence of anti-HBc antibodies, and quantitative determinations of HBsAg and HBV DNA are essential for establishing the prognosis, defining the phase of infection, making the therapeutic decision, and monitoring treatment.

Differential diagnosis with other causes of chronic hepatitis or cirrhosis – whether viral, metabolic, genetic, autoimmune or alcoholic – is based on the anamnesis and identification of risk factors (e.g. metabolic conditions or alcohol consumption), serological/virological markers, the presence of autoantibodies and histological evaluation of the liver.

In addition, in Romania, an important problem is **co-infection with the hepatitis D virus (HDV),** which causes a severe and rapidly progressive form of chronic hepatitis and cirrhosis in HBsAg positive patients. Therefore, ***all HBsAg positive patients should be tested at least once for HDV infection, by determining*** **anti-HDV antibodies** (IgG, IgM and total). In case of positivity, the level of viremia – PCR-RNA-VHD will be determined.

Treatment of chronic hepatitis HBV

In the long term, antiviral therapy in chronic hepatitis B aims to improve the quality of life and survival of patients by preventing the progression of the disease to cirrhosis, liver failure and hepatocarcinoma (HCC), as well as reducing the transmission of infection and managing extrahepatic manifestations.

In addition to these long-term objectives, the treatment also aims to achieve immediate results, essential for disease control: *cure of the infection* (seroconversion into the HBs system, with the disappearance of HBs Ag and the appearance of Ac anti HBs – an objective unfortunately achieved in only a maximum of a quarter of cases); *Suppression of viral replication* (permanent reduction of serum viremia to values ≤ 2000 IU/ml, ideally at undetectable values); control *of liver damage* (reduction of inflammation and ideally of the severity of fibrosis); *biochemical response* (normalization of transaminase values, expression of reduced inflammation); *HBe Ag seroconversion to anti-HBe antibodies*.

1. Therapeutic indications

Antiviral treatment in chronic HBV infection is based on a comprehensive assessment that includes the *level of viral replication* (measured by HBV DNA) and *ALT values*; *severity of liver disease* - the presence of necroinflammation, degree of fibrosis and/or cirrhosis, assessed by PBH or non-invasive tests; additional factors such as age, *family history of cirrhosis or HCC*, as well as *the presence of extrahepatic manifestations* (e.g. related to alcohol consumption or metabolic syndrome).

Thus, antiviral treatment is indicated in the following situations:

- In ***patients with cirrhosis*** (compensated or decompensated) who have detectable HBV DNA, regardless of ALT values;
- In ***patients with chronic hepatitis*** (either HBeAg positive or negative) who have an HBV DNA level greater than 2000 IU/mL and elevated ALT values (at least twice above normal) or have moderate to severe histological lesions;
- In patients with ***high viral replication***, over 30–40 years of age or with a family history of cirrhosis and/or HCC;
- In those who have ***extrahepatic manifestations***, significant for the evolution of the disease.

Patients who do not meet the initial treatment criteria require periodic monitoring: assessment of transaminases at 3 months, HBV DNA at 6–12 months, and the degree of fibrosis by non-invasive tests (e.g. elastography and biomarkers) at 12 months.

2. Therapeutic strategies and agents

There are two major strategies in the treatment of patients with chronic HBV hepatitis: interferon-based therapy and nocleosided/nucleotide analogue strategy (Table 18.IV)

-Peg-interferon alfa (PegiFNa) therapy has the following advantages: finite duration of therapy (48 weeks), absence of viral resistance, possibility of seroconversion into the HBsAg system. The disadvantages are related to parenteral administration (subcutaneous injections), common side effects (flu-like syndrome, thrombocytopenia, leukopenia, anemia, mental disorders, alterations in thyroid function) and contraindications (decompensated cirrhosis, depression, thrombocytopenia).

It is indicated in young, non-cirrhotic patients with elevated ALT and not very high HBV DNA with a favorable genotype (A>B>C>D). Monitoring is done by assessing viremia and HBsAg at 12 and 24 weeks to decide to stop therapy in case of insufficient response.

- *Nucleoside/Nucleotide Analogue Therapy (NUCs).* Over the years, several antiviral agents with action against HBV have been discovered. The first to enter the market were Lamivudine, the Adefovir that was later discontinued due to the high rate of resistance developed. *Entecavir (ETV), Tenofovir disoproxil fumarate (TDF)* and *Tenofovir alafenamide (TAF) are currently used*. The duration of administration is indefinite, as when treatment is interrupted, viral replication resumes.

The advantages of taking NUCs are oral administration, strong antiviral effect and high barrier to resistance, excellent tolerability with minimal side effects, as well as the fact that they can be used in all forms of infection, including cirrhosis and HIV co-infection. The disadvantages are the low rate of seroconversion of HBeAg and HBsAg, the need for long-term/indefinite treatment.

The indications for administration are all patients with chronic hepatitis or cirrhosis (even decompensated) HBV. Another indication is for pregnant women with high viremia in the last trimester of pregnancy to reduce maternal-fetal transmission (tenofovir is preferred), as well as as as prophylaxis during immunosuppressive therapy in chronic HBV infection (HBsAg positive patients, with low or undetectable viral replication)

Treatment efficacy - virological response (undetectable HBV DNA) is achieved in 97–99% of patients, with biochemical remission and histological improvement, but elimination of HBsAg is rare (<1% annually).

Table 18.IV. Therapeutic strategies in chronic hepatitis and HBV cirrhosis

	Peg-interferon alfa (PegiFNa)	**Nucleose(t)idic analogues (NUCs)**
Administration	Parenteral (subcutaneous injections)	Oral
Duration of treatment	Finished (48 weeks)	Long-term/indefinite
Antiviral effect	Moderate; Sustained immune control without continuous therapy	Strong; Maintained viral suppression (undetectable HBV DNA in 97–99% of patients)
Viral resistance	Practically absent	Low risk (possibility of resistance, especially with lamivudine, adefovir or telbivudine, currently discontinued)
HBsAg Seroconversion	Possible (in 4–12% of cases long-term)	Very rare (<1% annually)
Additional benefits	Durability of the viral response; useful for patients with a favorable genotype (A > B > C > D)	Excellent tolerability; indicated in all forms of infection, including cirrhosis and HIV co-infection
Contraindications/Side effects	Common side effects, contraindicated in decompensated cirrhosis and autoimmune diseases	Long-term treatment; Risk of viral resistance
Monitoring	Assessment at 12 and 24 weeks for the decision to stop early	Continuous monitoring of viremia and biochemical parameters

New therapies developed for hepatitis B aim to achieve functional healing – defined as obtaining undetectable HBV DNA and the disappearance of HBsAg after discontinuation of treatment – by implementing diversified therapeutic strategies, including HBV entry inhibitors (e.g., Bulevirtide), nucleic acid polymers (e.g., REP2139), capsid assembly modulators (CAMs), agents that interfere with HBV RNA (siRNAs and ASOs), and immunomodulatory therapies (vaccines). therapeutics and specific anti-HBV mediators).

Evolution, prognosis, complications

Chronic HBV hepatitis carries the risk of progression to fibrosis, cirrhosis, and its complications, including hepatocarcinoma. The risk of progression is related to the level of viremia and individual characteristics. Even if viral suppression is achieved under treatment, there is still a risk of hepatocarcinoma in patients with severe fibrosis/cirrhosis, due to the integration of the viral genome into infected hepatocytes.

In patients with chronic HBV infection (HBsAg positive, low viremia) there is a risk of about 1% per year of progression to chronic HBV hepatitis, if the balance between host organism immunity and virus virulence is broken. This is favored by immunosuppressive treatment or chemotherapy, which is why prophylactic treatment with NUCs is recommended in these patients.

Screening and Prevention

HBV infection screening is performed by determining HBsAg and is recommended for people at high risk (people who inject drugs, people with risky sexual behavior, patients on hemodialysis, medical personnel, institutionalized, spouses and family members of HBsAg positive patients, donors and pregnant women).

Primary prophylaxis includes universal vaccination at birth according to the **0-1-6** month schedule (with an efficacy of >95% and protection for at least 30 years, followed by a booster dose every 5 years in adulthood). For children born to HBsAg positive mothers, it is additionally recommended to administer specific anti-HBV immunoglobulin (HBIG) in the first 12 hours after birth to prevent maternal-fetal transmission, as well as vaccination as soon as possible.

Secondary prophylaxis involves prophylactic treatment of patients with chronic HBV infection who must undergo chemotherapy or immunosuppressive treatment, throughout the duration of treatment and 6 months after.

To note

- Chronic hepatitis B virus is a public health problem due to its high prevalence, but also the possibility of evolution to liver cirrhosis and its complications.

- The diagnosis is based on the presence of HBs Ag and cytolytic syndrome for more than 6 months, associated with the presence of necro-inflammation and liver fibrosis evaluated by invasive and non-invasive methods.

- The initial evaluation of these patients involves the determination of HBsAg, cytolytic syndrome, evaluation of liver lesions by invasive and non-invasive methods.

- Treatment options include peg interferon therapy (burdened with side effects, sometimes severe, but in the finite term, with the chance of obtaining seroconversion in the HBs system). The other treatment option is nucleoside/nucleotide analogues, a treatment without adverse effects, with oral administration, but with an indefinite duration, which achieves a good control of viral replication.

- Patients with chronic HBg negative B Ag virus infection (normal persistent cytolysis and viraemia ≤ 2000 IU/ml do not require antiviral treatment. However, these patients must be monitored to capture the moment when they move from chronic infection with HBe Ag virus to chronic hepatitis B virus.

CHRONIC HEPATITIS WITH HEPATITIS D VIRUS (HDV)

Definition

Viral hepatitis D is a particular form of chronic viral hepatitis, characterized by persistent liver necro-inflammation for more than 6 months, caused by a defective RNA virus. This virus is "orphaned" in the sense that it cannot reproduce without the presence of HBV, from which it "borrows" the envelope antigen (HBsAg) necessary both for infecting hepatocytes and for releasing new viral particles.

The evolution of the disease is rapid, severe and progressive. This can lead to fulminant liver failure in the acute phases, and in the chronic stage, cirrhosis of the liver can develop, with associated complications such as ascites, digestive bleeding and hepatic encephalopathy, as well as the risk of hepatocellular carcinoma.

Recently, major advances in the diagnosis of hepatitis D and the emergence of innovative therapeutic solutions have increased interest in identifying, characterizing and treating patients affected by this disease.

Epidemiology

The prevalence of HDV infection varies significantly by region. Areas with low prevalence (less than 5% of HBV-infected patients) include the United States, the Nordic countries of Europe and the Far East, while areas with medium endemic disease (10–15% of HBV-infected patients) are the Mediterranean Basin, the Middle East and parts of Asia. *In Romania, studies indicate that about 7% of HBsAg positive patients, the proportion being much higher in HBsAg positive patients and advanced liver disease (23-30%).* Thus, the epidemiology of HDV largely reflects the epidemiology of HBV infection, being influenced by socio-economic factors, hygiene conditions, national vaccination programs and population migration.

Pathophysiology

HDV was discovered in 1977 and is classified in the *genus Deltavirus* of the family Deltaviridae. The viral particle is spherical, about 36 nm, with a single-stranded circular RNA genome of about 1680 nucleotides. The virus encodes a single structural protein, AgVHD, which is expressed in two isoforms: *Protein S (small)* – p24, with essential functions in viral replication, and *Protein L (large)* – p27, involved in inhibiting replication and promoting viral RNA assembly through the process of isoprenylation of amino acids in the C-terminal end.

HDV replication occurs exclusively in the liver parenchyma and is based on the use of host RNA-polymerase (Pol II) in the presence of ribosomes, which allow cleavage and cycling of the viral genome. Although replication does not depend directly on HBV, its presence is indispensable for the assembly and release of viral particles, since HDV "borrows" HBsAg to bind to the NTCP receptor of hepatocytes.

The hepatitis D virus acts through dual mechanisms:

- *Direct cytopathic action.* In the acute phase of infection, HDV can cause hepatocytic damage through its direct effect, even if in the chronic stages this action is less obvious.

- *Immune-mediated response.* In chronic infection, the host's immune response leads to severe necroinflammation, which contributes to the destruction of liver tissue.

HDV infection can occur either as a *co-infection,* simultaneously with HBV infection, or as a *superinfection* in a chronic HBV carrier. In simultaneous HBV-HDV co-infection, a severe acute episode can be observed, with the simultaneous presence of markers for both viruses. In the case *of superinfection* in patients with chronic HBV, the occurrence of HDV infection is often associated with a rapid exacerbation of liver disease, rapidly progressing to cirrhosis and increasing the risk of liver decompensation and hepatocellular carcinoma. This duality is essential, since it determines both differences in the clinical presentation and in the evolution of the disease, with HDV having a negative impact on the prognosis in cases of superinfection, especially if it is a patient with advanced liver disease.

Morphopathology

Chronic hepatitis HDV is not histologically distinguished from other chronic viral hepatitis, however, histological examination shows aggressive hepatocytic necrosis with bridge necrosis and periportal and lobular inflammation. In chronic hepatitis VHD, these changes may be more severe, and immunohistochemical techniques may highlight AgVHD in the nucleus and cytoplasm of hepatocytes.

Clinical picture

The clinical picture of hepatitis D is varied and non-specific. *In acute infection* (either by co-infection or by superinfection) jaundice, alteration of the general condition can be observed. In HDV superinfection in a patient with B-virus liver cirrhosis, Delta virus superinfection can manifest as a sudden decompensation of liver disease, which can lead to the patient's death. In asymptomatic HBV carriers, an acute episode may represent the first clinical manifestation.

In the chronic stages, the symptoms are *nonspecific* (asthenia, weight loss, pain in the right hypochondrium) until the appearance of complications of cirrhosis (ascites, digestive bleeding, hepatic encephalopathy).

Diagnosis and initial evaluation of HDV infection

- The diagnosis of HDV infection is mainly based on *the serological detection of anti-HDV antibodies*, through validated tests. Anti-HDV IgM antibodies appear early during acute infection and remain at high titers in chronic infection as well, correlating with the level of viral replication and severity of liver damage. Decreased titer or anti-HDV IgM

negativity (spontaneously or under treatment) suggests resolution of infection. Anti-HDV IgG antibodies appear a few weeks after the onset of acute infection, increase in parallel with disease progression and remain at high values in chronic infection; however, they do not confer protective immunity.

- The presence of anti-HDV IgG/IgM antibodies indicates exposure to the virus, but *confirmation of active infection requires determination of HDV-RNA* by molecular techniques such as RT-PCR. The level of viremia VHD (RNA-VHD) correlates with the prognosis of the disease; therefore, repeated quantitative measurements (preferably carried out in the same laboratory) are useful to monitor the evolution of the infection, the response to therapy and the prognosis.

- *Characterization of HBV infection****.*** In order to differentiate HBV-HDV coinfection from superinfection in the acute phase, it is recommended to determine anti-HBc IgM, which will be positive in coinfection but negative in superinfection (HDV over chronic HBV). HBeAg/anti-HBe and HBV DNA level are also assessed, given that an active HBV infection is associated with a more aggressive course and a more reserved prognosis.

- Although invasive, *liver biopsy* remains the gold standard for assessing the severity of liver damage (degree of necroinflammation and stage of fibrosis). Biopsy is not necessary for the diagnosis of cirrhosis when imaging clearly reveals a liver with a nodular structure or signs of portal hypertension, nor for monitoring the progression of the disease (in this situation, repeated non-invasive methods are preferred).

- *Non-invasive methods of evaluating liver fibrosis.* Elastography techniques (impulse elastography – FibroScan, and shear-wave – SWE) (Figures 18.3-18.5) and fibrosis scores (APRI, FIB-4) allow a dynamic, numerical and non-invasive assessment of liver fibrosis.

Therefore, the diagnosis of HDV infection is based on a combined approach, which includes serological tests (anti-HDV antibodies), molecular methods (HDV-RNA determination), characterization of associated HBV infection and non-invasive assessment of the severity of liver damage. This approach is essential for establishing the therapeutic management and assessing the prognosis in patients with hepatitis D.

Evolution, prognosis, complications

Acute fulminant hepatitis can be the onset of HBV-HDV coinfection. Most commonly, co-infection evolves towards spontaneous cure, with the disappearance of HBs Ag and the appearance of anti-HBs Ace, with the maintenance of anti-VHD Ace, but with undetectable HDV viremia.

In the case of superinfection, the progression to liver cirrhosis is rapid, within 2–10 years, with an increased risk of decompensation. The risk of hepatocellular carcinoma is significantly increased in patients with mixed HBV-HDV infection compared to those monoinfected with HBV.

Treatment

Chronic hepatitis VHD is considered an orphan disease with limited therapeutic options. HDV does not have its own RNA polymerase, using host RNA polymerase in replication, which makes viral eradication difficult. In the context of HBV–HDV co-infection, HDV clearance is not possible without sustained control of HBV replication, ideally defined by the disappearance of HBsAg and the emergence of anti-HBs antibodies, associated with undetectable HDV RNA.

Therapeutic objectives are to obtain:

- *Virologic response (RV)* - HDV RNA undetectable at 24–48 weeks post-treatment, but does not equate to HDV eradication (possibility of reactivation if HBsAg persists).
- *Combined response* (recommended by most guidelines): decrease in HDV RNA by at least 2 log IU/mL or negative viremia, plus normalization of transaminases (ALT) 6–12 months after the end of treatment.

All patients with chronic hepatitis VHD can be potential candidates for antiviral therapy, the decision being individualized according to the stage of the disease, tolerability, comorbidities and risk/benefit ratio.

Treatment options

- Until recently*, interferon alfa (IFN) – conventional or pegylated (PegIFN)* was the only therapeutic option in HBV-HDV coinfection, having a dual mechanism of action (antiviral and immunomodulatory). Clinical trials have reported a virologic response (undetectable HDV RNA) at 24 weeks post-treatment in 17–47% of cases, but with a high rate of relapse. Predictors of response are low VHD viral load and low HBsAg levels.

The recommended duration of therapy is at least one year, which can be extended to two years. The combination of PegIFN with nucleo(t)idic analogues did not significantly improve the sustained virologic response.

Patients with decompensated cirrhosis have a contraindication to interferon treatment, and evaluation for liver transplantation is recommended. The main side effects are flu-like syndrome, myelosuppression, psychiatric reactions and risk of autoimmune hepatitis.

- *Anti-HBV nucleose analogues* (entecavir, tenofovir) are indicated in patients with HBV–HDV coinfection if HBV DNA ≥ 2000 IU/mL, in those with cirrhosis compensated with detectable HBV and all patients with decompensated cirrhosis, regardless of viremia B. However, controlling HBV replication alone is not sufficient for the elimination of HDV in the absence of other specific interventions.

- *New therapeutic strategies.* Recent advances target VHD replication cycle targets involving host proteins.

*Bulevirtide***,** approved by the EMA in July 2020 for the treatment of chronic HDV infection, also available in Romania from 2024, blocks the attachment of HDV and HBV

to the common receptor (NTCP) and their entry into the hepatocyte. It is administered subcutaneously daily and has been shown to significantly reduce VHD viremia, with improvement of biochemical parameters. The majority of patients in marketing studies experienced viral relapse after discontinuation of treatment, therefore indefinite administration is recommended for as long as clinical benefit is maintained. It is not recommended to be administered in decompensated cirrhosis.

Liver transplantation is the only solution for patients with acute liver failure or decompensated cirrhosis. The post-transplant prognosis is very good, with high long-term survival rates. Although histological recurrence of HDV in the transplanted liver is possible, lesions usually remain minimal in the absence of HBV recurrence. For the prevention of HBV recurrence, long-term anti-HB immunoglobulin-associated nucleosis(t)idic anti-HB (HBIG) prophylaxis is recommended, maintaining anti-HBs levels >100 mIU/mL.

In conclusion, the treatment of HDV hepatitis is based on controlling HBV–HDV co-infection and keeping HDV replication under control, using either PegIFN (where possible) or new specific therapies (Bulevirtide), in combination with appropriate management of HBV infection. Liver transplantation remains the only option in cases of advanced disease ineligible for other treatments.

Prophylaxis

Since HDV depends on the presence of HBV for replication, prevention of HBV infection through vaccination is the most effective hepatitis D prophylaxis measure. In addition to HBV vaccination, general measures to prevent parenteral transmission (use of disposable medical instruments, avoiding transfusion of contaminated blood, etc.) are essential to control the spread of infection.

Screening recommendations for HDV infection

Reflex testing (automatic - by the laboratory, without a new medical visit) for anti-HDV antibodies among all people who turn out to be HBsAg-positive was associated with an approximately 5-fold increase in the number of detected cases (the vast majority being young patients, with no known risk factors, but with significant liver fibrosis). Thus, universal screening in HBsAg-positive people can facilitate early diagnosis and prevent transmission by implementing specific control measures. Currently, the widespread introduction of reflex testing is still being debated and subject to cost-effectiveness assessments.

To note:

- The hepatitis D virus is a defective virus that can only replicate in the presence of the hepatitis B virus.

- HDV infection can occur simultaneously with the HBV virus and then we are talking about co-infection (the clinical and biological picture being like that of acute hepatitis) or it can superinfect a patient already infected with HBV, in this case, the evolution being chronic.

- Chronic hepatitis D virus is the most severe form of chronic viral hepatitis, with rapid progression to liver cirrhosis and decompensation, also with an increased risk of hepatocarcinoma.

- The diagnosis is made based on the presence of anti-VHD AC, confirmed by viremia detectable by PCR techniques, and by highlighting liver lesions by biopsy or non-invasive tests.

- The treatment is so far discouraging. It can be done with Peginterferon, s.c., for 12 to 24 months, but with the risk of relapse.

- A new treatment option that has recently entered the market in Romania is Bulevirtida, administered s.c. as long as the clinical benefit is maintained, which achieves a good control of VHD viral replication.

- Neither Peg-interferon nor Bulevirtide is used in patients with decompensated liver cirrhosis.

- If there is concomitant viral replication on the B virus, it will be treated with nucleoside/nucleotide analogues.

CHRONIC HEPATITIS WITH HEPATITIS C VIRUS (HCV)

Definition

Chronic hepatitis induced by the hepatitis C virus is a chronic necro-inflammatory and fibrotic liver condition characterized by a significant potential to cause long-term complications such as cirrhosis and hepatocellular carcinoma (HCC).

Formerly known as "non-A non-B hepatitis," HCV was identified as a distinct etiological agent only in 1989 by Choo et al. With its discovery, the serological diagnosis of hepatitis C became possible in 1990, which allowed the testing of transfused blood and the initiation of specific prevention measures.

The discovery and development of direct-acting antiviral therapies (DAAs) have revolutionized treatment, currently providing infection eradication rates of 95–100%. This progress led to the launch by the World Health Organization (WHO) in 2016 of the strategy to eliminate hepatitis C worldwide.

Epidemiology

Chronic hepatitis C virus remains a major public health problem worldwide. Estimates from the period before the widespread introduction of modern antiviral therapies reported up to 170–180 million people infected (about 2.5–3% of the world's population). With expanded access to new treatment regimens, current projections suggest that around 57 million people currently remain infected with HCV.

However, the distribution of the infection *worldwide* is uneven. Lower rates (<1%) are found in some Western European countries and the US, while areas such as Africa have a much higher prevalence, especially in Egypt, with an average prevalence of 22% and even 50% in rural communities), the Middle East (Iran, Pakistan) and the Asia-Pacific region (China, Indonesia). In addition, in recent years, the increase in intravenous drug use in certain regions (including the United States) has led to a significant increase in new cases of HCV infection, particularly in young adults (20–39 years) and women (with potential for mother-to-fetal transmission).

In Romania, the prevalence of hepatitis C was estimated to be around 3.2–3.23% in a population study conducted in 2008, but more recent data suggest that less than 2% of the adult population may be infected with HCV. Prevalence is higher among people aged 45 to 75 and female, a possible historical factor being exposure to invasive medical maneuvers, transfusions or illegal abortions during the communist regime. Before the introduction of donor blood testing (around 1990), post-transfusion hepatitis C reached values of 90–95% in the case of "non-A non-B" hepatitis. In the 1980s, another major source of infection was medical procedures performed with inadequately sterilized instruments.

Screening campaigns, improved diagnostic methods and increased access to antiviral therapy in recent years have contributed to a significant decrease in the prevalence rate, as indicated by preliminary data from regional screening programmes (LIVER02), which report values below 1% in some regions.

The main ***route of HCV transmission*** is ***parenterally***:

- *Transfusions of contaminated blood or blood products*, especially before 1990, when specific anti-HCV screening was not possible.
- *The use of intravenous drugs* (sharing needles and instruments), which is currently the most common way of acquiring infection in many developed countries.
- *Tattoos and piercings* in non-sterile conditions
- *Nosocomial exposure* (in the hospital environment), surgery or dental interventions with inadequate non-sterilized instruments, but the risk has decreased significantly due to modern hygiene and sterilization protocols.
- *Percutaneous accidents and occupational exposure* among healthcare workers, the risk of transmission varying, but considered lower than in the case of HBV or HIV.

Non-parenteral ***transmission*** includes:

- *The sexual route*, more commonly associated with multiple partners, unprotected sex or co-infection with HIV. However, the rate of sexual transmission of HCV is lower than that of HBV or HIV.
- *Vertical transmission (maternal-fetal***),** which occurs in 3–6% of cases in the absence of HIV co-infection and can reach 10–17% in the presence of co-infection.
- *Non-sexual intrafamilial transmission* (3–10%), possible in situations with high viremia and prolonged close contact.

It is important to note that in about 30–40% of cases a clear source of infection cannot be identified, even after a detailed anamnesis.

Pathophysiology

HCV is part of **Family *Flaviviridae*,** Like *Hepacivirus*, and is distinguished by a positive single-stranded RNA genome, surrounded by a lipid envelope containing the viral glycoproteins E1 and E2. This genome encodes both structural (C, E1, E2) and non-structural (NS2, NS3, NS4A, NS4B, NS5A, NS5B) proteins involved in virion replication and assembly. HCV exhibits remarkable genetic variability, being classified into at least 6 major genotypes and numerous subtypes and quasispecies. This diversity, together with the mechanisms of viral evasion, explains both the difficulty of developing a vaccine and the pronounced tendency to chronicize the infection.

In Romania, over 90–95% of infections are caused by genotype 1b, frequently associated with transfusion transmission prior to 1990 and with an increased risk of severe evolution. In general, however, a significant proportion of infected individuals may remain asymptomatic or with slowly progressive liver disease, which underscores the need for screening and early identification of HCV infection.

The replicative cycle begins with the attachment and penetration of the virion into the hepatocyte through a process of receptor-mediated endocytosis. After releasing the RNA genome (decapsidation), the virus uses the cell's translation apparatus to produce a single polyprotein, which is subsequently cleaved into structural and non-structural

proteins. Viral positive RNA serves as a template for the synthesis of a negative RNA intermediate, which in turn underpins the generation of new viral RNA molecules. After the assembly of the new virions (nucleocapsid formation and addition of envelope glycoproteins), the viral particles are released into the extracellular space through exocytosis, ready to infect other hepatocytes.

Mechanisms of liver injury. HCV is not classically considered a strong cytopathic virus, liver damage results mainly from the immune response of the host. In the initial phase, innate immunity (via interferon type I and NK cells) tries to limit replication, but the virus has developed multiple evasion strategies (for example, NS3/4A and NS5A proteins can inhibit interferon signaling pathways). The essential component in viral control is specific cellular immunity (cytotoxic CD8+ T lymphocytes and CD4+ helper T), which can induce the lysis of infected hepatocytes or, in case of insufficient response, can favor the chronic persistence of the virus.

In chronic infection, inflammation and liver fibrogenesis are maintained by the continuous presence of viral antigens and the constant activation of the immune response. *Anti-HCV antibodies (humoral response) do not provide complete protection against reinfection*, but their presence serves as *the main serological marker of infection*.

Natural history

The natural course of HCV infection can range from spontaneous healing in the acute phase, to the development of liver cirrhosis and HCC (Fig.18.7.). In the acute phase, which begins 2–12 weeks after exposure, most patients (about 80%) are asymptomatic, and jaundice occurs in only a minority of cases. In rare situations, the acute infection can be severe (fulminant hepatitis), especially when it occurs against a background of pre-existing chronic liver disease, in coinfections (HBV-HCV) or in liver transplant recipients.

In 60–85% of infected people, HCV becomes chronic and, over the course of 20–30 years, can progress to cirrhosis of the liver in about 10–24% of cases. After cirrhosis, the annual risk of decompensation (ascites, varicellal hemorrhage, encephalopathy) is 3–5%, the risk of HCC is between 1–5% per year, and mortality can reach 2% per year. In patients with decompensated cirrhosis, survival decreases significantly, standing at around 50% at 5 years. Also, the recurrence of post-liver transplant infection is almost universal in patients who viremic at the time of transplantation, the evolution being accelerated to cirrhosis in about 20% of cases, 5 years post-transplant. Fortunately, this is no longer a problem under the conditions of modern treatment with direct antiviral agents, very effective even post-transplant.

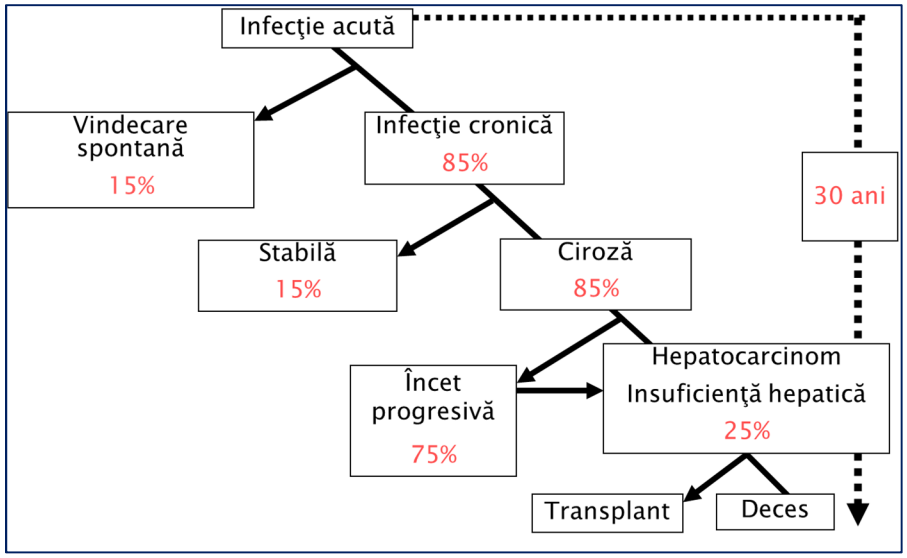


Figure 18.7. Natural course of HCV infection

Clinical picture

Most patients with chronic HCV hepatitis do not have specific symptoms, being frequently *asymptomatic* (in about 90% of cases). In situations where clinical manifestations occur, they are usually mild and non-specific, and may include: persistent *fatigue and asthenia*, often unrelated to exertion, accentuated fatigue; *nausea* and decreased appetite; *pain in the right hypochondrium* (hepatalgia), usually moderate and intermittent, more common towards the end of the day; *myalgia and arthralgia*; Unsystematized digestive discomfort, sometimes described as a vague dyspeptic syndrome.

When liver disease progresses, more obvious signs such as jaundice or hepatosplenomegaly may appear, but these are usually found in advanced stages.

Extrahepatic manifestations. In addition to the discrete hepatic clinical picture, chronic HCV infection may be associated with a wide range of extrahepatic manifestations, which may be present in 40–75% of patients. The most common are general symptoms (asthenia, nausea, myalgia, pruritus, cognitive disorders and depression), but there are also more specific manifestations, often correlated with autoimmune or immunological processes, such as thrombocytopenic purpura, systemic vasculitis; mixed cryoglobulinemia and associated syndromes; lichen planus, Raynaud's phenomena, late cutaneous porphyria; sicca syndrome (symptoms similar to Sjögren's syndrome); membranoproliferative glomerulonephritis; increased risk of insulin resistance and diabetes, as well as non-Hodgkin's malignant lymphoma

It is important to note that the severity of symptoms does not always correlate with the degree of liver damage, which is why many patients can remain undiagnosed for a long time. However, their early detection, including through serological tests, plays an essential role in the rapid initiation of treatment and the prevention of long-term complications.

The biological picture

- *Cytolysis syndrome.* Transaminases (ALT and AST) are the main indicators of liver damage. In chronic hepatitis C, transaminase levels may be increased (often <2× normal values), but may fluctuate markedly over time, without necessarily signaling a worsening of the disease. About 30% of patients may have transaminases within normal or near-normal ranges, despite the presence of an active infection.

- *Cholestasis syndrome.* Bilirubin and alkaline phosphatase (ALP) values, together with gamma-glutamyltransferase (GGT), may be useful for detecting a cholestatic component. In advanced forms of the disease, slight increases in these parameters may also occur, but they are not specific to HCV infection.

- *Hepatoprivation syndrome*. Serum albumin and prothrombin time (TP/INR) assess the synthesis capacity of the liver. Low albumin levels and prolonged prothrombin time may suggest advanced chronic liver damage.

- *Inflammatory syndrome*. Red blood cell sedimentation rate (ESR) and C-reactive protein (CRP) are non-specific indicators of inflammation and can only be slightly altered in chronic hepatitis C.

- *Serological tests (anti-HCV antibodies) - Screening by enzyme-linked immunoassay.* They detect anti-HCV antibodies in ~97% of infected people, usually 2-3 weeks after infectious contact. A positive result signals exposure to the virus, but does not necessarily indicate an active infection, as antibodies can persist long after spontaneous healing or post-treatment viral eradication. In the first two weeks after infection, serological tests can be false-negative (especially in immunocompromised people), because the antibodies have not yet reached a detectable titer, a period called the immunological window. In this situation, or in patients at high risk and clinically suspected, direct testing for viremia (HCV RNA) is recommended.

- *Rapid diagnostic tests (RDTs)* allow the detection of anti-HCV antibodies even in capillary blood or saliva, providing results in about 15 minutes. The advantage is the possibility of large-scale screening, including in non-hospital settings (prisons, disadvantaged communities, etc.).

- *Determination of viremia by PCR*. Confirmation of active infection is done by molecular techniques based on polymerase chain reaction (RT-PCR), which highlights the viral RNA and measures the viral load. Modern *real-time PCR* (rt-PCR) techniques have a very low detection limit (10–15 IU/ml), being useful both for diagnosis and for monitoring response to therapy.

- *Viral genotyping*. The identification of the HCV genotype and subgenotype is also done through molecular tests, they are useful but not mandatory in the choice of treatment regimen, with the emergence of pan-genotypic therapies. The genotype does not directly correlate with the severity of liver damage, but it does influence the duration and type of antiviral therapy. In Romania, the majority of infections (about 99%) are with genotype 1, predominantly 1b, which simplifies treatment options to a certain extent.

- *Serum cryoglobulins* and urinary sediment analysis (proteinuria, hematuria) may signal the presence of extrahepatic lesions such as mixed cryoglobulinemia or glomerulonephritis.

- *Autoantibodies* (ANA, SMA, LKM1) are tested because HCV infection can coexist with autoimmune hepatitis.

The "biological picture" in chronic hepatitis C involves the evaluation of laboratory parameters to detect liver injury (transaminases, synthesis tests) and, above all, to confirm the viral etiology (serological and molecular tests). Although transaminases may remain normal in some cases, the presence of anti-HCV antibodies, in conjunction with the determination of HCV RNA, establishes the diagnosis of chronic infection. Additional tests (cryoglobulins, autoantibodies, fibrosis tests) are useful for identifying extrahepatic lesions and for establishing the optimal therapeutic approach.

Evaluation of liver fibrosis

- *Liver biopsy* is an invasive method that provides information about the degree of inflammation and the stage of fibrosis. It can highlight associated lesions (co-infection with HBV, alcoholic or non-alcoholic steatohepatitis, autoimmune hepatitis). Its usefulness has decreased in recent years due to the risks of complications (bleeding, pain) and patient discomfort, being used especially when the results of non-invasive methods are inconclusive or when another cause of liver injury is suspected.

- *Specific biological tests (biomarkers)* are non-invasive methods increasingly used to evaluate fibrosis in patients with chronic HCV hepatitis. The most commonly used are simple biological tests (*APRI*, *FIB-4)* or more complex, patented (*FibroTest*, *FibroMax*, *ELF* - Enhanced Liver Fibrosis), etc. They have a good accuracy (80–90% or higher) to diagnose advanced fibrosis (F3–F4) and cirrhosis (F4), with cut-off values specific to each test. They are a simple and affordable method for monitoring the evolution of fibrosis over time.

- *Liver elastography* uses different ultrasound techniques to measure liver stiffness, considered an indirect marker of fibrosis. The best known method is *impulsive elastography* (FibroScan®, Fig.18.3,), with indicative threshold values for the stages of fibrosis: Values below 5 kPa are considered normal, above 10 kPa for severe fibrosis, and above 13-15 kPa for liver cirrhosis. Other elastographic techniques (point Shear Wave Elastography - pSWE, and 2D-SWE (Fig.18.4 and 18.5) or MRI elastography) provide comparable results, with their own cut-off values.

Diagnosis

Since most people infected with HCV do not have characteristic symptoms, the diagnosis is often made late, either in advanced stages of the disease or when the first complication of cirrhosis occurs. In many cases, the infection is discovered by chance,

through laboratory tests (abnormal transaminase values) or by highlighting anti-HCV antibodies.

The positive diagnosis is based on ***serological tests*** (detection of anti-HCV antibodies), which indicate exposure to the virus, but do not distinguish between active and cured infection, confirmed by ***molecular tests*** (HCV RNA and genotyping) to demonstrate viral replication and identify the genotype responsible, necessarily accompanied by ***fibrosis*** evaluation (by liver biopsy or non-invasive methods such as elastography and biomarker determination) to determine the degree of liver damage.

Differential diagnosis

The differential diagnosis of chronic hepatitis or cirrhosis of the liver with C virus implies the exclusion of other causes of chronic liver disease, such as those of viral etiology (HBV, VHD), metabolic (steatohepatitis associated with metabolic dysfunction), genetic (hemochromatosis, Wilson's disease), autoimmune or alcoholic. The correct guidance is based on medical and social history (alcohol consumption, metabolic risk factors), the determination of serological and virological markers (to exclude other liver viruses), as well as the identification of specific autoantibodies. In cases where the situation remains unclear, histological examination by liver biopsy can provide additional information to establish the final diagnosis.

Complications

The complications of chronic infection with the hepatitis C virus are the consequence of the evolution to liver cirrhosis (usually installed after 20–30 years of silent progression) and the appearance of its complications (ascites, jaundice, digestive hemorrhage, hepatic encephalopathy), which can ultimately lead to liver failure. HCC can also occur at a rate of 1–4% per year after cirrhosis occurs. In addition, patients may also present extrahepatic manifestations, such as purpura, glomerulonephritis with evolution to chronic renal failure and various autoimmune diseases.

Treatment

Purpose and objectives of therapy

The main goal of antiviral treatment in chronic HCV hepatitis is the eradication of infection (sustained viral response – SVR12), which has the consequences of preventing the progression of inflammation and fibrosis to cirrhosis and hepatocellular carcinoma (HCC), reducing overall and hepatic mortality, preventing extrahepatic complications and increasing patients' quality of life, as well as limiting HCV transmission to the uninfected population

The immediate goal of any regimen is *to achieve SVR12*, defined as undetectable HCV RNA 12 weeks after the end of therapy. Patients who obtain SVR maintain, in more than 99% of cases, their status as undetectable HCV RNA in the long term.

Indications and contraindications

All patients with chronic hepatitis C, confirmed with detectable viremia (HCV RNA positive), are indicated for antiviral therapy, regardless of the degree of fibrosis or the level of transaminases.

In the era of direct-acting antivirals (DAAs), absolute *contraindications* are rare. However, a few things must be taken into account, namely:

- Drugs that interact strongly with cytochrome P450 (e.g. phenobarbital, phenytoin) may lower AAD concentrations and need to be discontinued or replaced if the combination cannot be avoided.

- Protease inhibitor regimens (e.g. glecaprevir, grazoprevir, voxilaprevir) are contraindicated in patients with decompensated cirrhosis (Child-Pugh B or C).

- Therapy is not indicated in situations with limited life expectancy (terminal extrahepatic conditions), where eradication of the virus cannot improve the prognosis.

The pre-therapeutic evaluation involves several things

- *Staging of fibrosis* (elastography, biomarkers or, in selected cases, liver biopsy) to detect advanced fibrosis (F3) or cirrhosis (F4).

- *Evaluation of comorbidities and chronic medication* (the risk of drug interactions must be rigorously assessed).

- *Laboratory tests* (blood count, coagulation tests, kidney function, liver function, HBsAg and HIV status) to outline the complete picture.

- *Molecular tests* to confirm the infection – PCR-RNA-HCV. HCV genotyping can be omitted in pangenotypic regimens, but sometimes it is performed to customize the therapeutic regimen (e.g. genotype 3 with advanced fibrosis).

- *Pregnancy test* in women in the fertile period.

Modern antiviral therapy: direct-acting antiviral regimens (DAAs)

Since 2014, the use *of interferon-free regimens* has revolutionized the treatment of hepatitis C. These therapies include combinations of substances that target non-structural viral proteins (NS3/4A, NS5A, NS5B), being called direct-acting antivirals (DAAs). Their main advantages are very high viral eradication rates (SVR >95%), short duration of therapy (8–12 weeks in most cases), very good safety profile (minimal side effects, lack of injection), limited contraindications, increased adherence to treatment.

- *Pangenotypic regimens* can be used without requiring genotyping and are also indicated for patients with HIV co-infection, patients who have failed previous therapies and those with various comorbidities. Success rates reach 95–100% in clinical trials and in real practice. The pangenotypic combinations currently used are:

- Glecaprevir + Pibrentasvir (G/P), Maviret®, administered 8–12 weeks
- Sofosbuvir + Velpatasvir (SOF/VEL), Epclusa®, administered 12 weeks

- Sofosbuvir + Velpatasvir + Voxilaprevir, (SOF/VEL/VOX), Vosevi®, reserved for patients with previous treatment failure

- *Genotype-specific therapy*. In certain situations, genotype-adapted regimens such as Grazoprevir/Elbasvir, Zepatier® (for genotype 1b infection) may also be used. Genotyping becomes useful especially when genotype 3 with advanced fibrosis is suspected, a situation that may require longer regimens or the combination of ribavirin.

- In patients with *decompensated cirrhosis* (Child-Pugh B or C), the choice of the scheme should be made in specialized centers. As a rule, SOF/VEL in combination with ribavirin is used for 12 weeks, with close monitoring of liver and kidney function. Protease inhibitors are contraindicated in decompensated liver cirrhosis, Child-Pugh B or C.

Classical therapy (interferon and ribavirin-based)

In the past, the standard treatment for chronic hepatitis C was PegInterferon (weekly subcutaneous administration) in combination with ribavirin (oral administration). Today, interferon therapy has been replaced by AAD regimens, due to the latter's significantly superior efficacy and tolerance.

Post-treatment monitoring and follow-up

The evaluation of the viral response is done 12 weeks after the end of therapy (SVR12) by determining HCV RNA, and is the standard for confirming HCV eradication. Current regimens have few *side effects* (headache, fatigue, gastrointestinal disorders). In the case of ribavirin combination, haemoglobin is monitored to prevent haemolytic anaemia.

Patients with *advanced fibrosis (F3) and cirrhosis (F4)* require ultrasound follow-up at 6 months, with AFP performing, to detect the onset of HCC early, even if the HCV infection has been eradicated. In those with *mild fibrosis (F0–F2)* and SVR, the recommendation is a periodic reassessment especially if risk factors persist (alcohol, obesity, co-infections). In case of therapeutic failure (without SVR) a 'rescue' regimen (usually another combination of DAAs) is considered.

The treatment of chronic hepatitis C has undergone a major transformation with the introduction of direct-acting antivirals, which ensure cure rates of over 95% and have a very good safety profile. All patients with detectable viremia, regardless of the stage of the disease, can benefit from these regimens, with remarkable results in terms of preventing progression to cirrhosis, reducing mortality and improving quality of life.

To note

- Chronic hepatitis C virus infection is one of the most important causes of chronic liver disease.

- The route of transmission of the hepatitis C virus is mainly parenteral, through blood and blood products and through intravenous drug use.

-Taking into account that the virus was only discovered in the early 90s, any blood transfusion before this date must be considered as potentially infectious.

- The evolution of chronic hepatitis C virus is long and generally asymptomatic, but a large proportion of patients are at risk of developing liver cirrhosis and its complications.

- The initial evaluation of patients with chronic HCV hepatitis involves confirmation of infection by determination of anti-HCV antibodies and viremia, as well as evaluation of the severity of fibrosis, either by PBH or by non-invasive tests.

- Modern treatments with direct antiviral agents have revolutionized the natural evolution of this condition. They are administered by mouth, are highly effective (sustained viral response rates of over 95%), safe, with a duration of administration of 8-12 weeks. It is preferable to administer a pangenotypic regimen.

- The response to therapy is assessed by determining viremia 12 weeks after the end of treatment. An undetectable level of viremia at this time is equivalent to eradicating the infection.

- It should be taken into account that patients with severe fibrosis, cirrhosis in which the C virus infection has been eradicated remain at risk of hepatocarcinoma and must undergo the screening program, by ultrasound and determination of alpha-fetoprotein every 6 months.

19. AUTOIMMUNE HEPATITIS

Definition

Autoimmune hepatitis (AIH) is a chronic, immune-mediated, progressive liver disease that predominantly affects the female sex and is characterized by increased serum transaminase values, specific autoantibodies, hypergammaglobulinemia and interface hepatitis on histopathological examination.

AIH is generally suspected in patients with chronic liver disease who present with marked hypergammaglobulinemia, fever, and arthralgia, particularly when viral hepatitis markers are negative.

Epidemiology

AIH is a relatively rare and heterogeneous disease, with incidence and prevalence influenced by environmental, genetic, and infectious factors. The highest prevalence is observed among Caucasian populations in Western Europe, North America, and Australia. The disease predominantly affects women, with a female-to-male ratio of approximately 4:1, most commonly presenting in individuals under 40 years of age. AIH accounts for 12–20% of cases of chronic hepatitis.

Etiopathogenesis

AIH is an idiopathic disorder with a complex, multifactorial pathogenesis. In genetically susceptible individuals with underlying immunological abnormalities, the disease can be triggered by environmental factors such as viral infections, drugs, or other external stimuli.

In individuals with genetic susceptibility or following exposure to exogenous triggers, immune tolerance to liver tissue is lost, causing hepatocytes to be recognized as non-self. Among exogenous factors, hepatitis C virus is a frequent trigger, while hepatitis B virus is less commonly implicated. The immune response targets hepatocyte-specific membrane proteins (LSPs – liver-specific proteins), which may undergo structural alterations due to viral infection or toxic drug exposure, rendering them antigenic. This leads to the generation of autoantibodies and antibody-dependent cytotoxicity, resulting in immune-mediated hepatocyte injury. Repeated exposures to triggering agents can perpetuate the immune response against the liver and may extend to other organs, contributing to the development of AIH and other autoimmune disorders.

Pathology

Histological examination of liver biopsy specimens in AIH typically reveals interface hepatitis, a dense plasma cell infiltrate, and both degenerative and regenerative

hepatocyte changes. Degenerative changes include ballooned hepatocytes, while regenerative features include hepatocyte rosettes and multinucleated giant hepatocytes. Interface hepatitis (Fig. 19.1) and hepatocyte rosettes are considered characteristic of AIH. In severe cases, there may be widespread necrosis and extensive multi- or panacinar inflammation (Fig 19.2). Liver biopsy is also essential for disease staging and assessment of fibrosis severity.

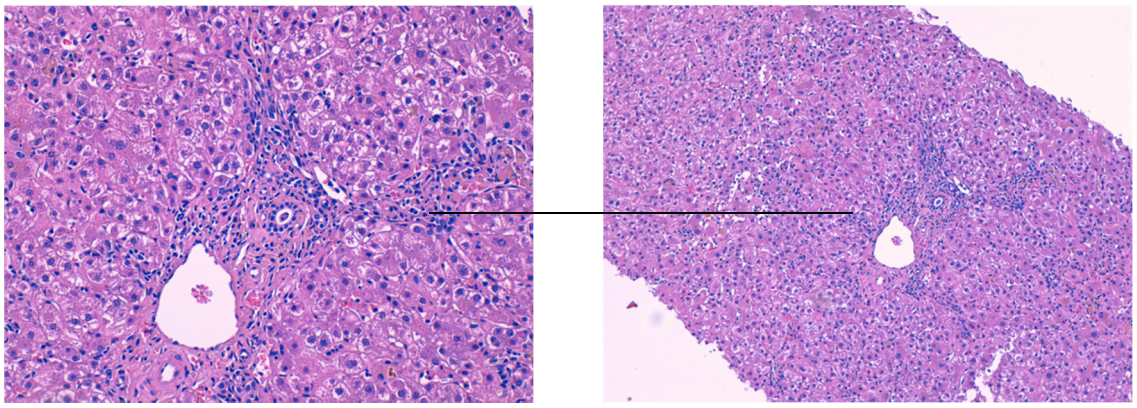


Figure 19.1 Interface hepatitis (left detail) - the hepatocyte-limiting blade is no longer continuous by lysis of hepatocytes at this level, followed by the penetration of the inflammatory infiltrate into the hepatic lobe.

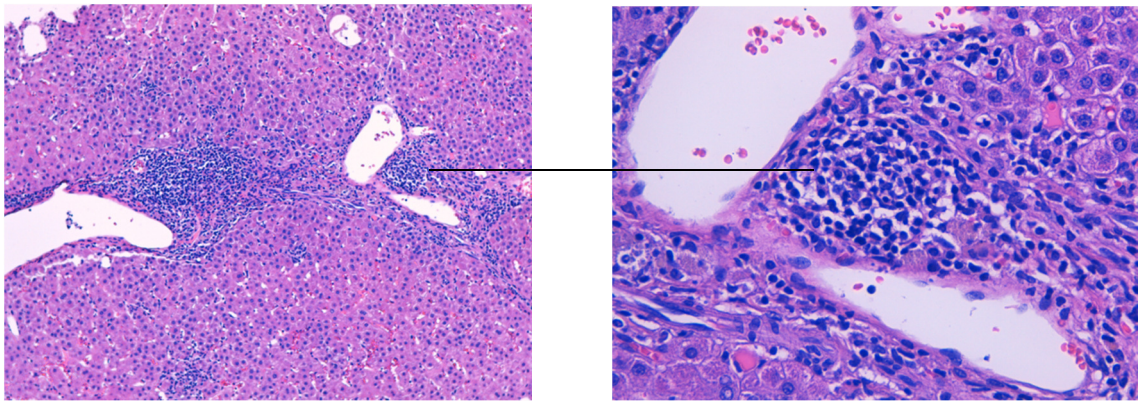


Fig. 19.2 Autoimmune hepatitis – bridge necrosis and detail (right) showing a rich inflammatory infiltrate with lymphocytes and plasma cells.

Clinical presentation

The clinical spectrum of AIH is broad, ranging from asymptomatic cases to manifestations of chronic hepatitis, acute hepatitis, or, in rare instances, fulminant liver failure.

Onset most commonly occurs in young women, though it may also present after age 40, typically with symptoms such as fatigue, asthenia, fever, and arthralgia. Extrahepatic immune manifestations are diverse and may include autoimmune thyroiditis, amenorrhea,

autoimmune hemolytic anemia, chronic glomerulonephritis, rheumatoid arthritis, and immune thrombocytopenic purpura, among others.

Laboratory findings

Biochemical tests in AIH typically demonstrates markedly elevated transaminases (ALT and AST), often ranging from 3 to 50 times the upper limit of normal, with ALT usually higher than AST. Other liver function parameters, including alkaline phosphatase, bilirubin, and serum albumin, may show variable alterations. A characteristic feature of AIH is hypergammaglobulinemia, predominantly affecting the IgG fraction, with levels 1.5–3 times above normal. Increases in alkaline phosphatase and bilirubin are generally modest, rarely exceeding 2–4 times the upper limit of normal.

Serological markers - detection of disease-specific autoantibodies:

- ANA (anti-nuclear antibodies): Typically present at titers >1:40
- Anti-SMA (anti-smooth muscle antibodies)
- Anti-LKM1 (anti-liver kidney microsomal type 1 antibodies)
- Anti-SLA/LP (anti-soluble liver/liver-pancreas antigen antibodies).

In addition to the conventional autoantibodies, the following may also be assessed: Anti-LC1 (anti-liver cytosol type 1 antibodies); Anti-LKM3 (anti-liver kidney microsomal type 3 antibodies) and, pANCA (perinuclear anti-neutrophil cytoplasmic antibodies). These markers can provide further diagnostic and classification information, particularly in atypical or seronegative cases.

Paraclinic

Abdominal ultrasound, depending on the stage of the disease, may be normal or may show signs of liver cirrhosis (heterogeneity of the liver parenchyma, irregular liver surface, hypertrophy of the caudate lobe, splenomegaly, etc.).

Percutaneous, surgical, or transjugular liver biopsy is important to confirm the diagnosis, rule out other liver conditions, and assess the severity of the disease. Histopathological examination typically demonstrates interface hepatitis, a hallmark feature of AIH.

Elastographic methods (Impulse Elastography – FiBroScan, but also other elastographic methods) can be used for the staging of fibrosis. However, elevated transaminase levels may lead to an overestimation of fibrosis, and results should be interpreted with caution in this context.

A definitive diagnosis of AIH is based on a combination of clinical, biochemical, serological, and histological criteria, alongside the exclusion of other causes of hepatitis or cirrhosis.

AIH should be suspected in patients presenting with features of acute or chronic hepatitis, particularly when systemic autoimmune manifestations are present. Laboratory findings typically include markedly elevated transaminases, hypergammaglobulinemia,

absence of viral hepatitis markers, and the presence of disease-specific autoantibodies such as ANA, SMA, or anti-LKM1.

AIH is classified into several types based on the specific autoantibodies detected:

- **Type 1 AIH** - characterized by the presence of ANA and anti-SMA. This form accounts for approximately 90% of AIH cases and typically affects women around 40 years of age. It is often associated with other autoimmune disorders. If untreated, about 50% of cases may progress to cirrhosis.

- **HAI type 2** - defined by the presence of anti-LKM1 antibodies. This type occurs in both sexes, frequently during childhood, and is associated with marked hypergammaglobulinemia. Type 2 AIH is often linked to hepatitis C virus infection, with up to 80% of cases progressing to cirrhosis if untreated.

- **HAI type 3** - is very rare. It is characterized by the presence of anti SLA/LP

Accurate diagnostic classification of autoimmune hepatitis (AIH), including both overall disease categorization and subtype determination, requires comprehensive and often costly serological evaluation. Omitting the assessment of key immune markers can result in missed or delayed diagnosis, increasing the risk of progression to cirrhosis over time.

According to the latest European guidelines on autoimmune hepatitis (AIH) subclassification (2025), routine subdivision into subtypes is no longer considered necessary, as recent epidemiological data have not demonstrated significant clinical or prognostic differences among the three subtypes.

The differential diagnosis of AIH must be made with the following pathologies:

- *chronic viral hepatitis* (where viral markers are positive). Pay attention to the coexistence of AIH with chronic HCV hepatitis (in which antiHCV antibodies are present, but viremia is also detectable).

- *Drug-induced hepatitis* - where the history may not always be relevant. The most frequently incriminated are Isoniazid – in TB patients; alpha-methyldopa; oxyphenisatin – present in some purgatives, but currently out of use.

- *Wilson's disease* - ceruloplasmin deficiency, often diagnosed only in the cirrhotic stage. Clinical features may include Kayser-Fleischer rings and neurological manifestations. Diagnosis is confirmed via serum ceruloplasmin, serum copper, and 24-hour urinary copper measurements.

- *Alpha-1 antitrypsin deficiency* can lead to chronic liver disease. The diagnosis is made by the alpha-1 dosage of antitrypsin, which will be low or absent.

- *Chronic alcoholic liver* disease - it is relatively common, it has a broad histological spectrum, ranging from acute alcoholic hepatitis, to steatosis, steatofibrosis and liver cirrhosis. History of alcohol consumption, increased levels of gammaglutamyltranspeptidase (GGTP) are useful for diagnosis. Alcohol abuse is not always recognized by the patient, which can make etiological diagnosis difficult.

- *Primary biliary cholangitis* (the old name was primary biliary cirrhosis) (PBC) is clinically characterized by chronic, intense pruritus. Biochemically, marked cholestasis is present with elevated GGT, alkaline phosphatase, and bilirubin. Diagnosis is supported by the presence of antimitochondrial antibodies (AMA). Early-stage diagnosis may be challenging.

Also in the presence of chronic cholestasis, we must distinguish AIH from:

- *sclerosing cholangitis*, where the clinical picture includes fever, the biological picture is characterized by severe chronic cholestasis, but AMA is missing. Diagnosis is made via MRI cholangiography, which typically shows marked attenuation of the intrahepatic biliary tree with a beaded (moniliform) appearance due to stenoses and dilatations of intrahepatic bile ducts.

Complications of AIH arise from the progression of either acute or chronic disease. In the acute form, there is a risk of acute liver failure and infectious complications. In chronic forms, progression to liver cirrhosis with complications related to portal hypertension (upper digestive hemorrhage, ascites, hepatic encephalopathy), liver failure, hepatocellular carcinoma.

The clinical course and prognosis of AIH depend on the disease subtype and response to therapy.

HAI type 1 is responsive to corticosteroid therapy and has a good long-term prognosis. Type 2 has a variable response to corticosteroid therapy and progressive evolution to cirrhosis. Type 3 is similar to type 1 but has the potential for severe progression with a variable prognosis.

Untreated cases of AIH progress to acute/fulminant liver failure or liver cirrhosis.

Treatment

Treatment objectives are: induction of complete remission; maintenance of remission without corticosteroid therapy and with minimal doses of immunosuppressive treatment; prevention of progression to cirrhosis of the liver.

HAI treatment is based on immunosuppressive medication and has two components: attack treatment and maintenance treatment.

The attack treatment - Induction of remission is achieved using corticosteroids in combination with azathioprine (Imuran). The standard regimen consists of Prednisone 30–60 mg/day (0.5–1 mg/kg/day) together with azathioprine 2–3 mg/kg/day until remission is achieved, typically indicated by normalization of transaminases within approximately 4 weeks. Following remission, Prednisone is gradually tapered by 5 mg per week and ultimately discontinued, while the azathioprine dose is maintained. As an alternative to systemic Prednisone, Budesonide, a corticosteroid with minimal systemic

effects, may be used at 9 mg/day for 2 months, after which it is discontinued. Budesonide is contraindicated in patients with cirrhosis.

Maintenance treatment is done by continuing treatment with azathioprine for a long time (years or even life). Discontinuation of treatment after years of treatment after histological remission has been achieved. Prednisone monotherapy is preferred in the case of cytopenias, in thiopurinmethyl transferase deficiency, which should be tested prior to administration of azathioprine.

Relapse after stopping treatment makes it necessary to resume therapy. A large proportion of patients with AIH must be treated for life, with only a small proportion remaining in remission without therapy. For patients with insufficient response or intolerance to azathioprine, Mycophenolate mofetil and Tacrolimus, considered 2nd line drugs, can be used.

Liver transplantation remains the only therapeutic option in cases of treatment-refractory AIH, fulminant liver failure and decompensated liver cirrhosis.

Adverse Effects of Immunosuppressive Therapy in Autoimmune Hepatitis (AIH)

Prednisone: Long-term use may lead to osteoporosis, aseptic bone necrosis, type 2 diabetes, cataracts, hypertension, increased susceptibility to infections, psychosis, Cushingoid facies, acne, and obesity. Consequently, prolonged corticosteroid therapy is generally minimized whenever possible.

Azathioprine: Potential adverse effects include cholestatic hepatitis, veno-occlusive disease, acute pancreatitis, severe gastrointestinal intolerance, rash, bone marrow suppression leading to cytopenias, and opportunistic infections. These risks are heightened in patients with thiopurine methyltransferase (TPMT) deficiency.

Key Points on Autoimmune Hepatitis (AIH)

- Autoimmune hepatitis is a more common chronic liver disease in women, with onset around the age of 40, mimicking acute hepatitis, less often than fulminant hepatitis.
- Clinical features - fatigue (asthenia) is a prominent symptom. Biochemically, marked elevations in transaminases that mimic acute hepatitis (tens of hundreds of times above the upper value of normal), as well as important increases in serum gamma globulins.
- Important serological markers are ANA (anti-nuclear antibodies) with a titer of over 1:40; anti SMA (anti-smooth muscle fiber); Anti-LKM1 (anti-liver kidney microsomal type 1); Anti-SLA/LP (anti-soluble liver-pancreas antigen). These markers are used to determine the AIH subtype.
- Histopathological examination is recommended for a positive diagnosis, the characteristic elements being interface hepatitis and rosette of hepatocytes.
- The treatment has two components: attack treatment (corticosteroid therapy: Prednisone 0.5-1mg/kg/day, until remission is achieved - normalization of transaminases – generally 4 weeks); after achieving remission, the dose of Prednisone is progressively

decreased, by 5 mg/week and then discontinued) and maintenance treatment (with azathioprine 2-3 mg/kg body weight, which is started at the same time with corticosteroid therapy, and maintained for a long time at the same dose, generally for years).

- Relapse after treatment discontinuation necessitates resuming therapy. Most patients require long-term or lifelong treatment, with only a small proportion maintaining remission without therapy. For those with insufficient response or intolerance to azathioprine, mycophenolate mofetil or tacrolimus may be employed as second-line agents.

- Liver transplantation remains the only therapeutic option in cases of treatment-refractory AIH, fulminant liver failure, or decompensated cirrhosis.

20. STEATOTIC LIVER DISEASE ASSOCIATED WITH METABOLIC DYSFUNCTION (MASLD)

Definition and general considerations

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a clinical and pathological entity characterized by excessive accumulation of lipids in hepatocytes, in the absence of significant ethanol consumption. This name was adopted in 2023 by the main international hepatology societies, to more accurately reflect the correlation between metabolic dysfunction and liver pathology, ending the stigma associated with the previous terminology, NAFLD (Non-Alcoholic Fatty Liver Disease).

MASLD includes a wide spectrum of clinical-pathological manifestations, from simple hepatic steatosis, characterized by the accumulation of lipids without significant inflammation, to metabolic steatohepatitis (MASH - Metabolic Associated Steatohepatitis), which can progress to liver fibrosis, cirrhosis and, in advanced stages, hepatocellular carcinoma (HCC). The condition is closely associated with metabolic syndrome, central obesity and type 2 diabetes, and its prevalence is increasing exponentially, in correlation with global changes in lifestyle and diet.

The Importance of Redefining MASLD

The adoption of the term MASLD is a fundamental change in the understanding of this condition, allowing for a more proper diagnostic and therapeutic approach. It explicitly recognizes the role of insulin resistance, chronic systemic inflammation and dyslipidemia in the pathogenesis of the disease. The redefinition has significant implications in clinical practice, facilitating the identification of patients at high risk and promoting personalized therapeutic strategies.

Etiological factors

The pathogenesis of MASLD is complex and multifactorial, resulting from the interaction between genetic, metabolic, inflammatory and environmental factors. The condition can be considered a liver marker of metabolic syndrome, being influenced by multiple physiological and biochemical disturbances.

a) Obesity and adipose dysfunction. Obesity is the most important predisposing factor of MASLD. According to WHO data, the prevalence of obesity has increased dramatically in recent decades, affecting more than 800 million people. Visceral obesity, defined by the excessive accumulation of adipose tissue around internal organs, is particularly relevant to the progression of MASLD, as it favors increased lipolysis, the release of free fatty acids, and the production of proinflammatory cytokines such as TNF-α and IL-6, contributing to liver lipotoxicity.

In addition, adipokine imbalance (decreased adiponectin and increased leptin) contributes to chronic low-grade inflammation and liver fibrogenesis. These mechanisms explain why obese patients are at increased risk of progression from simple hepatic steatosis to advanced fibrosis and cirrhosis.

b) Type 2 diabetes and insulin resistance. Type 2 diabetes is a major determinant of MASLD severity, being associated with a significantly increased risk of liver fibrosis. The prevalence of diabetes is constantly rising, estimated to exceed 1.3 billion cases by 2050. Chronic hyperglycemia and hyperinsulinemia favor oxidative stress, induction of pro-fibrotic enzymes, and accumulation of toxic lipid intermediates in hepatocytes, contributing to mitochondrial dysfunction and hepatocyte cell death.

c) Dyslipidemia and metabolic disorders. Atherogenic dyslipidemia, characterized by hypertriglyceridemia, a decrease in HDL-cholesterol and an increase in small and dense LDL particles, accelerates the intrahepatic accumulation of lipids and promotes liver inflammation. Dysfunction of nuclear receptors, such as PPAR-α and FXR, plays an essential role in these lipid disruptions, easing progression to steatohepatitis and fibrosis.

d) Genetic and epigenetic factors. Genetic studies have identified PNPLA3 variants I148M, TM6SF2 and MBOAT7 as susceptibility factors for MASLD. These genes influence hepatic lipid homeostasis and fibrogenesis processes. Furthermore, epigenetic factors, including DNA methylation and post-translational histone changes, contribute to the regulation of gene expression involved in the development of the disease.

Pathogenetic mechanisms

The pathogenesis of MASLD is the result of a complex interaction between metabolic, inflammatory, immunological and genetic factors. It involves multiple interconnected pathophysiological pathways, which lead to hepatic lipid accumulation, chronic inflammation, fibrogenesis and, in advanced cases, liver failure and carcinogenesis.

Excessive lipid accumulation in hepatocytes is a central element of MASLD, affecting hepatic lipid homeostasis through several mechanisms. Hyperinsulinemia and excessive consumption of refined carbohydrates stimulate de novo lipogenesis, thus favoring hepatic fatty acid synthesis. In parallel, dysfunctional adipocytes release increased amounts of free fatty acids into the circulation, which are taken up by hepatocytes, thus contributing to the metabolic overload of the liver.

Insulin resistance plays a key role in the initiation and progression of MASLD, disrupting liver metabolic balance. This causes compensatory hyperinsulinemia, which stimulates hepatic lipogenesis but inhibits fatty acid oxidation, worsening intrahepatic lipid accumulation.

Hepatocytes exposed to an excessive lipid load develop accentuated *oxidative stress*, which leads to the generation of reactive oxygen species (ROS) in large quantities. This process causes the peroxidation of membrane lipids, triggering cell death and activation of inflammatory pathways.

Chronic inflammation plays a decisive role in the transformation of MASLD into MASH. Kupffer cells, the resident macrophages of the liver, are activated by toxic lipid metabolites and reactive oxygen species, which causes the release of proinflammatory cytokines such as TNF-α, IL-1β and IL-6, contributing to the maintenance of a persistent inflammatory environment, which causes the activation of fibrogenesis and damage to the liver architecture.

The gut microbiome plays a crucial role in the pathogenesis of MASLD and altering its composition favors disease progression. Increased production of bacterial lipopolysaccharides (LPS) causes a liver inflammatory response. Decreased production of beneficial microbiome metabolites, such as short-chain fatty acids, contributes to the maintenance of systemic inflammation, worsening liver damage.

In the advanced stages of MASLD, persistent inflammation causes *the activation of hepatic stellate cells,* which pass into a myofibroblastic state and begin to produce excessive collagen and other components of the extracellular matrix stimulating progressive fibrotic deposition, which reshapes the liver architecture. In the long term, these processes lead to the loss of elasticity of liver tissue, contributing to the development of portal hypertension and the onset of liver failure.

A subset of patients with MASLD develop hepatocellular carcinoma (HCC), even in the absence of cirrhosis, suggesting that *oncogenic processes are activated early* in the course of the disease. Genomic instability induced by oxidative stress favors the accumulation of oncogenic mutations.

Pathology

MASLD histopathology provides essential information for staging the disease, identifying progression factors, and differentiating from other liver conditions. The histological course of MASLD ranges from simple hepatic steatosis to metabolic steatohepatitis (MASH), advanced fibrosis, and cirrhosis.

Hepatic steatosis - is the excessive accumulation of triglycerides in hepatocytes and constitutes the first stage of MASLD. Histologically, it is characterized by the presence of lipid vacuoles in the cytoplasm of hepatocytes, predominantly of the macrovesicular type, which cause the nucleus to move to the periphery of the cell. Steatosis can affect distinct areas of the hepatic lobe, initially predominant in the centrolobular area (Rappaport's zone 3), and in advanced stages it can become diffuse.

Metabolic steatohepatitis (MASH)

In more advanced stages, hepatic steatosis can progress to metabolic steatohepatitis, characterized by a combination of steatosis, hepatocyte ballooning, and lobular inflammation (Fig. 20.1). Hepatocyte ballooning is a distinctive histological sign of severe hepatocytic involvement. This is often accompanied by the formation of Mallory-Denk bodies. Lobular inflammation is of variable intensity and consists predominantly of macrophage and lymphocyte infiltrates.

Liver fibrosis. As the inflammatory process becomes chronic, the activation of hepatic stellate cells causes the deposition of collagen and other components of the extracellular matrix, which leads to the development of fibrosis. Initially, fibrosis is perisinusoidal, found around hepatocytes and in the Disse space. With the progression of the disease, fibrosis advances to enlarged fibrotic septa that disrupt the hepatic architecture, culminating in the formation of regenerative nodules and the development of cirrhosis.

Cirrhosis of the liver. Cirrhosis is the final stage of MASLD, characterized by the loss of normal hepatic architecture, the presence of regenerative nodules separated by thick fibrous septa, and the onset of severe liver dysfunction. This stage is associated with an increased risk of complications, including portal hypertension, liver failure, and hepatocellular carcinoma.

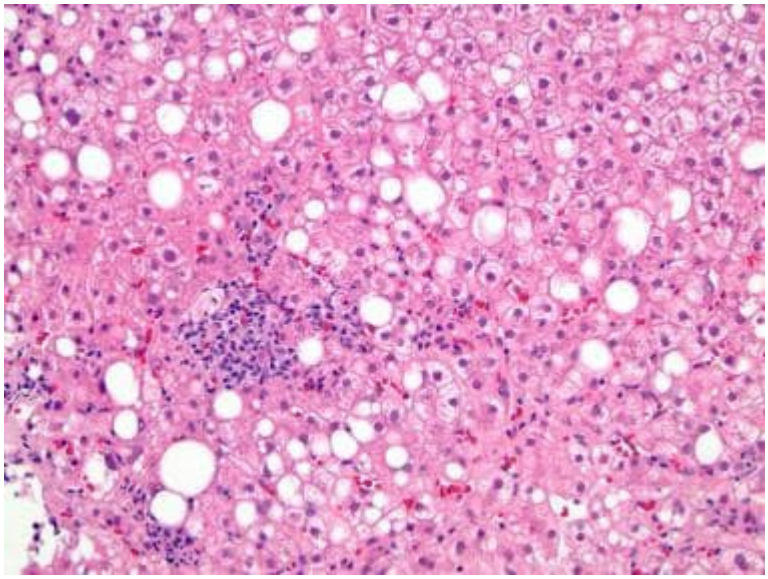


Fig 20.1. Steatohepatitis associated with metabolic dysfunction (MASH), stained with hematoxylin and eosin (H&E). Macrovesicular steatosis, characterized by hepatocytes loaded with large lipid vacuoles, ballooning of hepatocytes, a sign of advanced cellular dysfunction, and lobular inflammation, with inflammatory infiltrate consisting predominantly of lymphocytes and neutrophils, is seen.

Diagnosis

1. Diagnostic criteria for MASLD include the presence of hepatic steatosis shown by imaging or histological examination, along with at least one metabolic criterion:

- Body mass index (BMI) ≥30 kg/m² or increased waist circumference.
- Type 2 diabetes.
- Dyslipidemia (triglycerides ≥150 mg/dL and/or low HDL cholesterol).
- Hypertension.
- Insulin resistance.

In addition, it is recommended to use clinical algorithms for fibrosis risk stratification, such as FIB-4 and NAFLD Fibrosis Score (NFS), to identify patients who require further investigation.

- FIB-4 (Fibrosis-4 Index) is a score calculated based on the patient's age, AST, ALT, and platelet count, used to estimate the presence of advanced liver fibrosis. A low score indicates a low risk of fibrosis, while a high score suggests the presence of significant fibrosis.
- The NAFLD Fibrosis Score (NFS) includes additional factors, such as BMI, diabetes, and albumin levels, providing a more detailed estimate of the risk of liver disease progression.

2. MASH diagnosis

MASH represents the progressive form of MASLD and involves inflammatory and hepatocytic injury processes. The diagnosis is based on:

- Confirmation of hepatic steatosis (by imaging techniques or biopsy).
- Highlighting hepatocyte balooning and lobular inflammation (by histological analysis).
- Exclusion of other causes of chronic hepatitis.

A suggestive biochemical indicator is the persistent increase in transaminases (ALT, AST), although this change is not always present. Patients with MASH are also at significantly higher risk of progression to advanced liver fibrosis, cirrhosis, and its associated complications, including portal hypertension and hepatocellular carcinoma.

Paraclinical investigations

a) Imaging investigations are essential for diagnosing and stratifying the risk of patients with MASLD/MASH. The most used techniques include:

- *Liver ultrasound*: an affordable method, useful in detecting moderate-severe steatosis. The ultrasound appearance of hepatic steatosis is hyperechoic liver (whiter, brighter), with acoustic attenuation and difference in echogeneity compared to the cortical of the right kidney (which appears blacker, more hypoechoic, compared to the steatotic liver) (Fig. 20.2).

- *Impulse elastography* (FibroScan + CAP): evaluation of liver rigidity and quantification of steatosis for the staging of fibrosis and steatosis.
- *MRI-PDFF* (Proton Density Fat Fraction): advanced method for accurately quantifying liver lipid load.
- *Computed tomography (CT) and magnetic resonance imaging (MRI):* used for the advanced evaluation of patients with suspected hepatocarcinoma occurring as a complication of advanced fibrosis/cirrhosis.

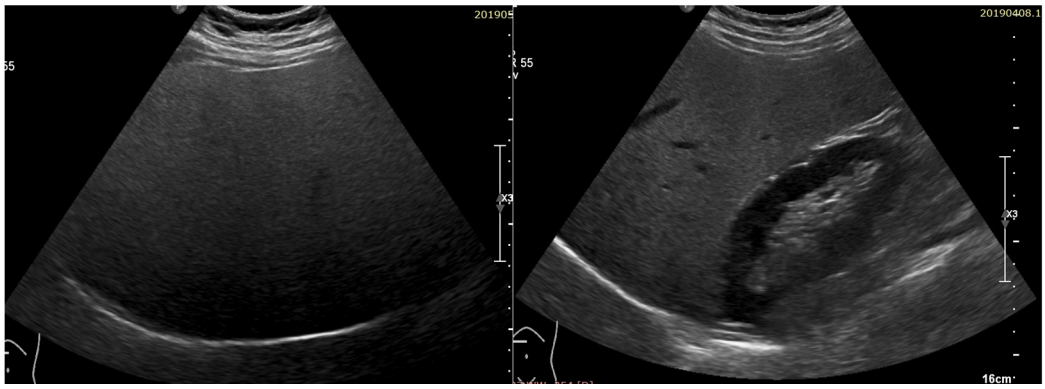


Figure 20.2. Hepatic steatosis detected by abdominal ultrasound. Hyperechoic liver with posterior ultrasound attenuation (left) and elevated hepatorenal index (right).

b) Laboratory tests. Biochemical tests provide indirect information about liver status, but they are not always sensitive or specific enough for diagnosis:

- Hepatic transaminases (ALT, AST): may be normal or slightly increased.
- GGT and alkaline phosphatase: may present moderately elevated values.
- Serological scores for fibrosis: FIB-4, NAFLD Fibrosis Score (NFS), Enhanced Liver Fibrosis (ELF) test.

c) Liver biopsy is still *the gold standard* for the diagnosis of MASH and the staging of fibrosis. Indications for liver biopsy include:

- Suspicion of rapidly progressing MASH.
- Discrepancies between imaging and biochemical tests.
- Evaluation of patients with risk factors for advanced fibrosis.

Differential diagnosis

The differential diagnosis must take into account other causes of liver damage, including: alcoholic steatosis (history of significant alcohol consumption), Viral hepatitis (HBV, HCV – presence of specific markers), primary biliary cholangitis (significant cholestasis, AMA positive), hemochromatosis (ferritin, increased transferrin saturation), Wilson's disease (low ceruloplasmin), alpha1 antitrypsin deficiency; drug toxicity (amiodarone, methotrexate, corticosteroids), celiac disease and other autoimmune liver diseases.

Treatment and management

1. Lifestyle modification

The management of MASLD and MASH is primarily based on lifestyle interventions, with the main goal of improving metabolic dysfunction and preventing the progression of liver fibrosis. Key interventions include:

- *Weight loss* – Clinical studies have shown that reducing body weight by a minimum of 7-10% is associated with a significant improvement in steatosis, inflammation, and liver fibrosis. Weight loss should be achieved through a combination of calorie restriction and sustained physical activity.
- *Nutritional interventions* - The adoption of a Mediterranean diet, characterized by increased intake of monounsaturated and polyunsaturated fatty acids, dietary fibers and vegetable proteins, contributes to the improvement of the metabolic profile and the reduction of hepatic oxidative stress. Avoiding refined carbohydrates and trans fats is essential.
- *Regular physical activity* - Aerobic exercise and resistance training are associated with a reduction in fatty liver disease and improved insulin sensitivity. At least 150-300 minutes of moderate physical activity per week is recommended.

2. Pharmacological treatment

Currently, there is no approved pharmacological treatment specific to MASLD/MASH, but many molecules are in various stages of clinical investigation. Classes of drugs with therapeutic potential include:

- *GLP-1 receptor agonists (e.g. semaglutide, liraglutide):* These molecules have proven beneficial effects on body mass and glucose homeostasis, being associated with the reduction of steatosis and liver inflammation.
- *Sodium-glucose cotransporter type 2 (SGLT2-i) inhibitors:* These drugs, used in the treatment of type 2 diabetes, may improve liver metabolism and reduce cardiovascular risk.
- *Pioglitazone*: Especially indicated in patients with type 2 diabetes and MASH, this agent improves insulin sensitivity and reduces liver inflammation. However, its use should be carefully monitored due to the risk of weight gain and peripheral edema.
- *Vitamin E:* Its administration has been associated with improving liver histology in non-diabetic patients with MASH, due to its antioxidant effects. However, caution is advised in its long-term use, given the potential cardiovascular risks.

3. Comorbidity management

Given the strong correlation between MASLD/MASH and metabolic syndrome, control of comorbidities is essential for improving patients' prognosis:

- *Type 2 diabetes:* Rigorous glycemic management, using liver-safe pharmacological therapies (e.g. GLP-1 agonists, SGLT2 inhibitors), is crucial for preventing the progression of liver fibrosis.
- *Dyslipidemia:* Statins are considered safe and effective in the treatment of patients with MASLD and MASH, having a beneficial effect on lipid profile and cardiovascular risk. It is accepted that if the eventual cytolysis caused by the administration of statins does not cause an increase in transaminase values of more than 3 times the value above normal, the treatment can be continued due to their favorable effect, both on cardio-vascular and hepatic protection by decreasing cholesterol values.
- *High blood pressure:* Proper monitoring and treatment of high blood pressure helps prevent cardiovascular and liver complications.

4. Indications for liver transplantation

In advanced stages of liver disease, in the presence of decompensated cirrhosis or secondary MASH hepatocarcinoma, liver transplantation remains the only therapeutic option with curative potential. Criteria for inclusion on the liver transplant list include increased Model for End-Stage Liver Disease (MELD) score, signs of severe portal hypertension, liver decompensation with refractory ascites, hepatic encephalopathy or recurrent variceal hemorrhage, Hepatocarcinoma within the limits of the Milan criteria for transplantation.

Close monitoring of these patients and early referral to transplant centers are essential to maximize survival and optimize post-transplant outcomes.

Prognosis and evolution

The natural course of MASLD and MASH varies significantly depending on metabolic, genetic, and behavioral factors. While a significant proportion of patients with MASLD remain in the early stages, an important subset develops MASH, with an increased risk of progression to advanced fibrosis, cirrhosis, and severe liver complications.

Prognostic factors

The prognosis of patients with MASLD and MASH is influenced by the following factors:

- Severity of liver fibrosis - It is the most important determinant of liver mortality. Patients with advanced fibrosis (F3-F4) are at significantly higher risk of decompensated cirrhosis and hepatocarcinoma.
- The presence of type 2 diabetes - Increases the risk of liver disease progression and cardiovascular complications.
- Body mass index (BMI) – Obese patients have a faster progression to advanced stages of liver disease.

• Genetic factors – Genetic variants such as PNPLA3, TM6SF2, and HSD17B13 influence individual susceptibility to fibrosis progression and risk of hepatocellular carcinoma.

• Lifestyle and adherence to treatment - Adopting a healthy diet and maintaining an optimal weight are essential factors in preventing the progression of the disease.

Evolution of the disease

MASLD can remain stable for a long time, but about 20-30% of patients will develop MASH. Of these, about 30-40% progress to significant fibrosis, and a subset of patients may develop.

• *Liver cirrhosis* - The final stage of liver fibrosis, associated with decompensation (ascites, variceal hemorrhage, hepatic encephalopathy) and liver failure.

• *Hepatocellular carcinoma (HCC):* The risk of HCC is significantly higher in patients with MASH and advanced fibrosis. Periodic screening is recommended in patients with compensated cirrhosis.

• *Cardiovascular complications:* Patients with MASLD are at increased risk of cardiovascular events, which is the leading cause of mortality in this population.

To note:

- MASLD is a clinical and pathological entity characterized by excessive accumulation of lipids in hepatocytes in the absence of significant ethanol consumption.
- MASLD includes a wide spectrum of clinical-pathological manifestations, from simple hepatic steatosis (accumulation of lipids without significant inflammation) to MASH (with associated inflammation), which can evolve to fibrosis, cirrhosis, liver failure, hepatocellular carcinoma.
- Diagnostic criteria for MASLD include the presence of hepatic steatosis shown by imaging or histological examination, along with at least one metabolic syndrome criterion: BMI ≥30 kg/m^2 or increased waist circumference, type 2 diabetes, dyslipidemia, hypertension, insulin resistance.
- The management of MASLD and MASH is based on the control of the determinants (obesity, diabetes, dyslipidemia) through lifestyle changes and specific medication.
- Weight loss (achieved through diet and exercise) with at least 7-10% of the initial weight leads to the improvement of steatosis and finally fibrosis.

21. ALCOHOL INDUCED LIVER DISEASE

Definition

Alcohol-associated liver disease (ALD) defines the spectrum of alcohol-related disorders, which clinically ranges from asymptomatic hepatomegaly to severe liver failure, and histopathologically from changes specific to simple steatosis (SA), alcohol-related steatohepatitis (ASH), progressive alcohol-associated fibrosis (ALD Fibrosis), alcoholic liver cirrhosis (ALD cirrhosis), alcoholic (acute) hepatitis (AH) and up to hepatocellular carcinoma.

Epidemiology

The prevalence of alcoholic liver varies greatly depending on the country, being influenced by specific traditions, religious life and lately, especially by the ratio between the price of alcoholic beverages and the income of the population. Although alcohol consumption is higher in countries with higher economic levels, the impact on liver disease is more pronounced in countries with low socioeconomic status. In Romania, the country with the highest death rate from liver disease in Europe, most deaths are correlated with ~~BHA~~ ALD.

According to the WHO (World Health Organization), excessive alcohol consumption causes more than 3 million deaths annually worldwide, about 6% of all deaths. Alcohol is incriminated in over 200 diseases, the first 3 causes of mortality being cardiovascular diseases, gastroenterological diseases (mainly liver cirrhosis) and cancers (liver, pancreas, esophagus, breast, etc.). In Europe, 41% of deaths from liver disease are due to ALD, and Romania has the highest rate of death from liver disease in Europe, with most deaths being correlated with ALD.

Etiology

The threshold from which alcohol becomes harmful and involved in the occurrence of liver disease is not clearly defined. The dose considered to have no harmful effects is 2 servings (standard doses of 10 g of pure alcohol) of alcohol per day for women and 3 servings for men. According to the WHO, a standard dose of about 10 g of pure alcohol is contained in 100 ml of wine, 250 ml of beer, 40 ml of strength (Fig.21.1). Some studies define the standard unit as 20 gr of pure alcohol, other authors consider that a dose of 12 g/day is already critical for damage to the body.

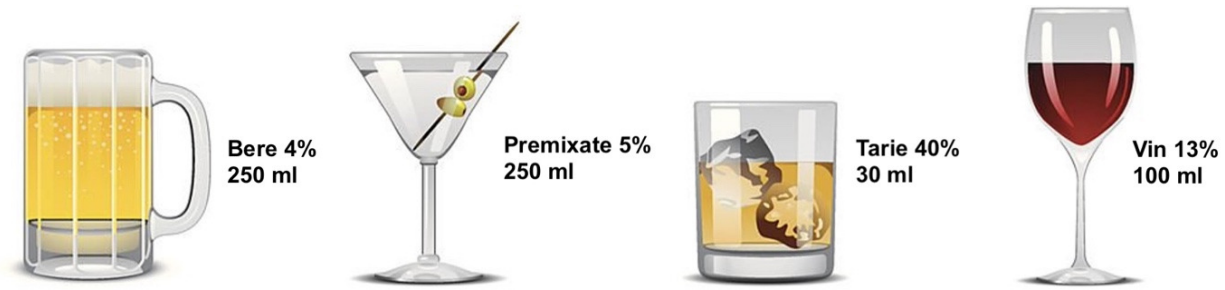


Figure 21.1. Definition of Standard Alcohol Unit

The most used score for assessing alcohol consumption is the AUDIT (Alcohol use disorder inventory test) score, which can also be used as a screening method. The AUDIT score includes 10 questions (3 questions in the case of the abbreviated AUDIT-C score) that assess the extent of alcohol consumption, addiction and problems associated with alcohol consumption. An AUDIT score above 8 suggests harmful drinking, and a score above 20 points indicates a moderate or severe drinking disorder.

Pathophysiology

The pathogenesis of ALD is complex. The metabolism of alcohol in the liver is done in three ways, the result being the same, acetaldehyde – a metabolite with high hepatotoxicity. The three pathways of metabolism are:

1. The alcohol-dehydrogenase (ADH) pathway, the major pathway of alcohol metabolism.

2. Oxidative stress and the MEOS system (microsomal oxidative system) – cytochrome P450 intervenes in the oxidation of alcohol when the blood concentration rises above 50 mg/dl.

3. The catalase pathway, which has a secondary role.

Acetaldehyde is subsequently oxidized to acetate, but in alcoholics the ability of mitochondria to oxidize acetaldehyde with its accumulation is gradually reduced, leading to the promotion of lipid peroxidation and the formation of protein complexes.

In addition to the toxic effects of acetaldehyde, the cyrogenic role of alcohol per se should not be forgotten either. It has been shown that Ito cells (pericytes located in the perisinusoidal space – the Disse space) involved in fibrogenesis are activated after chronic alcohol consumption.

Alcohol affects the liver through two mechanisms: directly on hepatocytes through intracellular fat accumulation and subsequent hepatocyte destruction, and by indirect mechanism through action on enterocytes. Alcohol leads to increased intestinal permeability, disruption of the microbiota, dysbiosis, endotoxinaemia, all transmitted via the portal vein to the liver, where the activation of a local inflammatory response will lead to apoptosis and hepatocytic necrosis.

There are a number of ***risk factors for liver damage*** in case of excessive alcohol consumption:

- *Duration and type of alcohol consumption*: the dose of alcohol of more than 3 standard units per day for men and more than 2 standard units per day for women, over 30 gr/day and respectively, over 20 grams per day, i.e. 60 g of absolute alcohol/day for men and 40 g/day for women, is considered toxic. The duration of consumption is also important. To be at risk of ALD, the duration of binge drinking must be longer than 5 years. Continuous consumption is more dangerous than intermittent consumption. Also, liver injury does not depend on the type of drink, but on its alcohol content.

- *Sex* - women are much more susceptible than men, because, at the same amount of alcohol ingested, higher blood concentrations are reached in women, gastric metabolism being lower and cytochrome P450 being less efficient in women.

- *Nutritional factor* - obesity or malnutrition increase susceptibility to ALD.

- *Environmental factors* – smoking, hepatotoxic drugs increase susceptibility to ALD.

- *Genetic factors* - the most involved and studied gene is PNPLA3.

- *Hepatic comorbidities*: co-infection with hepatitis viruses (B or C), presence of fatty liver associated with metabolic dysfunction, autoimmune or cholestatic liver diseases.

Pathology

There are three forms of histological liver damage in alcohol users that are also major histological stages:

1. Alcoholic fatty liver is a benign, reversible form produced by the accumulation of large droplets of lipids in hepatocytes.

2. Alcoholic hepatitis includes vacuolizing degeneration and hepatocyte necrosis, acute neutrophilic infiltrates, sometimes pericellular, perisinusoidal and perivenular fibrosis, as well as characteristic Mallory bodies (alcoholic hyaline).

3. Alcoholic cirrhosis involves the presence of extensive liver fibrosis, from the portal spaces to the centrolobular veins, as well as the presence of regeneration nodules.

Ballooned hepatocytes (affected by vacuolizing degeneration) include macrovesicular steatosis (rarely microvesicular), have granular cytoplasm with dispersed microparticles that give the impression of a veil. The nucleus is small in size and is hyperchrome.

Hepatocytes containing Mallory bodies are usually surrounded by polymorphonuclear and other inflammatory cells, indicating that they are either the target of the cell destruction process, or possess chemotactic properties or are involved in the secretion of cytokines (TNF-alpha).

Severe forms of cholestasis can occur in SHA and CHA. Although central fibrosis is predominant, portal fibrosis is not excluded. Fibrosis of the hepatic veins

(phlebosclerosis) and perivenular fibrosis can also be observed, which are known as sclerosing hyaline necrosis. Fibrosis expands septally during evolution, generating the premises of cirrhosis, which is frequently micronodular, or less rarely mixed.

In acute alcoholic hepatitis (AH), the presence of bloating, Mallory bodies, neutrophil inflammation, cholestasis and fibrosis are poor prognostic factors. Ductal reaction and cholestasis indicate infection. Positive predictors for corticosteroid response in AH are lobular neutrophyte, reduced steatosis, and ductular reaction.

Advanced fibrosis is an independent indicator of the risk of long-term complications in ALD.

Clinical picture

In clinical practice, the diagnosis pursues two objectives: the diagnosis/screening of alcohol consumption through specific tests or questionnaires (AUDIT) and the diagnosis and evaluation of the severity of liver damage.

In the face of a patient with chronic and excessive alcohol consumption, with or without clinical manifestations, we are obliged to perform the screening and diagnosis of a possible ALD by non-invasive and/or invasive clinical and paraclinical methods. Being a pathology often superimposed on other liver diseases, it is always necessary to make a differential diagnosis with viral hepatitis, autoimmune hepatitis, cholestatic liver diseases, hematochromatosis and hepatic steatosis associated with metabolic dysfunction.

Clinically, the following *signs and symptoms* may occur:

- Cutaneous: vascular stellates, palmar erythema, Dupuytren's contracture
- Musculoskeletal: cachexia due to loss of muscle mass (in advanced forms of the disease)
- Abdominals: hepatomegaly, ascites, vascular stars, abdominal pain
- Sexual: gynecomastia, testicular atrophy, amenorrhea
- Neurological: withdrawal syndrome (tremor, agitation, tachycardia, vomiting, hallucinations), Wernicke's encephalopathy.

Another complication of alcoholic fatty liver is Zieve syndrome, which consists of jaundice and abdominal pain accompanied by hyperlipemia, hemolytic anemia.

Paraclinical Board

Biologically, direct and indirect ***markers of alcohol consumption*** are present. Direct, specific markers are urinary ethyl-glucuroride (EtG), alcoholuria, aloolemia. Indirect markers are the most used in clinical practice, being represented by AST, ALT, GGTP, AP, CDT (carbohydrate-deficient transferrin), hematological changes (macrocytic anemia or thrombocytopenia from cirrhosis).

The following biological changes ***can be observed in ALD*:**

- GGT increased to 3-5 times normal, or even much more in recent heavy alcohol consumption (where values are tens, hundreds of times higher than the upper limit of normal). The dynamic evolution of GGT is suggestive for the alcoholic etiology of its increased values: high values at hospitalization that decrease rapidly, at half of the initial value after 2 weeks and at normal values after 5 weeks after stopping alcohol consumption, in the absence of a resolved biliary obstruction, are diagnoses for alcohol abuse.

- AST and ALT increased 2-6 times, usually no more than 300-400 IU/L. The AST/ALT ratio, known as the Rittis ratio, >1 is suggestive of alcoholic hepatitis.

- AP can be increased in advanced cases of ALD - cirrhosis of the liver with cholestasis.

- CDT - has the ability to identify only high alcohol consumption (minimum 50-80 g/day at least 1-2 weeks)

- Hematological changes: macrocytosis, anemia, thrombocytopenia - in advanced forms, leukocytosis - in HA.

Non-invasive tests for the diagnosis of BHA

The severity of fibrosis can be assessed by patented biological methods (FibroTest, ELF – Enhanced Liver Fibrosis score, Fibrometer) and non-patented tests, easy to implement in daily practice (APRI score, FIB-4 score). Also, liver stiffness is considered to be a faithful marker of fibrosis severity, especially for moderate, severe fibrosis and cirrhosis (F2, F3, F4). Liver stiffness (RH) can be assessed by imaging methods, the most commonly used being elastographic methods – such as impulse elastography (FibroScan) or point or two-dimensional elastography. It is recommended that the assessment of RH in patients with alcohol consumption be done after a period of abstinence of at least 2 weeks (active consumption leads to liver inflammation, increased AST and the possibility of falsely increased values). The stage of fibrosis can also be estimated by MRI elastography, considered to be the most accurate method, but it is rarely used due to high costs and low availability.

The "gold-standard" method of diagnosing the severity of BHA is ***the liver biopsy***, both for the diagnosis of a liver disease and for determining its cause, but it remains a method that is less and less used due to the newly emerging non-invasive diagnostic techniques. The most common histopathological aspect is that of hepatic steatosis, where hepatocytes are observed that contain large, clear vacuoles, which push the nucleus of the cell towards the periphery. This aspect is characteristic *of macrovesicular steatosis*, i.e. the accumulation of fats (lipids) in liver cells (Fig.21.2).

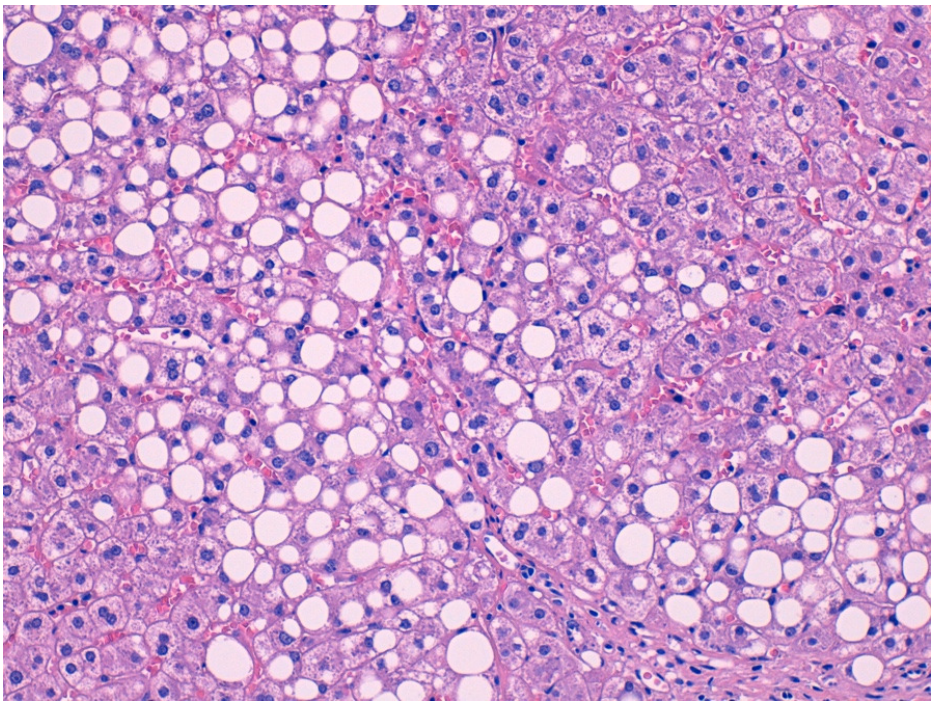


Figure 21.2. Histopathological image, hematoxylin and eosin staining. Hepatocytes are observed that contain large, clear vacuoles that push the cell nucleus towards the periphery and large clear vacuoles. The general structure of liver tissue is relatively preserved, with no obvious signs of necrosis or severe inflammation in this microscopic field. This aspect is characteristic of macrovesicular steatosis. Source: Department of Morphopathology, University of Medicine and Pharmacy "Victor Babeș" Timișoara

Positive diagnosis

The positive diagnosis in alcoholic liver starts from the documentation of alcohol consumption through the individual anamnesis, family anamnesis, but also by completing the tests related to alcohol consumption (AUDIT or AUDIT-C score). The clinical picture includes signs of alcohol consumption, hepatomegaly, possibly splenomegaly and signs of advanced liver disease (ascites, collateral circulation, etc.). The biological picture includes increases in transaminases, GT range with normal or almost normal alkaline phosphatase. To highlight alcohol-induced fatty liver disease, transabdominal ultrasound is an essential step. It is also important to assess the severity of liver damage by liver biopsy or non-invasive tests.

Differential diagnosis

The differential diagnosis must be made with all other causes of chronic liver disease, including chronic infections with hepatitis B, C and D viruses, hepatic steatosis associated with metabolic dysfunction, hemochromatosis, Wilson's disease, cholestatic liver diseases, autoimmune hepatitis.

Evolution and prognosis

The evolution and prognosis in ALD are favorable if alcohol consumption is stopped before the onset of severe lesions characteristic of liver cirrhosis. The degree of liver fibrosis is the one that gives the prognosis, especially in alcoholic (acute) hepatitis, if it occurs against the background of cirrhosis, especially decompensated, mortality exceeds 50%.

The complications are given by the progression of liver disease from steatosis to steato-hepatitis with evolution to fibrosis and cirrhosis of the liver, and its complications, all aggravated by the overlap of alcoholic (acute) hepatitis.

Treatment

Treatment primarily involves achieving and maintaining abstinence, as this is associated with improved clinical response at any stage of the disease.

The first step in achieving abstinence are psychosocial and behavioral interventions, later nutritional support, hepatoprotective agents such as silymirin and specific treatment of complications - decompensated liver cirrhosis or alcoholic hepatitis.

ALCOHOLIC (ACUTE) HEPATITIS

Alcoholic (acute) hepatitis (AH) ***is defined*** as a particularly severe clinical syndrome with high mortality, characterized by the recent onset of jaundice associated or not with other signs of liver decompensation (ascites, encephalopathy, etc.) in a person who consumes large amounts of alcohol.

The histopathological substrate is represented by steatohepatitis lesions characterized by steatosis, hepatocytic bloating, inflammatory infiltrate with polymorphonuclear, with or without fibrosis.

The diagnosis is mainly *clinical*, based on the recent onset of jaundice, frequently associated with fever (even in the absence of an infection), influenced general condition, anorexia, weight loss and malnutrition in a patient who consumes alcohol in toxic quantities >60 gr per day in men and >40 gr/day in women. The onset of jaundice and excessive alcohol consumption must be more recent than 8 weeks from the time of presentation.

The following biological changes *are added to the clinical picture*: total bilirubin above 3 mg/dl, increased transaminases (generally less than 300 IU/L) with the Rittis AST/ALT ratio > 1.5-2. In severe forms, hypoalbuminemia, prolongation of prothrombin time, thrombocytopenia occur.

Other causes of liver injury, such as biliary obstruction, primary biliary cholangitis, acute viral or drug hepatitis, autoimmune hepatitis, ischemic hepatitis, should be excluded by imaging and biological methods.

Liver biopsy puncture, although valuable, is not routinely recommended for diagnosis and prognostic evaluation, but only in clinical trials or when the diagnosis is uncertain. When indicated, transjugular biopsy is preferred due to the lower risk of bleeding.

The prognosis of AH is reserved and is given by the specific scores, presented in Table 21.I. A Maddrey score (MDF) ≥32, i.e. a severe form, is associated with a mortality of more than 50% at 30 days. The prognosis is also given by the lack of response to corticosteroid treatment appreciated by the Lille score. A Lille score ≥ 0.45 is predictive for a mortality of over 70% at 6 months. The prognosis is influenced by possible complications of the disease such as infections, hepato-renal syndrome, multiple organ failure, as well as complications given by treatment. Infections are very common in HA, being present at the time of diagnosis in up to 25% of patients, occurring in about 50% of cases during corticosteroid therapy.

Table 21.I. Prognostic scores in alcoholic (acute) hepatitis

Score	Parameters						Severe HA
	Bil	PT/INR	Creatinine	Age	White	Lion	
MADDREY DISCRIMINANT FUNCTION- MDF	+	+					≥32
MELD	+	+	+				>21
ABIC	+	+	+	+			>9
GAHS	+	+	+	+		+	>9
Model LILLE	+	+	+	+	+		≥ 0.45 non-responder to treatment

MDF-Maddrey Discriminant Function; MELD- model for end stage liver disease; ABIC- age, bilirubin, INR, creatinine; GAHS- Glasgow Alcoholic Hepatitis Score; PT/INR – prothrombin time/ international normalized ratio; AH- alcoholic hepatitis, Bil- bilirubin; ALB- albumin; Leukocytes

Treatment

1. General measures - permanent abstinence from alcohol is absolutely mandatory for all types of ALD.

2. Nutritional support. Caloric protein malnutrition is present in almost all patients and is associated with a poor prognosis, so proper nutrition is an integral part of HA treatment. A caloric intake of 35-40 Kcal/kgbody/day is recommended, the recommended protein intake being 1.2-1.5 g/kgbody/day. In case of digestive intolerance, parenteral nutrition can be tempted, but there are no data to confirm any benefit over the intake per bone, being also correlated with a higher rate of infections.

3. Corticosteroids are the treatment of choice for severe forms. They are indicated in severe AH treatment with MDF score > 32 and/or GAHS > 9. Prednisone, prednisolone 40 mg/day or methylprednisolone 32 mg/day are used. The response to corticosteroids at 7 days is assessed by the Lille score and, if the response is favorable (Lille score < 0.45) it is continued for up to 28 days, after which treatment is stopped abruptly or gradually over 3 weeks. If the Lille score is ≥ 0.45, corticosteroid therapy is stopped. The effect of corticosteroids in AH is controversial, they reduce short-term mortality by 28 days, but long-term survival is not influenced.

Before initiating corticosteroid therapy, as well as throughout the treatment, possible contraindications or complications will be evaluated: bacterial infections not controlled by medication, acute kidney injury, upper digestive hemorrhage, multiple organ dysfunction, concomitant diseases that can be aggravated – infections with HBV, HCV, HIV, TBC, etc.

4. Other therapies studied:

- combination with pentoxifylline that has not been shown to be beneficial
- N-acetylcysteine, through its antioxidant, pleiotropic and

minor adverse events, can be administered in AH.

- Granulocyte Stimulating Factor (GCSF)

5. Liver transplantation - is the only chance for patients who are not responsive to corticosteroid therapy. Traditionally, it takes a 6-month abstinence period for a patient to be considered eligible for liver transplantation, but patients who are not responsive to corticosteroid therapy have a poor prognosis and a mortality rate of over 70% at 6 months. It has been shown that patients in the first episode of HA who are not responsive to corticosteroid therapy have a significant improvement in survival if they are transplanted quickly.

To note:

- Alcohol abuse is one of the major causes of mortality and morbidity in the modern world.

- At the hepatic level, alcohol abuse leads to the appearance of hepatic steatosis, steato-hepatitis and finally with the development of liver fibrosis and cirrhosis and its complications.

- The dose of alcohol considered to have no harmful effects is 2 servings (standard doses of 10 g of pure alcohol) of alcohol per day for women and 3 servings for men. According to the WHO, a standard dose of 10 g of pure alcohol is contained in 100 ml of wine, 250 ml of beer, 40 ml of strength

- The positive diagnosis in the alcoholic liver starts from the documentation of alcohol consumption, continues with the clinical picture and the biological picture that includes increases in transaminases, of the GT range with normal or almost normal alkaline phosphatase.

- To highlight alcohol-induced fatty liver disease, transabdominal ultrasound is an essential step.

- It is also important to assess the severity of liver damage by liver biopsy or non-invasive tests.

- The treatment of alcohol-induced liver disease is primarily the definitive and complete cessation of alcohol consumption.

- Alcoholic hepatitis is a severe clinical syndrome with increased mortality, characterized by recent onset of jaundice associated or not with other signs of liver decompensation in a person who consumes large amounts of alcohol.

- The treatment of alcoholic hepatitis requires stopping alcohol consumption, and in severe forms, with a Maddrey score of over 32, corticosteroid therapy is the only medication that has proven its effectiveness.

- In patients who are not responsive to corticosteroid therapy, as assessed by the Lille score at 7 days after the start of treatment, mortality is 50% at 30 days.

22. CHOLESTATIC LIVER DISEASES BY AUTOIMMUNE MECHANISM

Cholestatic liver diseases by immunological mechanism include two entities: primary biliary cholangitis and primary sclerosing cholangitis, which have as a common element the presence of cholestasis syndrome (increase of GGTP and FAL) and the etiopathogenic autoimmune mechanism, but with different morphopathological substrate and prognostis.

PRIMARY BILIARY CHOLANGITIS

Definition

Primary biliary cholangitis (formerly called primary biliary cirrhosis – PBC) is a condition of unknown etiology, which evolves through chronic cholestasis, progressive destruction of the intrahepatic bile ducts and portal inflammation, leading, over time, to cirrhosis and liver failure. From a morphopathological point of view, the characteristic lesion is inflammation affecting the intrahepatic bile ducts - nonsuppurative destructive cholangitis. Walker first reported the association between PBC and antimitochondrial antibodies (AMAs), which subsequently became important diagnostic markers.

Due to the characteristic changes at the serological and histopathological level, PBC is considered a model of autoimmune disease. The name change – from "primary biliary cirrhosis" to "primary biliary cholangitis" – underlines the fact that cirrhosis is not mandatory at the time of diagnosis and helps reduce the stigma associated with this disease.

Epidemiology

PBC is prevalent in women (ratio between 6:1 and 9:1), mainly affecting people between 30 and 60 years of age, although it can occur between the ages of 15 and 90 years. A distinctive element is the family component: first-degree relatives have a much higher risk (up to 500 times) of developing the disease compared to the general population. The reported incidence in Europe varies between 1 and 2 cases per 100,000 inhabitants per year, and globally it falls between 0.7 and 4.9 cases per 100,000. Recently, an increase in prevalence has been observed in men, although the disease remains prevalent in women. However, men develop more severe forms and respond poorly to treatment with ursodeoxycholic acid (UDCA).

Pathophysiology

The causes of PBC remain unknown, however, research suggests that the disease develops through an interaction between genetic and environmental factors. Studies have identified more than 20 risk loci involved in immune system regulation, including T

cell differentiation and tumor necrosis factor signaling, and certain haplotypes – such as HLA DRW8, HLA DR3, and HLA DR4 – are frequently associated with PBC and other autoimmune diseases.

Triggers identify include: *Infections* (such as Epstein-Barr virus, Cytomegalovirus, urinary tract infections with Escherichia coli, parasites and fungi), *endocrine influences* (e.g., previous hormonal treatment, which may explain the higher prevalence in women), exposure to certain environmental factors (such as nail polish, smoking, toxic waste, and xenobiotics), and *Nutritional elements* that can influence the onset of the disease.

PBC is an autoimmune disease that involves both *cellular* and *humoral immunity* and is manifested by inflammation and destruction of the intrahepatic bile ducts (ductopenia). The main mechanisms include an autoimmune response with anti-mitochondrial antibodies and T lymphocytes ($CD4^+$ and $CD8^+$), amplified by cytokines (TNF, IL-12, interferons), apoptosis dysfunctions, and molecular mimicking mechanisms. PBC is often associated with other autoimmune diseases, such as Sjögren's syndrome, scleroderma, autoimmune thyroiditis, and Reynaud's syndrome.

Pathology

Macroscopically, in the early stages, the liver grows slowly in size and has a greenish-yellow tint with a flat, smooth surface. As the disease progresses, nodular changes characteristic of cirrhosis appear.

Microscopically, the characteristic lesions are ***chronic destructive inflammation*** of the small bile ducts, causing ***ductopenia*** and the formation of a ***granulomatous cell infiltrate***, composed of lymphocytes, eosinophils, histiocytes and plasmocytes. The evolution of the disease goes through histopathological stages, from a ductal phase inflammation (Stage I) to the appearance of macronodular cirrhosis (Stage IV) (Table 22.I).

Table 22.I Histopathological Stages in PBC

Stage	Description
Stage I (Portal, Ductal Phase)	Inflammation in the small ducts (less than 80–100 microns), destruction of the epithelium and rupture of the basement membrane, with possible granulomas.
Stage II (Periportal, Ductular Phase)	Continuation of canalicular destruction, severe ductopenia (over 50% of interlobular ducts) and diffuse portal fibrosis with persistent cholestasis, granulomas being present.
Stage III (Septal, Advanced Fibrosis)	Extensive portal fibrosis, severe ductopenia, copper accumulations, cholestasis, and progressive hepatocellular necrosis.
Stage IV (Cirrhosis)	The appearance of macronodular cirrhosis, the absence of bile ducts – a diagnostic element of PBC, severe cholestasis and reduced inflammation.

Clinical picture

PBC evolves slowly and insidiously, and in *the early stages patients* are usually *asymptomatic*. The literature indicates that antimitochondrial antibodies (AMAs) are present in approximately 90–95% of patients, which allows early identification of the disease through screening programs, even before alkaline phosphatase, gamma-glutamyltranspeptidase and bilirubin levels increase significantly.

The classic patient model is a middle-aged woman (between 40 and 60 years old) who complains of *severe asthenia and intense pruritus*, symptoms that can appear months or years before the onset of jaundice. On examination, hepatomegaly, splenomegaly, scratch lesions, melanic pigmentation, as well as changes in the skin such as xanthelasmas can be observed.

In the advanced stages, serious complications such as portal hypertension, ascites, digestive hemorrhages and encephalopathy develop. *Other manifestations* include deficiencies of fat-soluble vitamins (A, D, E, K), bone pain, and clotting disorders. PBC is also commonly associated with *other autoimmune conditions* (such as rheumatoid arthritis and autoimmune thyroiditis) and increases the risk of malignancies, including hepatocarcinoma and breast cancer in women.

Biological picture

Serum enzyme markers the most important are cholestasis enzymes, ***alkaline phosphatase*** *and* ***GGT***, which can be easily increased from the initial stages and become more pronounced as the disease progresses. There are also increases in the *serum bilirubin* (in particular the *Conjugated*) and *bile acids*, in particular *of cholic acid*.

Serum lipids (such as cholesterol, phospholipids, LDL, and VLDL) values increase as well, and HDL, initially normal or elevated, decreases at the stage of cirrhosis. *Transaminases (TGO and TGP)* may be normal or moderately elevated (up to 3× normal values), and larger increases may suggest an overlap syndrome with autoimmune hepatitis. Albumin levels decrease, and prothrombin time is prolonged in advanced stages.

Other analyses. The blood count can remain normal until the late stages of the disease, and the erythrocyte sedimentation rate is increased. Tests for associated diseases (anti-gliadin, anti-endomysium antibodies) are useful for identifying celiac disease, and copper and ceruloplasmin levels are moderate, usually twice the normal value. About 20% of patients have hypothyroidism, and TSH changes require ultrasound examination of the thyroid.

Immunoglobulins and autoantibodies are important for a positive diagnosis. *Hypergammaglobulinemia,* due to increased *IgM*, is common. ***Antimitochondrial antibodies (AMAs)*** are positive at a titer above 1:40 and are the most characteristic marker for PBC. About 5% of patients may be AMA-negative, in which cases re-examination by methods such as immunoblot or ELISA is recommended, and liver biopsy

is recommended. Markers for other autoimmune diseases such as rheumatoid factor (positive in 70% of cases), anti-smooth muscle antibodies (in 66% of cases), *anti-nuclear antibodies* (positive in 50% of cases, especially *anti-gp210 and/or anti-Sp100 fragments*) and anti-thyroid antibodies (positive in 41% of cases) may also be present.

Paraclinic

Imaging investigations of the liver and bile ducts are essential in cases of cholestasis.

- *Ultrasound* is the first-line imaging technique due to its accessibility and non-invasive, non-irradiating character, having a very good performance for differentiating between obstructive jaundice (in which intrahepatic bile duct dilations - IHBD are present) and parenchymal jaundice (without IHBD dilations. Ultrasound can also highlight changes specific to liver cirrhosis (see chapter on cirrhosis).

- Assessment of liver stiffness by various *elastography techniques* (including FibroScan) is useful for monitoring the severity of fibrosis, with liver stiffness >9.6 kPa being associated with severe fibrosis and an increased risk of decompensation.

- If the initial results or the test for AMA are unclear, *cholangioMRI* is recommended to rule out other conditions (e.g., primary sclerosing cholangitis or cholangiocarcinoma).

- *Osteodensitometry* is essential for the evaluation of primary bone damage and for the detection of changes secondary to possible corticosteroid treatment (repeated every 1–2 years).

- *Upper digestive endoscopy* is indicated for the detection of esophageal varices and the diagnosis of a possible celiac disease.

Positive diagnosis

The diagnosis of PBC is based on a set of clinical, biochemical and, in certain situations, histopathological criteria. The typical clinical picture is found in middle-aged women, who present with asthenia, intense pruritus, jaundice or subicter, xanthomas/xanthelasmas, hepatomegaly and/or splenomegaly. Laboratory tests support the diagnosis by increasing alkaline phosphatase, GGTP and bilirubin, along with the presence of antimitochondrial antibodies type M2. Liver biopsy, although not mandatory, can confirm the diagnosis by highlighting nonsuppurative destructive cholangitis and ductopenia.

Differential diagnosis

It should be done with other causes of cholestasis: intrahepatic or biliary, the most common being presented in Table 22.II

Table 22.II. Differential diagnosis in PBC

Cholestasis type	Diagnostics
Intrahepatic cholestasis	Alcoholic and non-alcoholic steatohepatitis
	Infiltrative diseases (amyloidosis, sarcoidosis)
	Drug-induced cholestasis
	Genetic diseases (benign recurrent intrahepatic cholestasis, intrahepatic cholestasis in pregnancy)
	Liver infiltration from malignancies (Hodgkin lymphoma)
	Sepsis
	Total parenteral nutrition
	Vascular diseases (Budd-Chiari syndrome, congestive liver disease)
	Viral hepatitis, cholestatic forms
Biliary cholestasis	Primary sclerosing cholangitis
	IgG4-associated cholangitis
	Secondary sclerosing cholangitis (choledocian lithiasis, ischemia, vasculitis, infectious diseases)
	Cystic fibrosis
	Drug-induced cholangiopathies ("drug-induced liver injury")
	Ductal malformations: Caroli syndrome, congenital hepatic fibrosis

Complications. Evolution. Prognosis.

The evolution of PBC is relatively slow, with an average survival rate of 15–16 years for asymptomatic patients and 8–10 years for symptomatic patients. After about 5–6 years, most patients without initial symptoms also become symptomatic, although there may be periods of improvement.

Complications can be caused by cholestatic syndrome (steatorhea, dyslipidemia, hypovitaminosis, osteoporosis, osteomalacia, gallstones), but especially by the evolution to cirrhosis and its complications.

The prognosis is unfavorable, being influenced by the underlying disease, associated diseases and bilirubin level (below 2 mg% – survival of 12–13 years; between 2 and 6 mg% – 2–7 years; over 10 mg% – under 2 years). The evolution was greatly improved by the introduction of treatment with ursodeoxycholic acid, most patients responding to this type of therapy. If treatment is introduced before the onset of jaundice, and the patient is responsive, the prognosis is greatly improved.

Age at diagnosis and other parameters (albumin, ascites, edema, prothrombin time) are also important in prognostic models for severe cases with indication for transplantation.

Treatment

1. There is no ***etiological treatment*** for PBC, as the cause is not known.

2. ***Pathophysiological treatment*** includes:

- *Ursodeoxycholic acid (UDCA),* initially used for the treatment of gallstones, later approved by the FDA for PBC, works by increasing hepatic secretion, respectively inhibiting the absorption of hydrophobic bile salts and stabilizing the hepatocellular membrane. According to the AASLD and EASL (American and European Society for the Study of the Liver) guidelines, *UDCA* is the first-line and long-term (lifelong) therapy in PBC, at doses of 13–15 mg/kg body weight/day, administered individually or in combination with other medications.

- *Obeticholic acid* has shown promising results in clinical trials. According to EASL recommendations, obeticholic acid is indicated **as a second line** of treatment in patients who do not tolerate UDCA or who have an inadequate response to it. The recommended starting dose is 5 mg per day, with the possibility of gradual increase to 10 mg per day.

- *Bezafibrate* may improve biochemical parameters, either administered as monotherapy or in combination with UDCA. Recent studies have reported improvements in cholestasis enzymes, but the long-term benefits remain unclear.

- *Corticosteroids* may temporarily improve biochemical parameters, but their long-term use is discouraged due to adverse effects (such as osteoporosis), and *azathioprine and methotrexate* have not demonstrated clinically significant benefits. For this reason, these drugs are not used in the routine treatment of primary biliary cholangitis.

3. ***Symptomatic treatment.*** Fatigue, a multifactorial symptom, is not influenced by UDCA treatment. *Pruritus* can be relieved with rifampicin, cholestyramine and serotonin antagonists, and *Sicca syndrome* is treated by humidifying the air, administering artificial tears and ophthalmic anti-inflammatories. *Osteoporosis* and *hyperlipidemia* require individualized treatment.

Patient monitoring

Monitoring involves assessing disease activity by determining bilirubin, GGT and alkaline phosphatase levels every 3–6 months, supplemented by annual thyroid hormone tests and osteodensitometry at 2–4 years. Response to treatment is usually assessed after 12 months, and the lack of an adequate biochemical response (seen in 25–50% of patients) is associated with a 5-fold higher risk of progression to cirrhosis and 3-fold higher mortality.

Throughout the evolution, the appearance of new signs or changes in the analyzes that could indicate an associated autoimmune disease is followed. In addition, in patients with severe fibrosis/cirrhosis, abdominal ultrasound and AFP determination are performed at 6 months for hepatocarcinoma screening. Upper digestive endoscopy is repeated annually for the detection of esophageal varices, according to the recommendations of the Baveno VII consensus.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

Definition

Primary sclerosing cholangitis (PSC) is a chronic, immune-related liver disease characterized by a progressive process of cholestasis. This involves inflammation, fibrosis and destruction of the bile ducts, both intrahepatic and extrahepatic, which leads to the formation of segmental stenosis. Without proper treatment, the disease progresses to liver cirrhosis, portal hypertension, liver failure, and in some cases, cholangiocarcinoma.

Epidemiology

PSC affects about 1 in 10,000 people, with an estimated incidence of 1 in 100,000 per year. In southern Europe, the values are about 10 times lower. In developing countries, the prevalence is likely underestimated, due to diagnostic difficulties requiring high-quality imaging (such as cholangioMRI). The disease usually starts at 20–30 years of age, although children or adolescents can also be affected, the average age at diagnosis being around 40 years. There is a preponderance of men (about 70% of cases) and an increased frequency in non-smokers.

Pathophysiology

The exact causes are not fully known, but it is believed that PSC develops through the interaction of factors acting on a *predisposing genetic background*, evidenced by the increased frequency of certain HLA alleles (e.g. HLA A1, B8, DR3). Factors involved include *infections* (both viral and bacterial), *ischemic lesions* that reduce blood flow to the bile ducts, exposure to *environmental toxins and antigens*, as well as an *aberrant immune response*, whereby the immune system attacks the bile ducts.

The evolution of the disease has several stages. Initially, an abnormal immune response causes chronic inflammation of the bile ducts. This persistent inflammation leads to the activation of fibroblasts, resulting in excessive collagen deposition and the formation of periductal fibrous tissue, which decreases elasticity and thickens the ductal walls. Over time, the combination of continuous inflammation and fibrotic process leads to damage to the structure of the bile ducts, generating multiple stenosis that obstructs the normal flow of the bile, a phenomenon that causes cholestasis and the appearance of subsequent complications.

An important aspect of PSC is *the autoimmune component*, evidenced by the frequent association of PSC with other autoimmune diseases. About 50–80% of patients develop inflammatory bowel diseases, especially ulcerative colitis, and in some cases conditions such as sarcoidosis, systemic lupus erythematosus, celiac disease, type 1 diabetes mellitus or autoimmune hemolytic anemia may also be associated. Also, in about 17% of cases, features of autoimmune hepatitis are identified concomitantly with PSC.

The risk of neoplasia is significantly increased in patients with PSC. Cholangiocarcinoma, a serious complication with a poor prognosis, is common, and the association with inflammatory bowel disease increases the risk of colorectal cancer.

Pathology

The diagnosis of PSC is initially based on non-invasive imaging evaluation, by cholangioMRI, which can highlight the typical "leafless tree" of the bile ducts, due to the reduction of intrahepatic branches. In situations where these changes are not obvious, or when damage to the small ducts or the presence of an autoimmune hepatitis process (identified by increases in transaminases, high levels of IgG and the presence of autoantibodies) is suspected, a liver biopsy is used. Histological examination may show specific lesions, such as concentrated periductal fibrosis with an "onion leaf" appearance (Figure 22.1). The histological evolution of PSC is classified into four stages (Table 22.III):

Table 22.III. Histological classification of PSC

Stage	Histological Features
I (Portal)	Hepatitis limited to the portal space, degenerative lesions of the ductular epithelium, periductal fibrosis "in onion leaves"
II (Periportal)	Periportal fibrosis and inflammation, ductular proliferation and/or ductopenia
III (Septic)	Septal fibrosis, bridge necrosis
IV (Cyrotic)	Biliary cirrhosis, nodules surrounded by fibrosis, and significant liver dysfunction

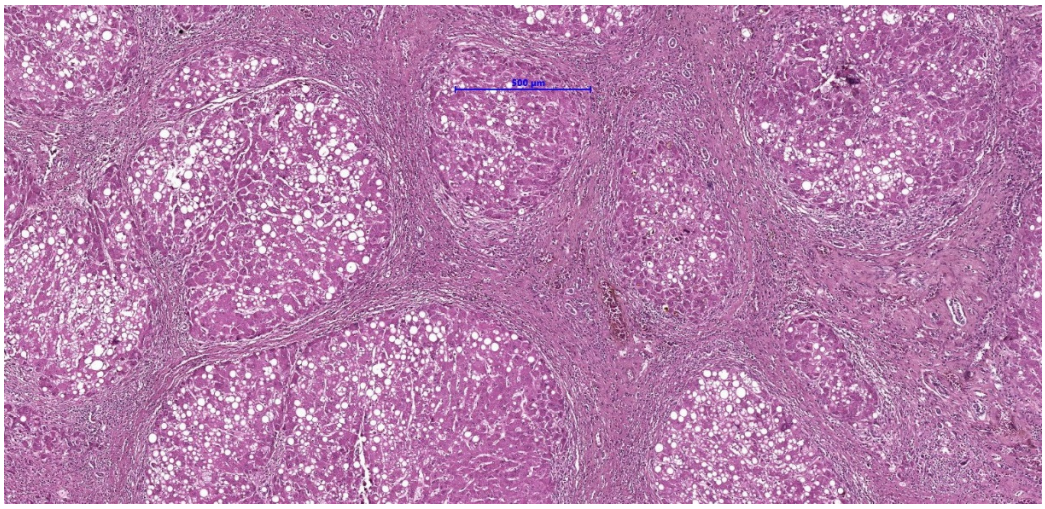


Figure 22.1. Histological picture: cirrhosis of the liver, nodules surrounded by fibrosis, and significant liver dysfunction.

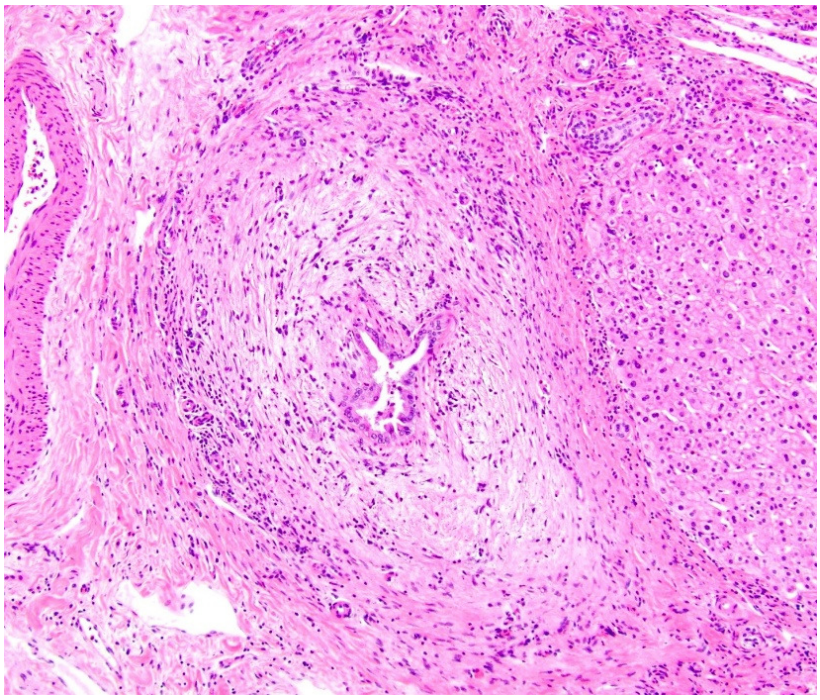


Figure 22.2. Histological image: pericanalicular fibrosis with chronic lymphoplasmacytic inflammation, suggestive of PSC.

Clinical picture

From a clinical point of view, PSC can present a variable picture. A significant percentage of patients (20–40%) may be *asymptomatic*, and the disease is discovered by chance following liver tests that show a cholestasis profile, even if liver ultrasound is normal. In symptomatic cases*, fatigue, itching and pain* localized in the right hypochondrium are noted, and sometimes it can manifest itself through episodes of *acute hepatitis* or *bacterial cholangitis*, with jaundice and fever.

The course of the disease leads to cirrhosis, portal hypertension and liver failure, and worsening symptoms (especially jaundice, pruritus or significant weight loss) may suggest the development of a cholangiocarcinoma.

In the case of patients with PSC associated with inflammatory bowel disease, inflammatory changes are usually noticeable in the right colon and terminal ileum, a phenomenon called "backwash ileitis", keeping the rectum relatively unaffected and providing a milder clinical evolution.

The biological picture

The biochemical profile of patients with PSC is not specific, but it presents some characteristic changes. A picture of ***hepatic cholestasis is constantly observed***, marked by increased alkaline phosphatase (FAL) and gamma-glutamyltranspeptidase (GGT) values, usually 3–5 times higher than normal values. Hyperbilirubinemia manifests itself mainly on the basis of the conjugate fraction, although serum levels may fluctuate

depending on the stage of the disease. At the same time, ***hepatic cytolysis***, evidenced by moderate increases in AST and ALT, is present, and in the context of cholangitis episodes, a *leukocytosis* with a predominance of neutrophils can also be recorded.

Associated inflammatory syndrome may be an expression of acute cholangitis or disease activity in patients with associated inflammatory bowel disease. About 30% of patients have hypergammaglobulinemia, and serological evaluation reveals *increases in IgM and IgG*.

Autoantibodies can also be an important indicator, but not a specific one. Thus, *perinuclear neutrophilic anticytoplasm* (pANCA) is present in about 84% of patients, *anticardiolipin* (aCL) in about 66% and *antinuclear antibodies* (ANA) in 53% of cases. In contrast, antimitochondrial antibodies (AMAs) are generally negative, which contributes to the exclusion of primary biliary cholangitis. Although the presence of these autoantibodies is common, the diagnosis of PSC cannot be established solely on their basis, and they are not useful for risk stratification in diagnosed patients.

To confirm the diagnosis of primary sclerosing cholangitis, it is necessary to carry out additional investigations, aimed at ***excluding secondary forms of the disease***. It is recommended, for example, to determine the serum level *of IgG4*, since an increased level is characteristic of autoimmune cholangitis associated with IgG4, an entity considered distinct. In addition, in the context of the occurrence of cholangiocarcinoma, an increase in serum levels of *carbohydrate antigen 19-9 (CA 19-9) can be observed,* providing an additional clue to malignant transformation.

Paraclinic

- *CholangioMRI (MRCP)* is the primary diagnostic method for PSC, having a sensitivity and specificity comparable to those of ERCP. MRCP highlights typical features of the disease, such as the "leafless tree" appearance of the biliary tree due to the reduction of the branches of the intrahepatic bile ducts, such as the succession of stenosis and dilations at the level of IHBD.
- *Other imaging techniques*, ERCP and percutaneous transhepatic cholangiography (PTC), are mainly used for therapeutic purposes or to exclude a malignant stenosis. These procedures can be supplemented, as appropriate, with cytology samples, intraductal biopsies and cholangioscopy, for a more detailed evaluation of suspicious lesions.

Positive diagnosis

The positive diagnosis of PSC is based on a set of clinical, biochemical and imaging data, obtained by a high-quality cholangiography (preferably cholangioMRI) that highlights the typical "leafless tree", after excluding the causes of secondary sclerosing cholangitis.

Evaluation of the intestine by ileo-colonoscopy with layered biopsies is essential, given the high frequency of inflammatory bowel diseases associated with PSC. The typical patient profile is that of a young man, around the age of 40, often diagnosed with inflammatory bowel disease and signs of cholestasis, without obvious biliary obstruction.

Differential diagnosis

PSC must be differentiated from other parenchymal cholestatic disorders, mainly primary biliary cholangitis, IgG4 cholangitis, autoimmune hepatitis, infiltrative diseases (sarcoidosis, eosinophilic cholangitis), cholestasis of infectious cause, as well as from obstructive cholestasis (choledocian lithiasis, papillary tumors, pancreatic tumors, choledocic cholangiocarcinoma, etc.). The imaging aspect is essential for differential diagnosis.

Evolution, prognosis, complications

PSC is a chronic disease characterized by recurrent episodes of *acute cholangitis* that lead to new *biliary strictures*, this time at the level of the dominant bile ducts and an unfavorable prognosis. The progression of the disease usually causes *secondary biliary cirrhosis*, portal hypertension and liver failure, accompanied by serious complications (variceal hemorrhage, encephalopathy, hepatorenal syndrome) and the effects of chronic cholestasis, such as steatorrhea, deficiencies of fat-soluble vitamins and osteoporosis. The assessment of the risk of decompensation is done initially and periodically through biochemical tests, imaging (cholangioMRI) and elastography. A severe complication is *angiocolitis*, which can lead to sepsis and death,

The risk of *cholangiocarcinoma* is about 35% and has a serious prognosis, while hepatocarcinoma is rare and usually of the fibrolamellar type, with a more favorable outcome. Cholangiocarcinoma is usually located at the confluence of the right and left hepatic ducts (Klatskin tumor), but it can also affect the intrahepatic bile ducts or the main bile duct.

PSC associated with ulcerative colitis increases the risk of *colorectal cancer*, a risk that persists even after liver transplantation.

Positive prognostic factors are young age at diagnosis, female gender, involvement of small ducts, association with Crohn's disease, and normal or slightly elevated TGP values. ***Negative prognostic factors*** include extensive bile duct damage, liver dysfunction, portal hypertension, decompensated cirrhosis, and jaundice. The average survival is about 12 years, but it reduces to about 5 months in the presence of cholangiocarcinoma. Liver transplantation remains the only option that can significantly improve the prognosis in advanced stages of PSC.

Treatment

The therapeutic approach is divided into medical, endoscopic and surgical treatment.

1. Medical treatment. Recent research has not demonstrated significant therapeutic benefits by administering *bile acids* (ursodeoxycholic acid – UDCA), *chelators* (cholestyramine), *steroids* (prednisolone and budesonide) or *immunosuppressive agents* (colchicine, penicillamine, azathioprine, cyclosporine, methotrexate, mycophenolate, etc.). All these therapies can be used to control symptoms, but they do not influence the course and prognosis of the disease.

Symptomatic treatment of PSC aims to control symptoms and associated complications. *Itching*, which significantly affects the quality of life, is treated either pharmacologically with bezafibrate or rifampicin, or by dilatations of the dominant bile ducts in the presence of the responsible strictures. In cases of *acute bacterial cholangitis*, antibiotics should be administered and, if an underlying stricture is present, biliary decompression by stent placement or dilation is used. Also, in case of a *deficiency of fat-soluble vitamins* (A, D, E and K), appropriate supplementation is recommended.

Future therapeutic options include *next-generation bile acids* (e.g., 24-nor-ursodeoxycholic acid), *farnesoid X bile acid receptor agonists* (obeticolic acid, cilofexor), or fibroblast growth factor therapy. To date, these therapies are not recommended in current practice.

2. Endoscopic treatment is recommended for patients with relevant strictures, who present signs or symptoms of obstructive cholestasis and/or bacterial cholangitis.

Endoscopic or percutaneous dilation of significant stenosis, whether with or without stent placement, relieves cholestasis and improves laboratory parameters, but has not been proven to date to alter disease progression. In general, balloon dilation is preferred to stent placement, due to a lower incidence of complications. As a high incidence of post-interventional cholangitis is reported, prophylactic administration of antibiotics is recommended prior to ERCP.

3. Surgical treatment. Surgical procedures in PSC include *biliary reconstructive interventions* for very tight strictures, inaccessible by endoscopic or radiological methods, colectomy for those with inflammatory bowel disease (IBD). *Colectomy* is recommended in patients who have colon cancer or high-grade dysplasia, or if symptomatic inflammatory activity persists despite optimal medical therapy.

In patients diagnosed with PSC, the identification of gallbladder polyps larger than 8 mm or increasing on repeated evaluations is an indication for *cholecystectomy*, due to the increased risk of malignancy or dysplasia.

Surgical treatment is also indicated in cases complicated with *cholangiocarcinoma*.

Liver transplantation is the only therapy that can truly change the prognosis of liver disease. PSC is a well-known indication for transplantation, associated with excellent results, although the optimal timing for transplantation remains uncertain. Indications for liver transplantation in patients with PSC include, according to current guidelines, complications that occur in the stage of decompensated cirrhosis (such as variceal bleeding, refractory ascites, hepatic encephalopathy or hepatocellular carcinoma), recurrent cholangitis, sarcopenia, treatment-resistant pruritus and the presence of strictures that cannot be dilated endoscopically. Liver transplantation may also be considered in patients with PSC and high-grade biliary dysplasia confirmed by cytology or ductal histology.

Although the risk of PSC recurrence on the graft is 15–20%, the post-transplant prognosis is encouraging, with a 5-year survival of 75–100% and about 70% at 10 years. It should be noted that the risk of IBD persists even after transplantation.

Monitoring

After establishing the diagnosis of PSC, an individualized approach is required, with long-term monitoring for prevention and early identification of complications. Clinical evaluations and laboratory tests (bilirubin, albumin, alkaline phosphatase, GGT, transaminases, blood count, coagulation tests) are repeated every 6–12 months, and noninvasive evaluation of liver fibrosis (by elastography or serological markers) every 2–3 years.

Imaging investigations (abdominal ultrasound and/or cholangioMRI) are performed annually to monitor the structure of the bile ducts and detect complications, which are essential especially in patients with damage to the main ducts for the early detection of cholangiocarcinoma. In patients in the cirrhosis stage, screening for hepatocellular carcinoma by ultrasound and AFP determination is performed every 6 months.

At the time of diagnosis, all patients are evaluated by colonoscopy with layered biopsies to identify inflammatory bowel diseases and subsequent monitoring of the colon adapts according to their presence.

The evaluation of bone density by DEXA, performed at diagnosis, helps to identify osteopenia or osteoporosis.

To note

- PBC and PSC are chronic liver diseases with an autoimmune component, biologically characterized by cholestasis, with progressive evolution to cirrhosis and its complications.

- PBC occurs more frequently in middle-aged women, has nonsuppurative destructive cholangitis as its morphological substrate, and antimitochondrial antibodies are specific, present in over 90% of cases.

- PSC is more common in young men, the morphopathological substrate being periductular fibrosis, which leads to stenosis and overlapping dilations of the biliary shaft, the investigation of choice for diagnosis being cholangioMRI.

- In both PBC and PSC, the treatment of choice is with Ursodeoxycholic Acid, at a dose of 13-15 mg/kg/z, with much better results in PBC than in PSC.

- If PBC is diagnosed in time, and is responsive to treatment with Ursodeoxycholic Acid, the prognosis is good.

- PSC has a worse prognosis, even under treatment with ursodeoxycholic acid, biliary stenosis being progressive, with rapid evolution to cirrhosis and its complications, in addition, patients at risk of bacterial cholangitis. Distal stenosis can benefit from endoscopic treatment, but the best treatment in advanced forms is liver transplantation.

23. HEREDITARY METABOLIC LIVER DISEASE. HEREDITARY HEMOCHROMATOSIS

Definition

Hereditary hemochromatosis is defined as a genetic mutation of iron metabolism, with autosomal recessive transmission, characterized by increased intestinal absorption of iron and its deposition in various tissues. It is caused by mutations in the HFE gene (human hemochromatosis protein), occurring in 80% of European individuals. Rarely, hemochromatosis is caused by recessive pathogenic variants of iron-coding genes. The identification of the specific genetic variant causing the disease is not necessary in patients with the onset of the disease in adulthood, nor sufficient for the diagnosis of hemochromatosis, which is based on phenotypic criteria. If left untreated, hemochromatosis can lead to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Hemochromatosis is also called "tanned diabetes", because it associates liver disease with diabetes mellitus and specific skin coloration.

Epidemiology

Hereditary HFE hemochromatosis is the most common metabolic disease in the general population (1/200 people), especially in the European Nordic countries. In Romania, the frequency of the C282Y HFE mutation is 1.75% and 13.25% for H63D whose role in the pathogenesis of the disease is questionable.

Etiopathogenesis

Hemochromatosis is caused by a deficiency in the synthesis or function of hepcidin due to pathogenic variants of genes that regulate its production or function, leading to increased intestinal absorption of iron and its release from macrophages, resulting in an increased amount of circulating iron, reflected by increased transferrin saturation. The consequence is the progressive accumulation of iron in the body, which is stored mainly in the liver. The homozygous variant of p.Cys282Tyr in HFE is by far the most common genetic variant that predisposes to hemochromatosis in individuals of European descent. In individuals of non-European origin or in individuals of European origin that are not homozygous for the p.Cys282Tyr variant of HFE, hemochromatosis is caused by mutations in other genes that control iron metabolism (e.g. HAMP- hepcidin antimicrobial peptides, SLC40A1- ferroportin-associated hemochromatosis, transferin receptor mutations, etc.).

Morphopathology

Cirrhosis from hemochromatosis is of the micronodular type. At the histopathological examination of the liver biopsy piece, lesions common to other liver diseases are present: inflammation, hepatocyte necrosis, fibrosis in various stages. The stored iron stands out on the biopsy by the Pearls staining.

Clinical picture

The clinical picture includes the classic triad of hepatomegaly, diabetes, skin hyperpigmentation.

- *Hepatomegaly* appears early, from the asymptomatic phase. In the advanced stages, with the onset of cirrhosis, hepatomegaly becomes firm, splenomegaly, jaundice, ascites, abdominal collateral circulation, etc. occur.

- *Diabetes mellitus* occurs in 50-60% of cases, being the result of iron toxicity on beta-islet cells. Two-thirds of patients are insulin dependent.

- *Hyperpigmentation of the skin* occurs in the advanced stages of the disease and mainly affects exposed areas. It is due to excess melanin and not to the storage of iron in the skin.

Other clinical manifestations include: *secondary hypogonadism* (characterized by reduced libido, early amenorrhea, infertility), *symmetrical arthropathy* (which can affect the metacarpophalangeal joints, proximal interphalangeal, spinal and knee joints), *cardiac manifestations* (heart failure due to ethanolic cardiomyopathy, rhythm and conduction disorders)

Paraclinical investigations

Paraclinical tests must evaluate iron overload on the one hand and the severity of liver damage on the other hand.

1. Biological tests for the evaluation of iron load:

- Sideremia evaluates transferin-bound serum iron and is increased in hemochromatosis. Although it is the most widely used biological parameter, its value in assessing the amount of iron in the body is limited.

- *ferritinemia* is the most faithful biological parameter for the evaluation of iron deposits and correlates with the hepatic load evaluated bioptically, being increased in hemochromatosis, over 200µg/L in women and over 300µg/L in men.

- *total iron binding capacity (CTFL)* is used for indirect determination of circulating transferrin concentration, being low in hemochromatosis

- *The transferrin saturation index or coefficient (STI)* is the first-line test indicated in patients in whom iron overload of the body is suspected. IST = (sideremia/CTFL) x 100. STI values > 45% in women and STIs > 50% in men are suggestive of hemochromatosis.

2. Tests to evaluate the tissue storage of iron

- *Liver biopsy puncture (PBH) with Pearls staining* (Fig.23.1) - confirms the hepatic load with iron, specifies the location of deposits (parenchymal accumulation), allows semi-quantitative evaluation of iron at the liver level, evaluates the degree of fibrosis and inflammation, the disadvantage being that it is an invasive method.

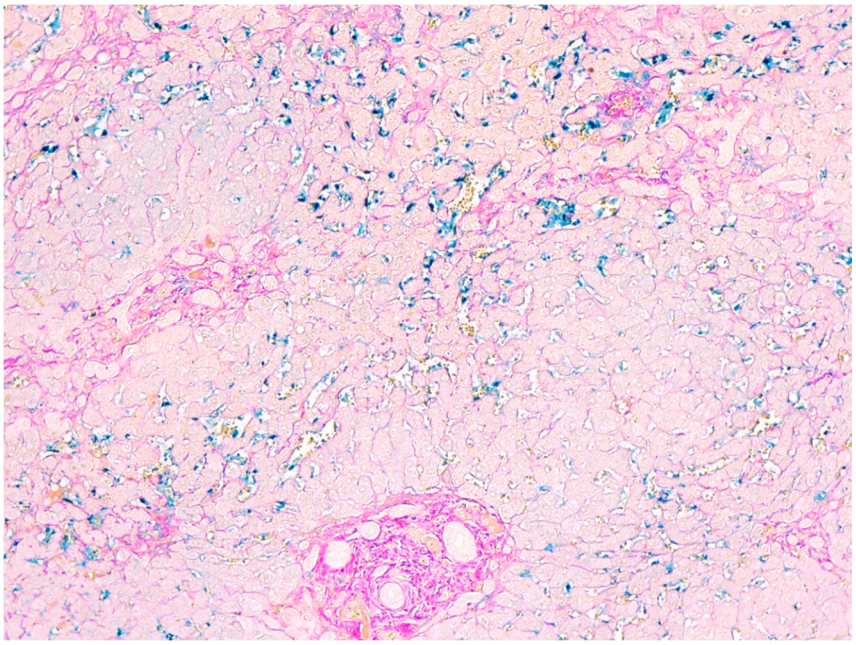


Figure 23.11 Pearls staining in hemochromatosis

- *Nuclear magnetic resonance imaging (MRI)* - a non-invasive method that allows quantifying the liver iron content and the stage of fibrosis, the major disadvantage being the high cost.

- *Biomagnetic* Liver Susceptometry (BLS) – the most specific and sensitive method of direct, non-invasive evaluation of liver iron. It measures variations in the magnetic field produced in the liver in response to the application of an external magnetic field.

3. Genetic testing is the gold standard assessment for the diagnosis of hereditary hemochromatosis. Homozygous p.Cys282Tyr status in HFE is the major diagnostic criterion.

4. Evaluation of liver fibrosis by non-invasive elastographic methods. Impulse Elastography (FibroScan) can assess the degree of fibrosis in hemochromatosis. A value < 6.4 kPa excludes advanced fibrosis and histological confirmation of iron deposits in the liver is no longer required in patients with HFE genetic mutations.

Diagnosis

The positive diagnosis starts from the classic triad (hepatomegaly with different degrees of fibrosis to cirrhosis, diabetes mellitus and melanoderma) and biologically the increase in the saturation coefficient of transferrin above 45% and the increase in serum ferritin over 200µg/L in women and over 300µg/L in men stand out. The next step is to confirm the tissue storage of iron using one of the methods described above, followed by the etiological/genetic diagnosis. Genetic diagnosis is mandatory in women with > 45% STIs and ferritinemia > 200µg/L and in men with >50% STIs and ferritinemia >300µg/L.

Differential diagnosis

Once an iron loading syndrome is discovered, the cause and mechanism of its production must be established. The differential diagnosis of hemochromatosis includes not only elucidating all causes of iron overload in the liver, but also differentiating the genetic forms of hemochromatosis.

Thus, the differential diagnosis will be made with secondary iron loading syndromes found in chronic hemolytic anemias, thalassemia major, sideroblastic/aplastic anemia, chronic liver diseases (hepatitis B and C, alcoholic liver disease, hepatic steatosis associated with metabolic dysfunction, etc.). Iatrogenic causes of iron loading can be considered repeated transfusions and hemodialysis, as well as excess administration of injectable iron.

Complications

The complications of hemochromatosis are related to excessive iron deposits in various organs. At the liver level, iron overload can lead to the development of cirrhosis and its complications, including the appearance of hepatocarcinoma. At the cardiac level, a common complication is dilated cardiomyopathy, with arrhythmias and heart failure. At the pancreatic level, hemochromatosis will lead to diabetes.

Evolution

The evolution of the disease is long, the average survival being 5 years from the moment of diagnosis in the cirrhotic stage. Death occurs through liver and heart failure, complications of diabetes, patients also being at increased risk of liver cancer.

Prognosis

The prognosis of the disease is favorable if the diagnosis was made early and the treatment instituted, but it becomes reserved in the stage of liver cirrhosis.

Treatment

The treatment includes several components:

- *Hygienic-dietary diet* - iron and vitamin C supplements, alcohol consumption, red meat consumption, seafood consumption will be avoided.

- *Phlebotomy* is the most effective treatment and is initially performed weekly or every 2 weeks until the ferritinmy level drops to about 50 μg/L. Then, in the maintenance phase, phlebotomy is performed at an interval of 1-4 months.

- *Drug* – consists of the administration of iron chelating agents (Desferoxamine - Desferal) being indicated in patients with anemic syndromes or chronic renal failure in whom phlebotomy cannot be performed.

To note

- Hereditary hemochromatosis is defined as a genetic mutation of iron metabolism, with autosomal recessive transmission, characterized by increased intestinal absorption of iron and its deposition in various tissues, mainly in the liver (where it can cause chronic liver disease progressive to cirrhosis and its complications), pancreas (with the appearance of diabetes mellitus over time) and skin (causing melanic hyperpigmentation).

- The biological picture includes the increase of sideremia and ferritin, the decrease in the binding capacity of iron, the most sensitive and specific being the increase in transferrin saturation over 45%.

- Confirmation of the diagnosis is made by the mentioned biological tests, with or without liver biopsy (Pearls staining highlighting the iron overload of hepatocytes), with or without liver MRI with quantification of iron deposits.

- Treatment is done by repeated phlebotomy so that the level of ferritinemia decreases to about 50 μg/L, or by administration of iron chelators.

24. WILSON'S DISEASE

Definition

Wilson's disease, also called hepato-lenticular degeneration, is a hereditary condition of copper metabolism, with the appearance of hepatic, neurological and psychiatric manifestations, ocular (Kaiser-Fleischer ring) with damage to other organs (kidneys, bones, skin). The disease is genetic, with autosomal recessive transmission.

Epidemiology

The prevalence of the disease is about 30/1,000,000 inhabitants, and the frequency of the genetic defect is estimated at 1/90-100 people.

Etiopathogenesis

In Wilson's disease, two important abnormalities occur: decreased ceruloplasmin synthesis, serum copper transporter protein, and decreased *bile excretion of copper.* Essentially, it is not an increased absorption of dietary copper, but a decrease in bile elimination, which explains the positive balance. Copper is found in plasma in two forms: ceruloplasmin-bound (90%) and free (10%). In Wilson's disease, free copper grows well above this percentage, diffusing from the vascular space into the tissues, where it produces cellular damage.

Pathology

Cirrhosis of the liver in Wilson's disease is of the macronodular type. Initially, hepatic steatosis developed, followed by mononuclear infiltrates. Copper is concentrated in lysosomes and is highlighted by rubeanic acid staining. In Wilson's disease, lesions caused by excess copper occur both in the nervous system and in the kidneys.

Clinical picture

The onset of symptoms occurs in adolescence in 50% of patients, only in 1% of patients the onset occurs after 50 years. The clinical picture is dominated by hepatological and neurological manifestations, the forms with predominantly neurological involvement having the most reserved prognosis.

- *Nonspecific liver manifestations* are the first to appear. Thus, patients may have hepatomegaly, isolated splenomegaly, persistently elevated transaminase values, hepatic steatosis, in advanced forms, with cirrhosis, jaundice, vascular stellates, ascites, as well as other complications of cirrhosis appear. A rarer form, but with a severe evolution, is acute fulminant hepatitis with hemolytic anemia as a way of onset. In this situation, progressive jaundice, ascites, liver and kidney failure occur. The prognosis in this situation is severe, with death occurring within a few days. Clinical and laboratory manifestations

are common with acute viral hepatitis. Chronic hepatitis occurs at the age of 10-30 years, with evolution to cirrhosis.

- *Neuropsychiatric manifestations. Neurological manifestations* can be present as early as childhood, but are more common in the third decade of life. Neurological manifestations are signs of extrapyramidal involvement, characterized by movement disorders (tremors, involuntary movements, dysarthria, rigid dystonia, seizures, pseudobulbar syndrome). *Psychic manifestations* are most frequently present since childhood and are represented by depression, loss of school performance, deterioration of intellectual capacity.

- *Ocular manifestations* are due to the deposition of copper in the Descement membrane on the periphery of the cornea. They appear in the form of a gray-brown or greenish, pathognomonic ring on the periphery of the iris (Kaiser-Fleischer ring) (Fig. 23.2), or/and deposits on the lens (causing cataracts). Cataracts have a characteristic arrangement of deposits and do not affect visual function.

Figure 23.2 Kayser-Fleischer ring (Source: https://wilsondisease.org)

- *Other manifestations* include cutaneous changes (skin pigmentation, blue coloration of the lunula), renal (nephrolithiasis, hematuria), joint (osteoporosis, arthritis), hematological (acute intravascular hemolytic anemia, with negative Coombs test).

Paraclinical Board

It is recommended to perform the following tests for diagnosis:

- *Serum ceruloplasmin* is low in > 80% of cases in patients with Wilson's disease. A serum level < 20 mg/dl is suggestive for diagnosis, and if the patient also has the Kayser Fleischer ring, the diagnosis is confirmed.

- *Cupremia* is low, with the proportion of free copper increasing. A free copper/total copper ratio ≥ 15% is suggestive for diagnosis, the normal value being ≤ 10%.

- 24h copper is increased (>100 µg/24h). Increasing copper above 500 µg/24h is one of the objectives of treatment with copper chelators.

- *Increase in ALT and AST* is frequently present and moderate.

- In advanced stages, *signs of liver failure are present* (increases in bilirubin, INR, hypoalbuminemia)

- *The evaluation of copper storage in the liver is* performed by puncture, liver biopsy, rubeanic acid staining.

- *Brain computed tomography* can identify atrophy in the basal ganglia, cerebral cortex, and cerebellum.

- *Brain MRI* is even more sensitive and reveals hyperintensities in the T2 sequence at the level of the basal ganglia, cerebellum, thalamus and white matter - characteristic appearance "compared to the giant panda"

- *Genetic testing* (ATP7B gene) is only useful for family screening of first-degree relatives of patients with Wilson's disease

Diagnosis

Wilson's disease is clinically suspected due to the presence of hepatic manifestations associated with neuro-psychiatric ones and the presence of the Kayser-Fleischer ring and confirmed paraclinically (low ceruloplasmin and cupremia and increased copper, high free copper/total serum copper ratio). Acute liver failure characterized by moderate increases in transaminases (2-4 x VN), jaundice, severe hemolytic anemia with negative Coombs test, coagulopathy that does not correct after vitamin K administration , may be an onset form of Wilson's disease.

Three clinical forms *are described* according to the dominant clinical manifestations: the hepatic form, the mixed hepatic and neurological form, and the neurological form. The neurological form has a more severe prognosis and evolution.

Differential diagnosis

The differential diagnosis should be made with chronic liver diseases of other etiologies (viral, alcoholic, autoimmune, associated with metabolic dysfunction, hemochromatosis, etc.), by determining specific markers.

Complications

Wilson's disease with untreated liver damage can progress to the development of different degrees of fibrosis up to the stage of cirrhosis with all its complications, including portal hypertension with the development of esophageal varices, ascites, liver failure and hepatocarcinoma.

A rarer form of onset with a poor prognosis is fulminant hepatitis with acute liver failure.

Evolution

Under treatment, the evolution is good, the liver damage improves, but the neurological damage is most often irreversible.

Prognosis

The neurological form has the most severe prognosis. The vital prognosis depends on the degree of liver damage. Acute liver failure or decompensated liver cirrhosis have a poor prognosis, but may benefit from liver transplantation.

Treatment

1. Hygienic-dietary diet consists of avoiding foods with high concentrations of copper (chocolate, nuts, seafood, soy, mushrooms, etc.) and avoiding the use of copper cookware and utensils.
2. Drug treatment aims to promote the elimination of excess copper.

- *D-Peniclamine* is an effective chelating agent that is administered orally at a dose of 1.5-2g/day in 4 doses and allows the elimination of copper in the urine. It is associated with 250 mg/day of vitamin B6.

- *Trientine* (1.2-1.8 g/day) is also a chelating agent that is indicated in the treatment of Wilson's disease in cases of intolerance to D-Penicillamine.

- *Zinc Acetate* (150mg/day) interferes with the absorption of copper in the intestine. The therapeutic effect is inferior to D-Peniclamine and is indicated in asymptomatic patients.

3. Liver transplantation is indicated in patients with acute fulminant hepatitis associated with hemolysis, as well as in patients with decompensated liver cirrhosis, which does not respond to chelating agents.

Prophylaxis and screening

Genetic screening is not feasible in the general population due to genetic polymorphism, but family screening is justified and is performed in first-degree relatives of any newly diagnosed patient. Family genetic counseling is also recommended for the early detection of homozygous forms.

Monitoring

Patients should be monitored for the first 4-6 weeks after initiation of chelating therapy. Clinical and biological evaluation is recommended (blood count, cupremia, copper/24 hours, urine and creatinine summary, urea, uric acid). Then the monitoring in the first year will be biannual, then annual.

To note

- Willson's disease is a hereditary disorder with autosomal recessive transmission of copper metabolism, with the appearance of hepatic manifestations (liver disease with sometimes fulminant onset, with chronic evolution to liver cirrhosis), neurological and psychiatric manifestations (extrapyramidal manifestations, mental retardation), ocular (Kaiser-Fleischer ring) and at the level of other organs.

- Biologically specific tests are decreased serum ceruloplasmin, cupremia, with the ratio of free copper/total serum copper increased and increased copper.

- The diagnosis is made based on the clinical picture associating liver, neurological, ocular damage, in the presence of specific biological tests, with positive genetic testing.

- Treatment is done with copper chelators and zinc administration.

25. LIVER CIRRHOSIS

Definition

Liver cirrhosis is the final stage of chronic liver diseases, characterized by extensive fibrosis and by the rearrangement of liver architecture, associating hepatocytic necrosis and the appearance of regenerative nodules. The name cirrhosis was given by Laennec, after the Greek word "kirrhos" (the reddish-yellow colour of the cirrhotic liver).

The cirrhotic evolutionary process is a long one, lasting years or decades (from 5 to 30 years), and in the evolutionary process there is the transition from acute to chronic hepatitis and cirrhosis. The appearance of necrotic and inflammatory lesions is followed by the progressive appearance of fibrosis, in the form of collagen bands, which disrupt the normal architecture of the liver, with the tendency to form regenerative nodules (which are however devoid of the centrolobular vein).

The two fundamental processes, fibrosis and regeneration in the form of nodules, are mandatory. *The histological activity* of cirrhosis is assessed on the presence or absence of inflammatory lymphoplasmacytic infiltrate in the fibrous connective tissue.

Epidemiology

Liver cirrhosis is a major cause of morbidity and mortality globally. World Health Organization (WHO) estimates indicate that about 1.32 million deaths worldwide are attributed to chronic liver disease each year, a substantial portion of which are caused by cirrhosis and its complications such as liver failure and hepatocellular carcinoma.

The overall prevalence of liver cirrhosis is estimated to be between 0.3% and 1% of the general population. The incidence varies by region, with higher values in countries with a high prevalence of viral hepatitis and excessive alcohol consumption. Countries with a high prevalence of viral hepatitis B (e.g. China, sub-Saharan Africa) have higher rates of HBV-related liver cirrhosis. In Eastern Europe and Russia, excessive alcohol consumption is the main cause of liver cirrhosis. In North America and Western Europe, the increase in the incidence of MASLD (fatty liver associated with metabolic dysfunction) has led to an upward trend in the prevalence of metabolic cirrhosis.

In Europe, liver cirrhosis is responsible for about 170,000 deaths annually. In Romania, the prevalence of liver cirrhosis is estimated at 0.5-1%, with an increased incidence due to viral hepatitis B and C, but also high alcohol consumption.

Cirrhosis of the liver is the 11th leading cause of death worldwide, and in many countries, it is one of the leading causes of death in people under the age of fifty. Annual mortality from cirrhosis is estimated at 10-20% depending on the stage of the disease.

Aetiology

The aetiology of liver cirrhosis (LC) is multiple, considering that any chronic liver disease, if it evolves long enough, can evolve into liver cirrhosis. The most important causes of liver cirrhosis are:

- viral causes: hepatitis B, C and D viruses
- alcoholic cause (Laennec cirrhosis)
- metabolic syndrome-associated steatohepatitis (MASLD) – the old name being non-alcoholic steatohepatitis.
- Cholestatic causes: primary biliary cirrhosis (cirrhosis by intrahepatic cholestasis, secondary to primary biliary cholangitis), primary sclerosing cholangitis, biliary cirrhosis secondary (after prolonged biliary obstructions, by extrahepatic cholestasis)
- autoimmune cirrhosis (secondary to autoimmune hepatitis)
- Metabolic causes:
    - Wilson's disease (ceruloplasmin deficiency),
    - Primary or secondary hemochromatosis
    - cirrhosis caused by alpha-1 antitrypsin deficiency.
    - glycogenosis (glycogen deposition)
- vascular causes: cardiac cirrhosis (in severe and prolonged heart failure), cirrhosis of Budd-Chiari syndrome (thrombosis of suprahepatic veins, veno-occlusive disease)
- Drug causes - (oxyphenisatin, methotrexate, amiodarone, carbon tetrachloride, isoniazide, etc.)
- nutritional causes – (malnutrition, by-pass)
- cryptogenic cirrhosis (of undetermined cause).

Pathology

Macroscopically, according to the size of the liver, cirrhosis can be hypertrophic, with hepatomegaly, with a better prognosis, or atrophic cirrhosis, with small liver, in which most of the liver tissue is replaced by fibrosis, with a reserved prognosis.

Microscopically, the normal architecture of the hepatic lobe is replaced by regenerative nodules, which include normal hepatocytes surrounded by bands of fibrosis, with or without inflammatory infiltrate, without the presence of the centrilobular vein (Fig. 24.1). Depending on the size of the nodules, cirrhosis can be micronodular (usually alcoholic), in which numerous small regenerative nodules are noted, 2 – 3 mm, in both hepatic lobes; macronodular cirrhosis (usually post viral, but also toxic, autoimmune), in which the regenerative nodules are uneven, larger than 3 mm in size (Fig. 24.2); and micro-macronodular cirrhosis (found in biliary cirrhosis).

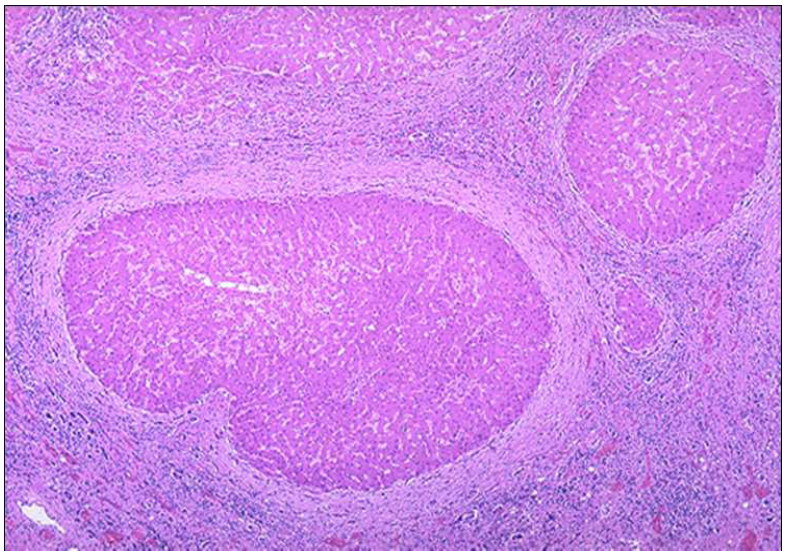


Fig. 24.1 Microscopic appearance of liver cirrhosis: normal hepatocytes (centre), surrounded by a ring of fibrosis – the regenerative node. In the vicinity 2 smaller nodules

Pathogenesis

All liver cirrhosis has as a common and mandatory starting point cell death, followed by inflammation and fibrosis, which in turn leads to the appearance of portal hypertension, considered to be the driver of decompensation and complications in liver cirrhosis.

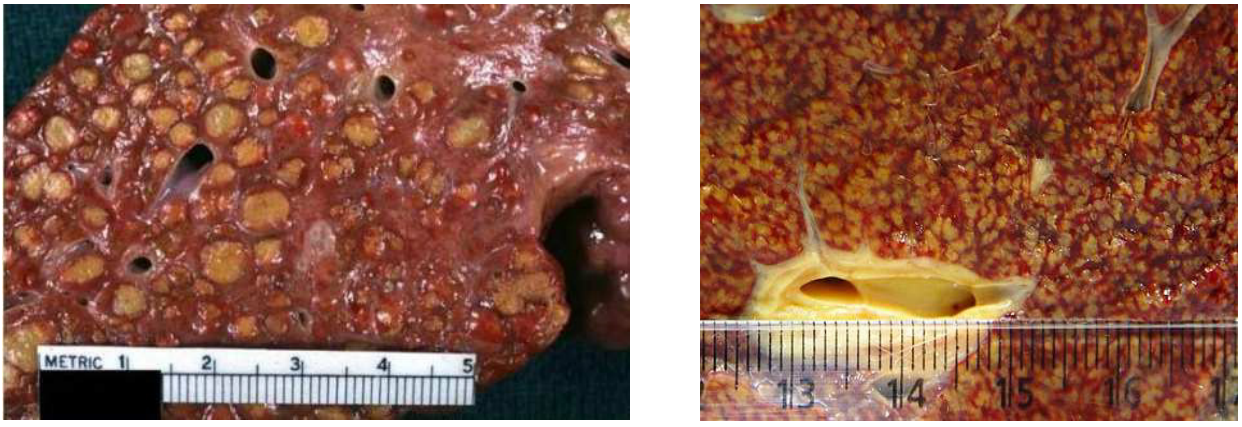


Fig. 24.2 Section through explanted liver: macronodular cirrhosis (left); Micronodular cirrhosis (right)

- *Cell death* differs depending on the aetiology. Most often it is cell necrosis, a violent death, following the direct aggression of pathogens. Other times, necrosis follows an inflammatory process and is the result of immune mechanisms. Cell death can also result from exacerbation of apoptosis (the naturally programmed death of hepatocytes), as happens in alcoholic aggression.

For cirrhosis to occur, necrosis must occur over time and not be massive, otherwise fulminant liver failure occurs. Cell necrosis can be focal or follow certain pathways like the inflammatory process (portal, porto-central or central-centre).

Following cell destruction, the collapse of the parenchyma occurs, a real collapse of the lobules. The hepatocytes will be framed in a collagen supporting tissue, following the collapse, these collagen frames overlap and converge, creating the fibrous matrix of the future cirrhosis.

- The second element is, therefore, the realization *of fibrosis*. On the path of matrix condensation, following lobular collapse, fibrosis develops, which follows the path of necrosis. Fibrosis is the result of an intense process of fibrogenesis, which is due to collagen. The fibroblasts in the portal space, Ito cells (precursors of myofibroblasts), and myofibroblasts in the Disse spaces are involved in the fibrogenesis process.

- *Cell regeneration* is the third element of the cirogen process. The process of regeneration is determined by cell death, but there is no balance between destruction and regeneration. As a rule, the regeneration is surplus and regenerative nodules are formed that compress the vascular system and cause the portal pressure to increase. Through the process of destruction, regeneration and fibrosis, shunts arise between the hepatic artery and the centrolobular vein, as well as between the arterial and portal system, with consequences on liver function.

- *Portal hypertension* (PH) in liver cirrhosis is primarily caused by extensive fibrosis that leads to a slowdown in blood flow through the liver, to which is added the release by the diseased liver of local vasoconstrictor agents, which in turn contribute to the increase of vascular resistance inside the liver. Portal hypertension is aggravated by splanchnic vasodilation (celiac trunk, superior mesenteric artery, inferior mesenteric artery) which amplifies blood flow through the portal vein, increasing portal pressure. PH is involved in the occurrence of several complications (ascites, oesophageal or gastric varices, hepatic encephalopathy), each with specific mechanisms of occurrence but all related to increased pressure in the portal system.

The pathogenesis differs depending on the etiological agent of LC. Thus, there is a directly proportional relationship in *alcoholic cirrhosis* between alcohol consumption and liver damage. Anatomo-clinical studies have shown that the frequency of liver cirrhosis is seven times higher in heavy drinkers compared to non-drinkers.

For cirrhosis, a certain dose of alcohol and a period is required. In men, it is considered necessary to consume more than 80 g of pure alcohol/day for 15 years, while in women the amount is lower (60 g of pure alcohol/day) and the shorter duration (10 years) for cirrhosis. The sex differences are due, at least in part, to the reduced ability of alcohol to metabolize in the stomach in women, due to deficient enzyme equipment. Alcohol-dehydrogenase, which ensures the oxidation of alcohol in the gastric mucosa, is found in a smaller quantity in the woman's stomach than in the man, so alcohol enters

the portal circulation unchanged in a greater proportion than in men. But even within the same sex, susceptibility to alcohol is different. The minimum threshold required for liver damage is 60 g of pure alcohol/day in men and 30 g of pure alcohol/day in women.

The sequence of lesions in alcoholic liver diseases is fatty loading, predominantly centrilobular necrosis with the appearance of Mallory bodies, fibrosis, cirrhosis.

In *viral cirrhosis*, cell death is the result of necrosis caused directly by the virus (cytopathic effect) or by the priming of cellular or humoral immune mechanisms. The supporting liver tissue consists of collagen, structural glycoproteins, proteoglycans, and elastin. All four of these components are grown in cirrhosis.

Clinical picture

The symptomatology of cirrhosis depends on the phase of the disease in which the patient finds himself: *in the initial stages*, symptoms may be absent or there may be physical and mental asthenia. Later, gingival bleeding, nasal bleeding, subicter or sclero-cutaneous jaundice appear. *In the late phases*, the appearance is typical, jaundiced patient, with abdomen enlarged by ascites, with gynecomastia (in men). The muscular atrophies of the belts, together with the abdomen enlarged by ascites, lead to the typical appearance of advanced cirrhosis, the appearance of a batrachian (Fig. 24.3).

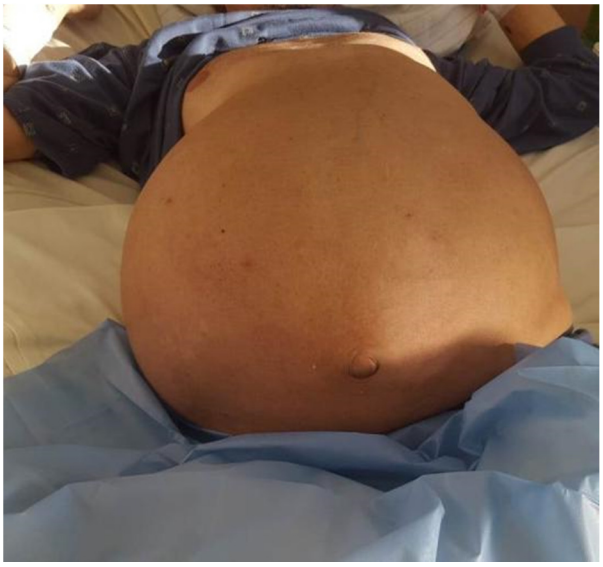


Figure 24.3. Patient with cirrhosis of the liver, jaundice, and ascites in tension.

The aetiology of the disease can also lead to *specific manifestations*: alcoholism – dyspeptic manifestations, paraesthesia, polyneuritis, diarrhea, autoimmune manifestations; in hepatitis C and autoimmune hepatitis – arthralgia, cryoglobulinemia; thesaurosis gives specific cutaneous-mucosal manifestations (cutaneous hyperpigmentation in hemochromatosis, Kaiser-Fleischer ring in Wilson's disease).

The clinical symptomatology of liver cirrhosis is determined by the two major consequences of morphological restructuring: the reduction of the liver parenchyma and the presence of portal hypertension.

Parenchymal dysfunction, the so-called hepatic functional failure, occurs over time, through the persistence of aggression (alcoholism, the presence of the virus, etc.). These signs can appear more quickly in viral cirrhosis or even in adolescence in Wilson's disease.

Parenchymal dysfunction translates into general phenomena: anorexia, asthenia, fatigue, weight loss. This last symptom may be absent in alcoholics in whom ethanol consumption compensates for nutritional deficiencies. Subsequently, hepatalalgia of exertion appears, and in periods of exacerbation, fever, and pruritus. Fever occurs because of intense cytolysis and is a sign of activity. Epistaxis and gingivorrhagia reflect coagulation disorder, due to the deficiency of synthesis of coagulation factors.

Portal hypertension has as minor clinical manifestations postprandial discomfort and bloating, gas syndrome. This is followed by the appearance of ascites. Other signs of severe portal hypertension are oesophageal varicose veins, which, in turn, can be complicated with upper digestive bleeding.

The clinical examination of a cirrhotic patient may reveal at inspection **the** presence:

- vascular stars on the antero-superior thorax (a particularly important sign because they are typical of LC) (Fig. 24.4).

-jaundice or scleral-cutaneous subjuncture (best visualized at the level of the sclera). Jaundice is present early in primary biliary cirrhosis, and in viral or alcoholic cirrhosis it occurs in advanced or exacerbated phases (Fig. 24.3). It is accompanied by hyperchromic urine and pruritus, especially in primitive biliary cirrhosis, with the existence of scratch marks.

- palmar and plantar rubeosis (Fig. 24.5).

- the presence of collateral circulation on the abdomen, either periumbilical, with the appearance of a jellyfish's head, or on the flanks (Fig. 24.6.).

- the presence of old, purple lesions, especially in the viral aetiology C

- the presence of ascites with the increase in volume of the abdomen (Fig. 24.3); but leg edema can also occur.

- muscle atrophy, especially on the limbs, is characteristic, and in the presence of ascites, it achieves the appearance of a batrachian or spider (Fig. 24.7).

- A series of endocrinological changes occur: the parotids are hypertrophied, the testicles are atrophic, and the hairiness has a ginoid disposition in men. In women, menstrual cycle disorders up to amenorrhea are observed. In men, gynecomastia is often common, but it can also be iatrogenic (after diuretic treatment with spironolactone).

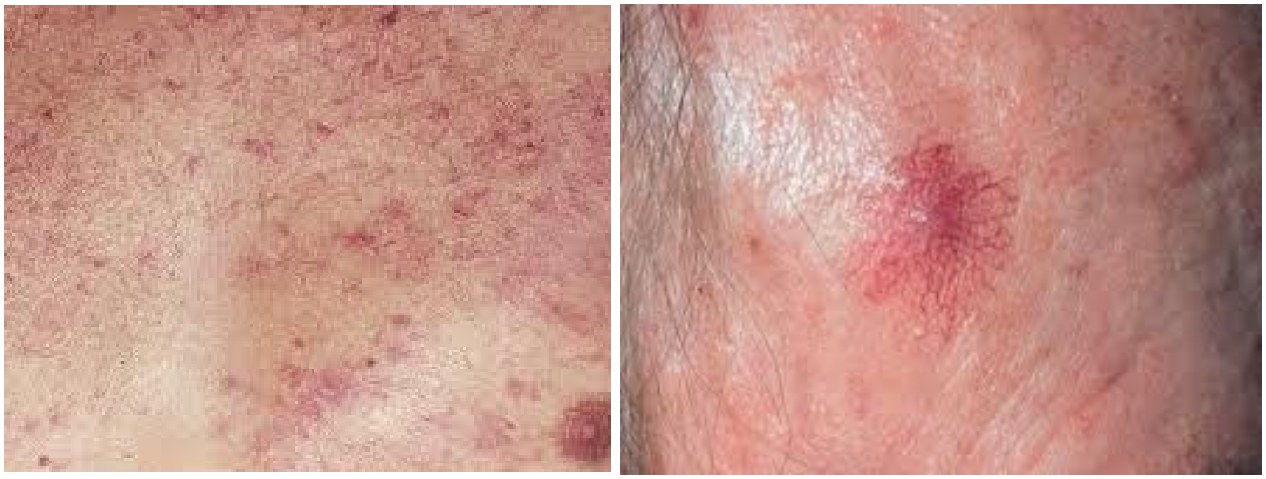


Figure 24.4. Explosive vascular stars on the antero-superior thorax in a patient with cirrhosis (left). On the right, close-up image of a vascular star.

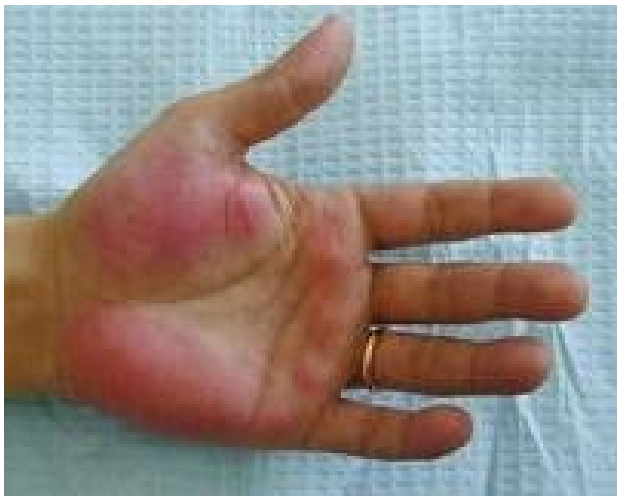


Fig. 24.5 Palmar rubea – red coloration of the tenar and hypopotenary eminences

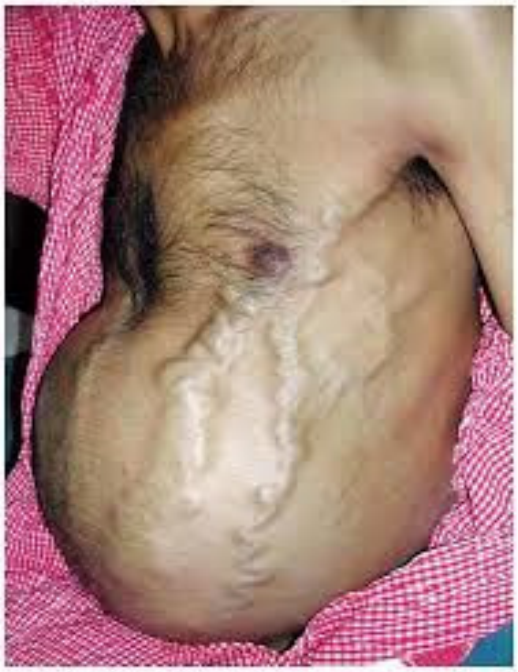


Fig. 24.6 Collateral Flank Circulation and Ascites

Fig. 24.7. Atrophy of the muscles of the limbs and abdomen relaxed by ascites fluid

Palpation of the liver will show, in the case of hypertrophic cirrhosis, a large liver with a sharp edge and increased consistency. Sometimes we can only palpate the right or left hepatic lobe. In the case of atrophic cirrhosis or if ascites is in copious quantities, the liver cannot be palpated and thus an important diagnostic element is lost.

The presence of ascites fluid achieves on palpation, in certain situations, the sign of the "ice ball", by palpation of the hard liver in the liquid, or the "wave sign" which suggests that the abdominal distension is through ascites fluid.

Splenomegaly from cirrhosis is almost a rule, so palpation of the spleen can be a diagnostic element for liver disease.

In front of an enlarged abdomen, **percussion** with the presence of fluid-type dullness raises the suspicion of peritoneal effusion (however, it is good to confirm this suspicion by ultrasonography, before a paracentesis).

A clinical examination revealing a patient with vascular stellates, subduction, or jaundice, with a firm hepatomegaly and splenomegaly, are particularly convincing arguments for the diagnosis of liver cirrhosis.

Zieve syndrome occurs in alcoholics, but especially in alcoholic cirrhosis, being a rare manifestation. It is a special and complex clinical form, characterized by hyperlipemia and haemolytic anaemia. Fatty loading of the liver is mandatory, regardless of the type of liver disease. Clinically, fever, jaundice, abdominal pain and hepatomegaly appear.

In cirrhosis of the liver, damage to other organs and systems is also observed:

Digestive:

- Oesophageal varicose veins and/or fundal varicose veins (occur in half of patients with cirrhosis).

- Gastritis frequently occurs in cirrhosis, most commonly in the form of gastric vascular manifestations of portal hypertension (portal-hypertensive gastropathy): congestion, marbled, mosaic or watermelon appearance.

- Gastric or duodenal ulcers occur more frequently in liver cirrhosis, an explanation would be the appearance of gastrin metabolism disorders, as well as a reduction in mucosal resistance. In the event of an episode of UGH in a cirrhotic patient, the possibility of an ulcer should also be considered.

- Gallstones occur more frequently in cirrhosis (20% of men and 30% of women). In its pathogenesis, the decrease in the secretion of bile salts is discussed. It is most commonly asymptomatic and does not require surgery.

Extra digestive

- Nervous system: hepatic encephalopathy occurs through brain damage, as a result of a significant reduction in liver function; Peripheral neuropathy occurs in alcoholics. Other neurological manifestations that may occur are Babinski's sign, muscle stiffness, exaggeration of ROT.

- Osteo-articular system: osteoporosis and osteodystrophy.

- Cardio-vascular system: pericardial collections, hemodynamic changes such as hypotension, toxic (alcoholic) myocardiopathy may occur.

- Haematologically, multiple changes occur. Coagulation disorders - all coagulation factors are synthesized in the liver, except for factor VIII, which explains the existence of coagulopathies. Although classically cirrhosis was considered as a hypo coagulant status due to the deficiency of synthesis of coagulation factors, it should not be forgotten that the liver is also involved in the degradation of procoagulant factors, so in liver cirrhosis there can be a hyper coagulant status. Thrombocytopenia frequently occurs in liver cirrhosis, being caused by decreased platelet production due to reduced levels of thrombopoietin (TPO) but also by increased platelet sequestration at the splenic level. It can result in epistaxis, gingivorage, petesia or bruising. Platelet function disorders may also occur, with platelet aggregation disorders. Microcytic, hypochromic anaemia may also occur because of small and repeated bleeding or heavy bleeding from the rupture of oesophageal varices, or haemolytic anaemia in the case of hypersplenism.

- The pulmonary system can be involved in several ways. Pleural (hydro thoracic) collections occur in 10% of cirrhosis, most of them on the right, most frequently due to the presence of communication between the peritoneal and pleural cavities. Hepatopulmonary syndrome occurs due to increased plasma levels of vasodilators or

lack of destruction or inhibition of circulating vasoconstrictors. Clinically, platypnea (improvement of dyspnea in decubitus) and orthodeoxia (decrease in SPO2 in orthostatism with improvement in clinostatism) occur.

- The renal system, the most severe manifestation being Hepato-Renal Syndrome, discussed in the case of complications.

Paraclinical investigations

The paraclinical investigations necessary for the diagnosis of liver cirrhosis are biological tests, abdominal ultrasound, upper digestive endoscopy, morphological evaluation (laparoscopy or liver biopsy sometimes), elastographic evaluation.

The biological picture of liver cirrhosis is usually intensely altered. Thus, changes occur in the four liver syndromes:

• *inflammatory syndrome*, with moderate or marked increase in gamma globulins (over 28-30% in active cirrhosis) and polyclonal immunoglobulins (but especially IgG in primary biliary cirrhosis or IgA in alcoholic cirrhosis).

• *hepatocytolytic syndrome*, translated by increased transaminases (GOT, GPT), but at lower values in cirrhosis than in chronic hepatitis, due to reduced cell reserve. There are quite frequently cirrhosis patients with normal or quasi-normal transaminases.

• *Hepatopriv syndrome* is obviously altered in cirrhosis, due to hepatocellular insufficiency. A decrease in the Quick index (IQ) occurs with prolongation of prothrombin time, an increase in urinary urobilinogen, a decrease in albuminemia (through decreased hepatic synthesis) and a decrease in cholinesterase (the latter investigation can often differentiate a chronic hepatitis from a cirrhosis, since in hepatitis cholinesterase has normal values).

• *bilioexcretory syndrome,* with increased total bilirubin, also alkaline phosphatase and gamma-glutamyl-transpeptidase when cholestasis is present.

The biological picture may include thrombocytopenia, as well as anaemia and leukopenia, in case of *hypersplenism*.

Apart from the altered liver picture, it is necessary to look for biological parameters that allow the etiological classification of liver cirrhosis. Thus, the following parameters will be evaluated:

• for viral aetiology: Ac anti HCV, Ag HBs, and if they are positive, Ac anti HDV (delta).

• For the aetiology of alcohol, the anamnesis is useful, knowing that the toxic dose in men is at least 60-70 ml of absolute alcohol daily, for a period of over 10 years, and in women the toxic dose is over 30-40 ml of absolute alcohol/day. The difficulty of the anamnesis for alcoholism is known, and its biological markers are insufficient (increased gamma glutamyl-transpeptidase being indicative for increased alcohol consumption in the last weeks).

• for Wilson's disease, the dosage of ceruloplasmin reveals low values, cupremia and copruria are increased.

• for hemochromatosis, along with possible pancreatic (diabetes) and/or cardiac damage, there will be increased sideremia, increased serum ferritin (over 200 ng/ml) and increased transferrin saturation coefficient (over 50%).

• for primary biliary cirrhosis, cholestasis enzymes (gamma glutamyl-transpeptidase, alkaline phosphatase, bilirubin) will be dosed, along with antimitochondrial antibodies (AMAs).

• in cardiac cirrhosis and Budd-Chiari syndrome, the diagnostic element is the underlying cardiovascular disease.

• in cirrhosis due to alpha-1 antitrypsin deficiency, its dosage shows low or absent values, pulmonary involvement is also present.

• in cirrhosis that occurs after autoimmune hepatitis, we will find high values of gamma globulins, as well as specific autoantibodies: ANA, Ac antiSMA and anti LKM 1.

Ultrasound diagnosis of cirrhosis is simple in advanced forms. Ultrasound will evaluate: ascites, as well as its approximate volume, spleen dimensions, the existence of liver heterogeneity (as an expression of cryogenic rearrangement) and irregular liver surface (Fig. 24.8), caudate lobe hypertrophy (relatively typical for cirrhosis) (Fig. 24.9), thickening and doubling of the gallbladder wall(by hypoalbuminemia, portal hypertension and lymphatic stasis), as well as ultrasound signs of portal hypertension (widening of the splenoportal axis, collateral circulation).

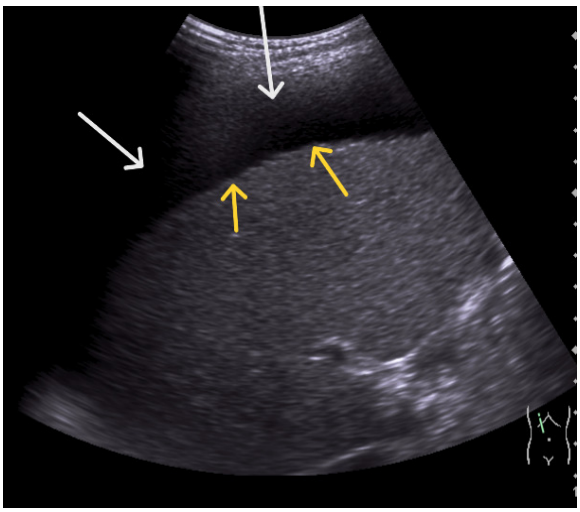


Fig. 24.8. Cirrhosis of the liver - Inhomogeneous liver structure, ascites fluid (white arrows), irregular liver surface (yellow arrows)

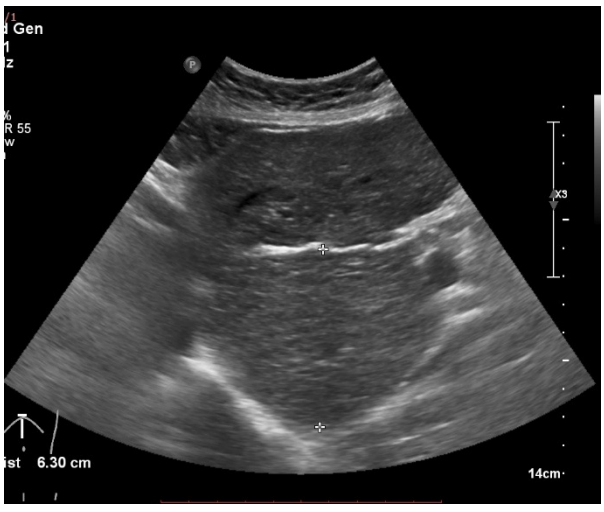


Fig. 24.9. Cirrhosis of the liver - Inhomogeneous liver structure, enlarged caudate lobe (between markers, anteroposterior diameter 6.3 cm)

Endoscopic diagnosis includes upper digestive endoscopy (gastroscopy), which evaluates the presence of significant portal hypertension by highlighting oesophageal varices or portal hypertensive gastropathy. The presence *of oesophageal varices* is a major sign of portal hypertension and, in the absence of other rare causes (portal thrombosis, thrombosis of the suprahepatic veins – Budd-Chiari syndrome, Schistosomiasis), it is a sign of liver cirrhosis.

There are several endoscopic classifications of oesophageal varices, but the easiest seems to be that of the Japanese Society of Endoscopy, in 3 degrees:

- oesophageal varices first degree: small varicose veins that disappear with insufflation with the endoscope.
- oesophageal varices grade II: varicose veins that do not disappear with endoscope insufflation.
- Grade III oesophageal varices: large varicose veins that partially obstruct the oesophageal lumen (Fig. 24.10).

It should be noted that there are also *fundal varices* (diagnosable by retrospective visualization), *esogastric varices* and, more rarely, duodenal varices.

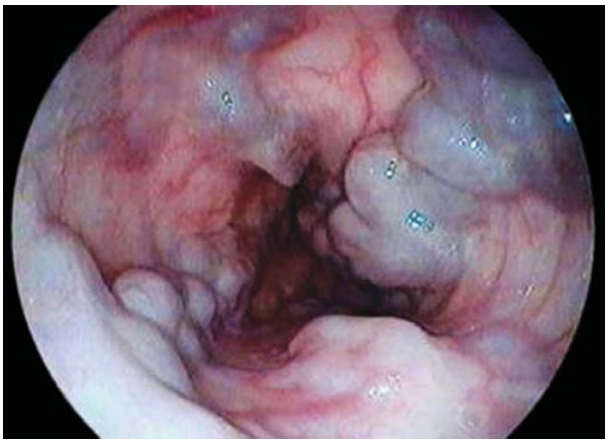


Fig. 24.10. Large oesophageal varices

Hypertensive portal gastropathy translates into antral changes, determined by portal hypertension, and which can have the appearance of "watermelon", mosaic, or diffuse bleeding. Mild forms and severe forms are described. The mild form appears in three endoscopic aspects: mosaic appearance ("snakeskin" type) (Fig. 24.11), hyperaemic appearance (striped type) and scarlet rash appearance. The severe form presents in two aspects: diffuse haemorrhagic spots and diffuse gastric bleeding. The location of the lesions can be in any region of the stomach.

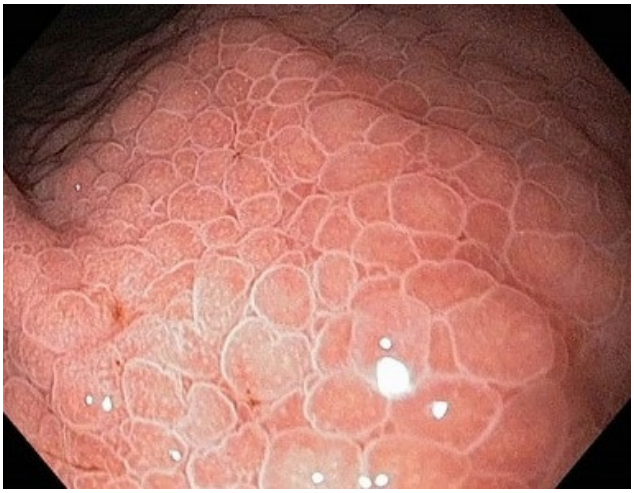


Fig. 24.11. Portal gastropathy in "snakeskin"

The morphological diagnosis of cirrhosis is necessary only in certain situations, namely in the early forms of cirrhosis, when typical clinical signs are missing. The presence of typical clinical signs of cirrhosis, cryogenic ascites or oesophageal varices on endoscopy make the diagnosis of cirrhosis and no longer require a morphological examination. In other cases, in which there is only clinical or biological suspicion of liver cirrhosis, two morphological explorations can be performed:

- *diagnostic laparoscopy*, which, by visualizing the hepatic surface, allows the assessment of regenerative nodules and thus macroscopically establishes the diagnosis of liver cirrhosis.
- *liver biopsy* that highlights the process of fibrous liver rearrangement on the histological fragment obtained by biopsy. The microscopic appearance of the cirrhotic liver is one of distortion of the normal lobular architecture by fibrous scars. Cell necrosis may be present especially near fibrous scars, and the inflammatory process may be absent. The fatty load of hepatocytes is present especially in alcoholic cirrhosis or those secondary to hepatic steatosis associated with metabolic dysfunction.

In general, in the face of a suspicion of compensated cirrhosis, we prefer diagnostic laparoscopy, because it easily and quickly appreciates the liver surface (the blind liver biopsy can "escape" the histological diagnosis of cirrhosis in about 10-20% of cases, due to the small size of the fragment, which cannot highlight the liver regenerative nodules). Liver biopsy puncture can be performed percutaneously (with ultrasound assistance or guidance) or transjugular (preferably when there is a risk of bleeding – altered coagulation, thrombocytopenia).

Elastographic diagnosis. The evaluation of liver fibrosis is currently done in most cases *by elastographic methods* using ultrasound. The oldest method (and recommended by most international guidelines) is *Impulse Elastography (FibroScan).* The method

evaluates the deformation of liver tissue caused by a mechanical impulse, by ultrasonographic measurement of the speed of the shear waves induced in the liver by this impulse (like the waves determined on the surface of a lake by the throwing of a stone). By mathematically transforming these velocities into the elastic mode, an estimate of the hepatic hardness (elasticity) expressed in kPa (kiloPascal) is obtained. The method has a sensitivity and specificity of about 95% for the diagnosis of liver cirrhosis. The evaluation cannot be done in the presence of perihepatic ascites. The values of liver hardness in cirrhosis are between 14 and 75 kPa, and with the increase in values, the risk of cirrhosis complications also increases. There are other elastographic methods that can also be performed in the presence of ascites (pSWE- point Shear Wave Elastography, 2D-SWE - 2D Shear Wave Elastography) (see the diagnosis of chronic hepatitis). Elastography is also used for the non-invasive prediction of clinically significant portal hypertension (see below).

Diagnosis of portal hypertension. Hepato-portal pressure gradient (HVPG) *measurement* is considered the "gold standard" for HTP assessment. It is an invasive test that measures the pressure difference between the hepatic vein and the portal vein.

Interpretation of HVPG:

- HVPG ≤ 5 mmHg is considered normal (without HTP)
- HVPG 6-9 mmHg suggests mild portal hypertension, usually without oesophageal varices.
- HVPG ≥ 10 mmHg indicates significant portal hypertension (PHSC), which is associated with risk of complications such as the formation of oesophageal varices and ascites.
- HVPG ≥ 12 mmHg is associated with an increased risk of variceal bleeding.

The severity of PH can also be assessed non-invasively, *with the help of impulse elastography (FibroScan) in association with platelet count* (Baveno VI consensus). Thus, if the liver hardness value at FibroScan is below 20 kPa and the number of platelets above 150,000/mm3, the presence of large oesophageal varices and therefore PHSC can be excluded, so these patients no longer need to undergo endoscopy to exclude oesophageal varices. In patients with liver hardness above 20-25 kPa and platelets below 100,000/mm3 there is a high probability of CSPH and large varicose veins, so beta-blocker treatment for variceal haemorrhage prophylaxis could be started without a confirmatory endoscopy. Patients with liver hardness between 15 and 20-25 kPa and platelets between 100-150,000/mm3 are in the gray zone and should be evaluated endoscopically.

Evolution of cirrhosis of the liver

The evolution of liver cirrhosis is long, with initially a ***compensated*** phase (without ascites or jaundice, a situation in which cirrhosis is often discovered by chance, at surgery or necropsy) and then the ***vascular*** decompensation phase (ascites, edema) or ***parenchymal*** decompensation (jaundice).

In compensated cirrhosis, the clinical picture may be totally asymptomatic or with minor clinical signs (asthenia, decreased appetite, gas dyspepsia, palmar erythema). Biological samples can be almost unchanged. With the progression of the disease, the clinical and biological picture become increasingly altered.

Hepatic functional reserve in cirrhotic patients can be assessed based on several prognostic scores.

a) One of the oldest is *the Child-Pugh classification,* (Table 24.I) which uses the following elements: albuminemia, ascites, bilirubin, Quick index, and encephalopathy (simple quantifiable parameters). The way of fitting into this score is done by summing the various parameters according to table 24.I.

Table 24.I Child-Pugh classification of liver cirrhosis

Parameter	1 point	2 points	3 points
Serum albumin (g%)	>3.5	2,8-3,5	<2.8
Ascites	Absent	moderate	severe
Encephalopathy	Absent	Lightweight (gr. I, II)	Severe (gr. III, IV)
Bilirubin (mg%)	< 2	2-3	> 3
Quick Index	> 70%	40-70%	< 40%

Child-Pugh grades fall as follows: Child A: 5-6 points.
Child B: 7-9 points; Child C: 10-15 points.

The Child Pugh class is a prognostic index for survival, the higher the number of points, the more advanced the cirrhosis and the worse the prognosis. The criticism of this classification is that it does not consider the presence and degree of oesophageal varices, which have a major influence on the prognosis of liver cirrhosis, nor on renal involvement, the occurrence of nitrogen retention being a major factor of poor prognosis.

b) The MELD (Model for End-Stage Liver Disease) score is a classification system used to assess the severity of liver failure in patients with cirrhosis and to prioritize the allocation of organs for liver transplantation. Initially developed for patients undergoing intrahepatic transjugular portosystemic anastomosis (TIPS), MELD has become standard in stratifying the risk of mortality at 3 months.

The MELD score is calculated by a mathematical formula that includes three essential biochemical parameters: Serum bilirubin (mg/dL) – reflects the excretion function of the liver; Serum creatinine (mg/dL) – evaluates kidney function; INR (International Normalized Ratio) – indicates the severity of synthetic liver dysfunction. The formula is available on the internet for the automatic, quick calculation of the MELD score. It ranges from 6 to 40, where higher values indicate severe liver failure and an increased risk of mortality at 3 months.

Interpretation of the MELD score:

- MELD <10 → Low risk of mortality.
- MELD 10-19 → Moderate risk
- MELD 20-29 → Increased risk
- MELD 30-40 → Very high mortality without transplantation

The MELD score is used for: selection of patients for liver transplantation (patients with high scores having priority for transplantation); for prognostic assessment, helping to establish therapeutic strategies; treatment guidance (assessment of the need for admission to intensive care units, prioritization on the transplant list.

c) the MELD-Na score is an adaptation of the MELD score, which also includes the value of serum sodium, in addition to the other components, starting from the idea that hyponatremia is an extremely poor prognostic factor when it occurs in patients with liver failure. The higher the MELD-Na score, the more severe the liver failure, the higher the mortality at 3 months and the greater the need for transplantation.

d) The Baveno classification of cirrhosis of the liver has begun to be used in recent years, starting from the role of portal hypertension as an essential factor in the progression of cirrhosis from the compensated to the decompensated stage. It is used to stratify patients with chronic liver disease with severe fibrosis/cirrhosis based on the risk of portal hypertension and associated complications. This classification, as its name suggests, was developed at the Baveno conferences, which provide guidelines for the management of portal hypertension.

In this framework, the concept of Compensated Advanced Chronic Liver Disease (cACLD) was defined, which includes patients with severe liver fibrosis/cirrhosis (F3-F4 at biopsy), but in whom, despite extensive fibrosis, there are no signs of liver failure. However, these patients are at risk of developing Clinically Significant Portal Hypertension (CSPH), associated with the appearance of oesophageal varices with a risk of bleeding. The risk of developing PHSC can be assessed invasively (by measuring the porto-cav gradient - HVPG) or non-invasive (by combining the liver hardness values assessed by elastography - FibroScan, with the platelet value). Decompensation is defined by the occurrence of one or more of the following events: variceal haemorrhage, ascites, jaundice, encephalopathy.

Stages of Baveno classification

The Baveno classification divides patients with cirrhosis of the liver into six functional stages (Fig.24.12) as follows:

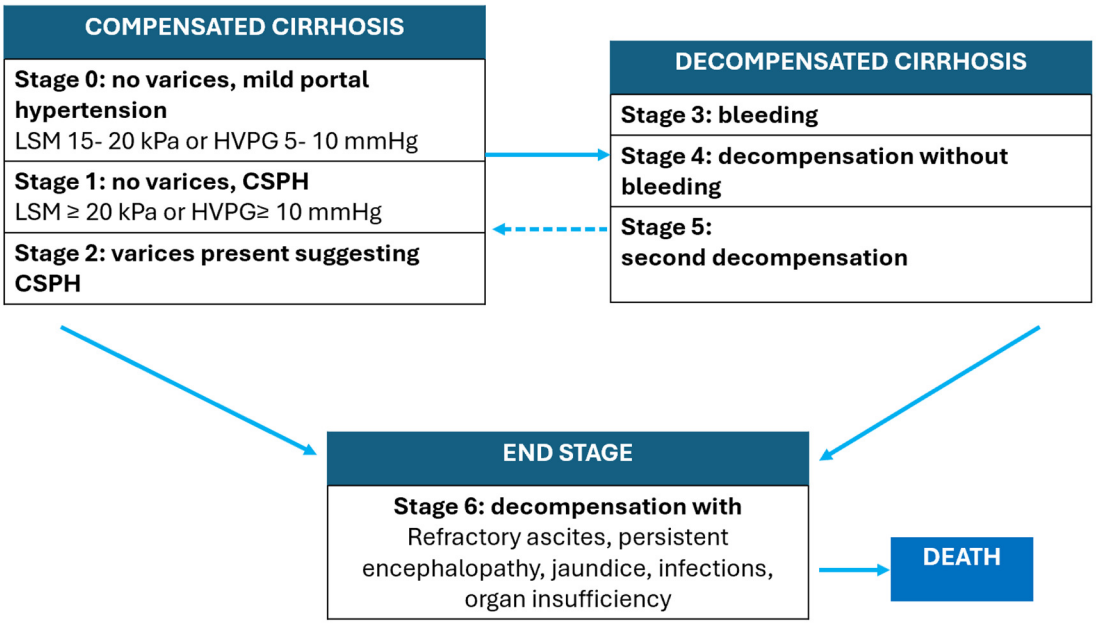


Fig. 24.12 Baveno classification of cirrhosis of the liver

Compensated cirrhosis

Stage 0 - no varicose veins, mild portal hypertension (FS 15 - 20 kPa or HVPG 5 -10 mmHg)

Stage I – no varicose veins, CSPH (FS ≥20 kPa and/or HVPG ≥10 mmHg).

Stage II – varicose veins present, suggestive of CSPH (clinically significant portal hypertension).

Decompensated cirrhosis

Stage III – variceal haemorrhage present or in history

Stage IV – decompensation without bleeding.

Stage V – second decompensation

Terminal cirrhosis

Stage VI - Decompensation with refractory ascites, persistent encephalopathy, jaundice, infections, organ failure

Using the Baveno classification. The Baveno classification is essential in guiding the treatment of patients with cirrhosis, helping to reduce complications and improve survival.

Screening and prevention of PH – Patients in stages 0 and I require periodic monitoring by elastography + platelets and/or upper digestive endoscopy.

Prophylaxis of variceal haemorrhage:

- Primary prophylaxis - Baveno II patients benefit from treatment with beta-blockers or, when they are contraindicated or not tolerated, variceal ligation.

- Secondary prophylaxis - after resolution of the haemorrhagic episode, Baveno III patients must undergo endoscopic ligation until the varicose veins disappear, associated with beta-blocker treatment.

Advanced disease management – Baveno V and VI patients require advanced interventions, such as TIPS or liver transplantation.

During the evolution of cirrhosis, episodes of exacerbation may occur, through an untimely consumption of alcohol or a new viral infection, in fact true acute hepatitis, which overlap with the already existing cirrhosis. Clinically, fever, jaundice, marked asthenia, loss of appetite, varying degrees of hepatic encephalopathy occur. Biologically, against the background of the usual picture, there are significant increases in transaminases and, sometimes, in cholestasis samples. Such an episode can lead to the precipitation of liver failure and the death of the patient.

Complications of liver cirrhosis

The complications of liver cirrhosis are numerous and will eventually lead to death. The main complications that can occur in a patient with cirrhosis are:

1. Upper Gastrointestinal Haemorrhage (UGH).
2. Hepatic encephalopathy.
3. Ascites (vascular decompensation).
4. Spontaneous bacterial peritonitis (SBP).
5. Hepatocarcinoma.
6. Hepatorenal syndrome.
7. Hepatopulmonary syndrome.

1. Upper Gastrointestinal Haemorrhage (UGH)

UGH is most commonly given to cirrhotic patients with *rupture of oesophageal varices*. This complication occurs in the presence of large varicose veins (grade II or III) frequently associated with specific endoscopic signs (cherry red spots) as an expression of severe portal hypertension. Variceal rupture is caused by a sudden increase in portal hypertension: related to lifting or defecation, sneezing, coughing, rapid increase in ascites, but it can also occur after eating hot food.

Other predictors of haemorrhage are skin collateral circulation, the presence of ascites, profound alteration of coagulation and red marks on the variceal wall ("cherry red spots").

Other times UGH can be generated by *the rupture of the fundal varices* (sometimes, after ligation of oesophageal varices, portal hypertension leads to the

appearance of fundal varices) or from *hypertensive portal gastropathy,* when bleeding is diffuse.

The evaluation of the patient with liver cirrhosis for the presence of oesophageal varices will be done endoscopically, and the re-evaluation endoscopy will be done every 2 years. An alternative for risk stratification is the annual use of elastography in combination with platelet counts (see above, Baveno consensus). The absence or presence of varicose veins of the first degree at the first examination will make the re-examination continue annually.

Grade II and III varicose veins benefit from beta-blocker treatment (preferably Carvedilol 2 x 6.25 mg/day) for primary bleeding prophylaxis and do not require endoscopic surveillance.

UGH due to variceal rupture is one of the leading causes of death in cirrhosis, and it is estimated that one year after the first haemorrhage, about 30% of patients with cirrhosis will die.

UGH *therapy for oesophageal variceal rupture comprises* several stages:

- patient balancing: it is done by treating haemorrhagic shock with blood or plasma expanders (hydroelectrolyte rebalancing). The Hb value will remain around 8 g%. A volume overload from excessive transfusions increases the risk of rebleeding.
- Arterial vasoconstrictor medication – is administered to lower pressure in oesophageal varices (*vasopressin or terlipressin* is administered as an IV infusion, usually in bolus, followed by continuous infusion for 48-72 hours). The effectiveness of vasoactives has been shown to be similar in studies, but only with terlipressin has a decrease in mortality in patients with variceal UGH been demonstrated.
- Endoscopic treatment of ruptured oesophageal varices involves *elastic ligation with rubber rings* (therapy of choice) or endoscopic *sclerotherapy* (a sclerosing solution - ethoxysclerol, hystoacryl, etc.) will be injected with the sclerotherapy needle, through the endoscope canal. First, the bleeding variceal group will be treated, then other variceal groups will be treated (between 5 and 10 rings/session). The ligation sessions are repeated every 2-4 weeks, until the varicose veins are completely eradicated.
- if endoscopic haemostasis cannot be performed and the bleeding is massive, compression haemostasis with *the Sengstaken-Blackmore balloon probe can be used*. With this method, haemostasis can be achieved in 70 – 80% of cases, but the rebleeding rate after removing the balloon is 50%. The Blackmore tube should not be left in place for more than 24 hours because it increases the risk of esophageal necrosis. It can be a temporary alternative (bridging) until access to a digestive endoscopy service.
- If the patient with variceal UGH also has ascites, prophylactic antibiotic treatment (with cefotaxime) is recommended to prevent the risk of developing spontaneous bacterial peritonitis.

The treatment of torn fundal varicose veins is more difficult, as it lends itself more difficult to sclerotherapy or elastic ligation. In addition to rebalancing (like that of UGH through oesophageal varices), haemostasis is performed by injecting a histoacryl (or ethoxysclerol) type sclerosing substance through the endoscope located in the rear.

The prophylaxis of rupture of oesophageal and/or gastric varicose veins is done in patients with varicose veins of the second and third degree who have never bled (primary prophylaxis), as well as in those who have already had a haemorrhagic episode (secondary prophylaxis). It consists of the administration of beta-blockers, which decrease venous return - Carvedilol (2x6.25 mg/day) or Propranolol 40-120 mg/day (the dose that decreases the resting heart rate by >25%). In patients in whom beta-blockers are contraindicated (hypotensive, atrioventricular block, asthmatics), prophylactic ligation of varicose veins is performed.

In patients who have already had an episode of UGH due to the rupture of varicose veins, several elastic ligation sessions (or endoscopic sclerotherapy) will be performed, until the oesophageal varices are completely eradicated.

In the case of fundal varicose veins, if repetitive ligations fail to eradicate varicose veins and there are repetitive haemorrhages, as well as in case of refractory ascites, decompression of portal hypertension can be resorted to by *special techniques*:

a. *TIPS* (trans-jugular intra-hepatic portosystemic shunt) is a minimally invasive interventional procedure used to reduce portal hypertension in patients with cirrhosis of the liver and severe complications. The main indications of TIPS are:

- Acute variceal haemorrhage refractory to endoscopic and pharmacological treatment.
- Secondary prophylaxis of variceal haemorrhage in patients at elevated risk of rebleeding.
- Refractory ascites that does not respond to repeated diuretics and paracentesis.
- Hepatorenal syndrome in selected cases.

The TIPS procedure consists of accessing the internal jugular vein, through which a catheter is inserted through the venous system to one of the hepatic veins, after which an expandable metal stent is inserted that will create an artificial channel (a shunt) between the portal vein and the hepatic vein, which will reduce portal pressure, preventing complications of portal hypertension.

The main complications and contraindications of TIPS are hepatic encephalopathy (may be precipitated or aggravated due to redirection of blood from the portal circulation); liver failure in patients with advanced cirrhosis (MELD > 18-20). The absolute contraindications of TIPS are severe heart failure or active sepsis.

TIPS is an effective solution for the control of portal hypertension and the prevention of severe complications, but it requires careful patient selection and rigorous post-procedural monitoring.

b. *Surgical anastomoses* (porto-cav or spleno-renal shunt) are almost not used at all, being extremely invasive procedures.

It should be noted that up to a third of UGH in cirrhosis can be generated by bleeding from a *haemorrhagic gastroduodenal ulcer*. Therefore, in front of any UGH, an emergency endoscopy is required, which highlights the cause of the bleeding and, at the same time, allows endoscopic haemostasis (elastic ligation or variceal sclerotherapy, respectively endoscopic haemostasis of the ulcer).

In haemorrhagic ulcers, endoscopic haemostasis is performed by one or more of the following techniques: injection of 1/10,000 adrenaline solution (never used alone); thermal haemostasis with bipolar probes; endoscopic placement of a hemoclip on the bleeding source. Endoscopic therapy was associated with injectable antisecretory proton pump blocker medication (esomeprazole, omeprazole, pantoprazole).

In case of failure of endoscopic therapy (in approx. 3% of haemorrhagic ulcers), radiological embolization for haemostatic purposes can be attempted. Surgery is addressed only to cases in which these means have not achieved haemostasis, given the increased operative risk in the patient with cirrhosis (increased intraoperative bleeding, postoperative appearance of liver failure).

In *portal hypertensive gastropathy,* treatment associates endoscopic haemostasis with argon-beamer (APC – argon plasma coagulation) and decreasing portal hypertension with beta-blockers.

2. ***Hepatic encephalopathy (HE)***

HE is a neuropsychiatric syndrome that occurs in cirrhosis patients.

Clinically, behavioural disorders occur that can range from alteration of the sleep-wake rhythm to agitation or slowness, to drowsiness with difficulty in answering questions, intellectual disorders with difficulty in performing simple arithmetic operations, and finally a more superficial or deeper coma may occur.

Objectively, neurological signs appear such as "flapping tremor" (asterix) - the major neurological sign, characterized by movements of the upper limbs with high amplitude, with low frequency, asymmetrical, spontaneous, or provoked.

The etiopathogenesis of HE is complex, incriminating several triggering factors:

- hyperammonemia – ammonia generated in the intestine by ammonia-forming flora, starting from a protein substrate; ammonia formed in the stomach under the influence of ureasis secreted by Helicobacter Pylori. This ammonia easily enters the systemic circulation through the porto-systemic shunts; the blood-brain barrier is permeable, and ammonia has a neurotoxic action.
- increase in false neurotransmitters (tyramine, octopamine) and decrease in the synthesis of true neurotransmitters (dopamine, norepinephrine).

- increase in the serum concentration of aromatic amino acids - (tryptophan, tyrosine, phenylalanine).
- decrease in the concentration of branched-chain amino acids (leucine, isoleucine, valine).

The precipitating causes of HE are multiple: high-protein diet; UGH (by proteins in the blood reaching the intestine, and by the associated hypoxia that induces cytolysis); administration of sedatives or hypnotics; various infections (especially spontaneous bacterial peritonitis); acute over added hepatitis (alcoholic or viral); post-diuretic hydroelectrolyte imbalances; Constipation; Surgery.

HE staging is done in four stages:

- stage I - apathetic, confused patient, loss of ability to concentrate, alteration of sleep-wake rhythm.
- stage II - drowsy, confused patient, difficult to answer questions.
- stage III - marked drowsiness, temporo-spatial disorientation, response only to strong stimuli.
- stage IV - coma, lack of response to stimuli.

Psychometric tests or graphic tests can highlight latent phenomena of HD, which are particularly important in people with cirrhosis of the liver in the workplace.

HE treatment has several components:

- The search for and treatment of the precipitating causes described above (hyperprotein diet, UGH, constipation, electrolyte imbalances due to diuretics, infections) are essential for the treatment of HD.
- The diet will be normoprotein in cirrhotic patients (1.3-1.5 g protein/kg body weight). In the past, it was considered that with the onset of HD, the hypoprotein diet is indicated, considering that the ammonia resulting from protein metabolism has an enteropathogenic role in the appearance of HD. However, a low-protein diet has not proven its benefits for survival, given that malnutrition and sarcopenia are often present and ignored in the cirrhotic patient. The diet should provide 30-45 kcal/kg body weight, and proteins should be easily absorbed (preferably coming from egg whites, dairy products, vegetable proteins, white meat, fish, seafood). Proteins in red meat are more harmful than those in dairy products, the best tolerated being proteins of vegetable origin (they contain a lower amount of methionine and aromatic amino acids).
- Obtaining a regular intestinal transit will ensure the intestinal reabsorption of a smaller amount of ammonia. For this, ***lactulose*** (osmotic purgative, non-absorbable, which acidifies the intestinal environment) is used, at a dose of 30-60 g/day. Enemas (with or without lactulose) can be used in emergency situations, emptying the colon contents.
- Inhibition of the activity of the ammonioforming flora is done by administering ***rifaximin (Normix)*** 3 x 400 mg/day. Rifaximin is a non-absorbable antibiotic.

3. Ascites (vascular decompensation)

Ascites is a common complication in the evolution of liver cirrhosis. It is due to hypoalbuminemia, portal hypertension, and lymphatic stasis. The diagnosis of ascites is clinically suspected (distended abdomen, sign of the "wave" present), but it is confirmed by ultrasound. Ultrasound also allows the semi-quantitative assessment of the volume of ascites.

Exploratory paracentesis is recommended to be performed in all patients with de novo ascites. It allows the evaluation of ascites and the determination *of proteins in the ascites fluid* with the classification of transuded (proteins < 3 g/dL) or exudate (proteins > 3 g/dL). In the cirrhotic patient, ascites is usually transuded. It is also recommended to determine *the serum to ascites albumin gradient (SAAG).* SAAG > 1.1 g/dL is found in cirrhotic ascites and cardiac ascites, and SAAG < 1.1 g/dL in tuberculous or carcinomatous ascites. Also on this occasion, it is mandatory *to count the elements in the fluid* (leukocytes, PMN, erythrocytes), and the fluid can be seeded to discover a possible spontaneous bacterial peritonitis (SBP). It should be noted that, due to the high opsonization index, sometimes even in infected ascites, the culture is sterile; therefore, the PMN/ml or leukocyte count/ml is particularly useful.

Thus, a number of more than 250 polymorphonuclears/ml or more than 500 leukocytes/ml is diagnosed for fluid infection, even in the absence of a positive culture.

In a patient without ascites initially, periodic weighing and/or measurement of the abdominal circumference is recommended, and in the case of weight gain or increase in the circumference of the abdomen, an abdominal ultrasound should be indicated to confirm ascites.

Therapy of ascitic syndrome will include the following measures:

a) Hygiene and dietetics:

- prolonged bed rest (not absolute) – it is recommended that the patient, in addition to sleeping at night, lie in bed, or in a semi-sitting position, two more times during the day, for 1-2 hours or more.

- *low-sodium diet*. A salt restriction to 5-6.5 g/day is recommended (basically the patient is told not to add salt to cooking). The patient's attention should be drawn to foods that contain salt in a "masked" way: mineral water, canned food, instant soups, spices such as Maggi, Vegeta, etc. Looking at bread without salt, it can be recommended in cases with high ascites. "Sodium-free salt" should also be avoided because it can cause hydro-electrolyte imbalances and precipitate hepatic encephalopathy, being a mixture of potassium chloride, ammonium chloride, calcium chloride.

b) Medicines:

Diuretic therapy is usually associated with diet:

- Spironolactone, a potassium-sparing anti-aldosteronic diuretic, is the basic drug in the treatment of cirrhotic ascites, which is administered in doses of 50-400 mg/day (the average dose is 100-200 mg/day). Spironolactone is administered daily, the effect appearing 2-3 days after administration, being weak. Do not administer in case of hyperkalaemia or renal impairment (creatinine above 2 mg%). After prolonged administration, gynecomastia may occur.

- Furosemide, a potent loop diuretic, acts quickly and is usually associated with potassium-sparing diuretics. The daily dose is 40-160 mg/day (1-4 tb/day), generally one or two tablets are sufficient. In other cases, spironolactone is given daily, and furosemide every two days.

To monitor the effectiveness of the diuretic treatment, daily diuresis (which must be at least 1500 ml to be effective), body weight will be followed. The aim is to achieve a weight loss of 500 g/day (if the patient has only ascites) or a maximum of 1000 g/day if the patient also has edema and ascites. During hospitalization, it is recommended to dose urinary sodium and potassium every two days. Thus, a daily sodium elimination (natriuresis) of more than 100 mEq is a good omen, especially with a reduced potassium elimination (less than half of the sodium eliminated). The dose of the diuretic may be adjusted according to the volume of ascites, daily diuresis, and daily weight loss.

c) Paracentesis

An alternative to diuretic therapy is therapeutic *paracentesis*. It is generally addressed to cases with high ascites, in tension (where, for the "drying" of the patient, it would take a long time) or with ascites refractory to therapy (diuresis below 1000 ml/day despite a maximum diuretic therapy – 400 mg Spironolactone + 160 mg Furosemide daily) or in patients who do not tolerate maximum doses of diuretic (hypotension, dyselectrolitemia).

According to international guidelines, therapeutic paracentesis consists of the complete evacuation of ascites through paracentesis in a single session. To avoid hypovolaemia, with hypotension and renal ischemia, which may occur after massive paracentesis, it is recommended to administer human albumin at once (8 g per Liter of evacuated ascites). If albumin is not available, the volume of ascites extracted should not exceed 5 l and a plasma expander (Dextran type 70 - 500 ml) should be administered.

d) TIPS (trans-jugular intra-hepatic porto-systemic shunt)

TIPS, described above, is recommended in refractory ascites (which, at maximum doses of 400 mg spironolactone/day + furosemide 160 mg/day, ascites cannot be eliminated), or in patients who do not tolerate maximum doses of diuretic (untreatable ascites). TIPS can also be performed in patients who develop hydrothorax in the context of cirrhosis (much more difficult to treat than ascites).

The algorithm for treating ascites in the cirrhotic patient is as follows:

- The first measure is to restrict salt to 5-6.5 g NaCl/day (no salt is added to cooking) – it may be sufficient in patients with low ascites.
- In patients with moderate ascites, concomitant with the low-sodium diet, Spironolactone should be started at a dose of 100 mg/day, titrated up to 400 mg/day if necessary.
- If the response is inadequate, start taking Furosemide at 40 mg/day, which can be titrated up to 160 mg/day.
- Throughout the diuretic treatment, body weight should be monitored (the goal is weight loss 500 g/day, or 1000 g/day if the patient also has edema), diuresis (to be effective it must be at least 1500 ml/24 hours), natriuresis and possible adverse effects (hypotension, dyselectrolitemia, nitrogen retention)
- After obtaining the therapeutic response, the doses of the diuretic can be reduced, maintaining the minimum dose that keeps the patient without ascites or with low ascites.
- In large ascites, in blood pressure, or in patients with refractory ascites or in those intolerant to high doses of diuretic, large-volume evacuator paracentesis, in which an attempt is made to remove the entire volume of ascites, with the administration of human albumin at a dose of 8g albumin/Liter of extracted ascites.
- TIPS is reserved for refractory ascites and untreatable ascites.

4. Spontaneous bacterial peritonitis (SBP)

SBP is found in up to 10% of hospitalized cirrhosis. Undiagnosed and not treated promptly, it has a mortality rate of 90%. Also, the one-year survival of such a patient is around 30%. SBP is defined as infection of ascites fluid outside of a surgically treatable condition (such as appendicitis, cholecystitis, etc.) and an invasive manoeuvre (such as exploratory paracentesis). SBP is produced by translocation of germs through the intestinal wall, most commonly involving E. coli, Klebsiella. Patients with protein in ascites fluid below 1.5 g/dL are thought to have an increased risk of developing SBP.

The clinical picture is not noisy, most frequently being the appearance of unexplained encephalopathy, altered general condition, possibly abdominal discomfort, subfebrilities, alteration of diuresis and renal function or sudden worsening of the evolution of the disease. Less often, fever and chills may occur, but sometimes clinical signs are completely absent, especially in dragged people.

The diagnosis is made on the increased number of leukocytes (> 500/ml) or over 250 polymorphonuclears/ml in the ascites fluid or by positive culture. Very often the culture of ascites is negative, the diagnosis being based on the increase of cellularity.

Treatment begins as soon as possible after diagnosis with empirical antibiotic therapy. Third-generation *injectable cephalosporins are preferred*: cefotaxime 2 g every

6-8 hours or ceftriaxone 1 g every 12 hours i.v. After 48 hours from the start of therapy, a diagnostic paracentesis is performed. If there is no therapeutic response (decrease in the number of leukocytes, respectively PMN below the diagnostic limit), the treatment of carbapenems will be escalated. In cases with a positive culture of the ascites fluid, treatment will be conducted after the antibiogram. Therapy is for 7-14 days.

Human albumin at a dose of 1.5 g/kg on day 1, and 1 g/kg on day 3 after diagnosis, has been shown to be of real benefit in improving survival in patients with SBP, especially in patients with creatinine ≥ 1 mg/dL, in those with signs of severe hepatic impairment (bilirubin ≥ 5 mg/dL).

Despite proper treatment, mortality can reach 50%. In the first year after treating SBP, relapses may occur in up to half of the cases. Since relapse is related to low protein levels in the ascites fluid and the degree of hepatocellular insufficiency, in cases predisposed to reinfection, reinfection prophylaxis can be performed with norfloxacin 400 mg/day or ciprofloxacin 500 mg/day for a long time.

5. ***Hepatocellular carcinoma (HCC)***

Hepatocarcinoma is a common complication in cirrhotic patients, about one-third of cirrhotic patients will die from liver cancer. In turn, hepatic HCC occurs in 80-90% of cases against the background of liver cirrhosis. Viral cirrhosis B and C, as well as hemochromatosis, particularly favour the appearance of HCC.

HCC occurs in the process of liver regeneration, being a long-term liver disease. It is most commonly single centric HCC, but multicentric or diffuse forms are also described.

Considering that HCC is a common complication of LC, it is recommended that cirrhotic patients undergo a screening program (surveillance) so that HCC, if it occurs, is diagnosed at a therapeutically useful stage. The following categories of patients should be screened:

- Child Pugh class A and B liver cirrhosis regardless of aetiology (viral, alcoholic, autoimmune, hemochromatosis, CBP, MASLD).
- Liver cirrhosis class Child Pugh C, if the patient is included in the liver transplant list.
- Patients with severe hepatic impairment (F3), including that post-therapy with direct-acting antivirals, depending on the degree of risk.

The classic clinical picture includes weight loss, ascites that increases rapidly or becomes refractory to diuretics, fever or subfebrility, pain in the right hypochondrium. In contrast, there are completely asymptomatic cases, occasionally discovered during an ultrasound examination. The clinical examination reveals a hard, tumored liver (but in the case of small tumours these signs may be missing).

The diagnosis of HCC is made by two methods: serological by alpha-fetoprotein assay, and imaging (ultrasound, including contrast-CEUS ultrasound, computed tomography, and nuclear magnetic resonance with contrast substance).

- Alpha fetoprotein (AFP) (normal values: 10-20 ng/ml) has a sensitivity below 60-70%. Values above 200 ng/ml are considered pathognomonic for HCC in patients at risk. However, two-thirds of HCCs with dimensions below 4 cm may have AFP values below 200 ng/ml and about 20% of HCC do not produce AFP even if they are large.

- Ultrasonography performed by an experienced examiner with high-performance ultrasound equipment easily highlights lesions. Ultrasonography can detect lesions between 3 - 5 cm in a percentage of 85 - 95% (Fig. 24.13). Usually on a cirrhotic, inhomogeneous liver, a nodule with dimensions around 1 cm (hypo, hyper, isoechogenic or with mixed echogenicity) may be more difficult to highlight. Once highlighted, it will benefit from complementary explorations. The method has a sensitivity of 60-80% in detecting small lesions (between 1-2 cm). The use of contrast ultrasound (CEUS = contrast enhanced ultrasonography) with the help of second-generation contract agents - SonoVue increases the performance of ultrasound in the characterization of nodules discovered by ultrasonography and allows a correct diagnosis in approximately 80% of the nodules discovered on the cirrhotic liver (Fig. 24.14 and 24.15).

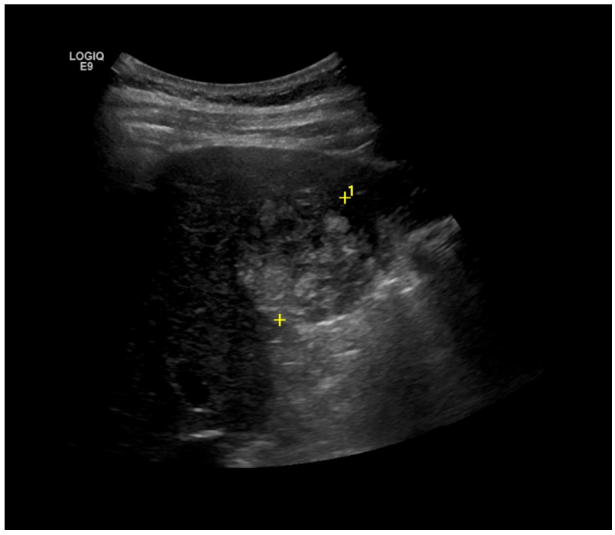


Fig. 24.13. HCC of approximately 4 cm in a known patient with cirrhosis of the liver

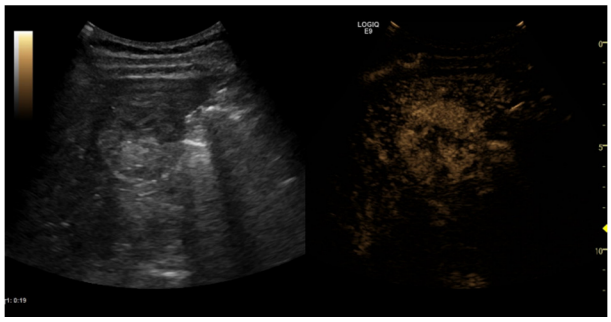


Fig. 24.14. Ultrasound with contrast substance. Arterial phase hyperuptake specific to HCC in the arterial phase.

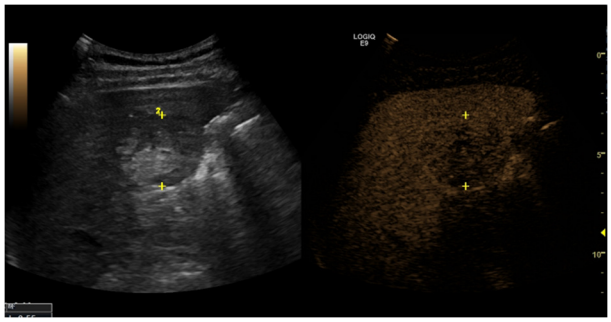


Fig. 24.15. Ultrasound with contrast substance. Late phase: slow wash-out specific for HCC

- Computed tomography and nuclear magnetic resonance imaging (MRI) performed with contrast are used as gold-standard methods for characterizing liver nodules.

- The biopsy of the nodule in the suspicion of HCC will be done only when the classic criteria (imaging +/- AFP) have not made the diagnosis. The ultrasound-guided biopsy (or guided CT) will be done with a fine needle (fine needle biopsy = FNA: needles with an external diameter of less than 1 mm) or it will be of the "core biopsy" type (needles with a diameter of more than 1 mm). In general, CEUS or CT or MRI with contrast clarify most lesions discovered on a cirrhotic liver.

In conclusion, for HCC screening in cirrhotic patients, ultrasound examination by an experienced sonographer with a high-performance ultrasound machine is recommended, at an optimal, but not ideal, interval of 6 months, accompanied by AFP determination. Any new nodule found on a cirrhotic liver should be considered HCC until proven otherwise. A lump found on ultrasound will be confirmed by one of the contrast imaging methods (CEUS, CT, or MRI), and the biopsy is reserved for cases that have remained unclear until this stage. A newer screening procedure that has come into use is abbreviated MRI, with very good performance but much more expensive than the classic strategy.

HCC Treatment

Once an HCC is diagnosed, it must be staging, considering size, metastasis, but also liver function. Thus, the Barcelona Classification is used to stratify patients for optimal treatment. Ideally, HCC treatment should be led by a multidisciplinary team that includes a hepatologist, a liver surgeon, an interventional radiologist, and an oncologist.

The first option, when possible, is *resection surgery* (if the liver functional reserve allows it) or *liver transplantation* (which resolves both cirrhosis and HCC). However, transplantation is reserved for small tumours, without signs of metastasis or vascular invasion.

If the HCC is inoperable (large tumours, patient with bilirubin over two, with oesophageal varices) transarterial *chemoembolization* (TACE) with doxorubicin and lipiodol (or gelspon) through the hepatic artery, on the vascular branch corresponding to the tumour (TACE) can be chosen.

In small tumours (less than 3-5 cm), *radiofrequency ablation (RFA) or microwave ablation can be performed.* Under ultrasound or CT guidance, a needle (electrode) is inserted into the tumour. After its correct placement, the radiofrequency current is started, respectively the microwaves, which will cause the heating and thermal destruction of the HCC. An older procedure was *ultrasound-guided percutaneous tumour alcoholization* (PEIT). Through this technique, an ultrasound-guided spinal needle is inserted into the tumour through which absolute alcohol is injected into the tumour, achieving its chemical destruction.

In cases where none of these techniques can be used (large, metastatic tumours or with portal thrombosis), *antiangiogenic therapy* or *immunotherapy, palliative therapies* are indicated.

6. Hepatorenal syndrome

Acute kidney injury (AKI) is one of the main negative predictors in cirrhotic patients. AKI has as diagnostic criteria an increase in serum creatinine by at least 0.3 mg/dL in 48 hours or by ≥ 50% in the last 7 days. In the cirrhotic patient AKI recognizes as the main causes, hypovolemia (can be induced by UGH, diarrhoea, abuse of diuretics, massive paracentesis), acute tubular necrosis (in severe infections, treatment with nephrotoxic drugs: aminoglycosides, non-steroidal anti-inflammatory drugs, iodinated contrast agents) and hepato-renal syndrome (SHR-AKI)

SHR-AKI is defined as functional renal impairment that occurs in a patient with advanced cirrhosis, ascites, and severe hepatic impairment, in the absence of signs of renal disease (proteinuria, haematuria). The main pathophysiological mechanism is splanchnic and systemic vasodilation that occurs as a result of hyperactivity of the sympathetic nervous system, disruption of the regulatory mechanisms of the renin-angiotensin-aldosterone systems, respectively vasopressin in the context of severe liver failure, which result in a decrease in effective blood volume and finally vasoconstriction and renal hypoperfusion. The result is renal ischemia, with reduced glomerular filtration.

For the diagnosis of SHR-AKI, the causes mentioned by AKI must be sought and treated, the persistence and worsening of nitrogen retention under the conditions of correct management and resolution of the causes of AKI being suggestive for diagnosis.

Treatment of AKI in the cirrhotic patient should be rapid and vigorous. Precipitating causes (infections, UGH) should be sought and treated. If hypovolemia is present, diuretic treatment should be suspended, and volume rebalancing should be performed using albumin and plasma expanders. For SHR-AKI, the combination of vasoactive medication (terlipressin or norepinephrine) in combination with albumin has been shown to be effective in approximately 50% of cases.

The only definitely effective therapy for SHR is liver transplantation.

7. Hepatopulmonary syndrome

Hepatopulmonary syndrome is a complication associated with advanced cirrhosis, being present in up to 30% of patients on transplant lists. The main pathophysiological mechanism is pulmonary capillary vasodilation which leads to poor oxygenation of the blood.

Symptoms of hepatopulmonary syndrome include dyspnea, which becomes more pronounced in orthostatism (orthodeoxy) and improves in clinostatism, associated peripheral cyanosis in advanced stages with Hippocratic fingers, and hypoxia. Patients often do not have obvious dyspnea; the diagnosis being suspected from hypoxia detected by pulse oximetry.

The only truly effective treatment is liver transplantation.

After reviewing the complications of liver cirrhosis and their therapy, we notice that this disease is marked by numerous complications, which makes the prognosis reserved. It is better in compensated cirrhosis, to become reserved in decompensated cirrhosis with oesophageal varices, HCC or SBP, complications that further obscure the prognosis of these patients.

Treatment of liver cirrhosis

The evolution of liver cirrhosis is progressive, and the structural disorganization is irreversible, so therapeutic measures can only cure the sick liver by replacing the diseased liver.

The objectives of the treatment are:

- Removal of the etiological agent (alcohol, virus).
- Stopping evolution.
- Maintaining the state of compensation and inactivity of cirrhosis.
- Prevention of decompensations and complications.
- Treatment of complications when they occur.

Thus, we can group the treatment of liver cirrhosis into five groups:

General measures (hygienic-dietetic) – applicable to all cirrhosis regardless of aetiology.

Rest is necessary in decompensated cirrhosis and in case of complications. Patients with compensated cirrhosis can carry out their activity normally, avoiding exaggerated efforts. Post-feeding rest in clinostatism may be indicated after the main meal.

The diet is quasi-normal in cirrhotic in terms of caloric intake, proteins, carbohydrates, lipids, but more dietally cooked. Highly restrictive diets are not recommended, especially in terms of protein intake, considering the risk of malnutrition and sarcopenia in these patients. Alcohol is prohibited in any form of cirrhosis.

The diet should provide 30-45 kcal/kg body weight, and proteins (1.3-1.5 g/kg body weight) should be easily absorbed (preferably coming from egg whites, dairy products, vegetable proteins, white meat, fish, seafood). Proteins in red meat are more harmful than those in dairy products, the best tolerated being proteins of vegetable origin (they contain a lower amount of methionine and aromatic amino acids).

Fluid consumption should not exceed 1.5–2 Liters/day.

Salt intake should be reduced to 5-6.5 g/day, as the first step of treatment in patients with ascites.

Etiological treatment. The treatment of liver cirrhosis can be etiological when we have a known cause:

In cirrhosis *of viral aetiology*, antiviral treatment can be administered (Entecavir, or Tenofovir in aetiology B and combination of drugs with direct antiviral action - DAA in viral aetiology C). In decompensated viral cirrhosis, PegInterferon cannot be used.

In *primary biliary cirrhosis* and in cholestatic forms of cirrhosis with other etiologies, treatment with ursodeoxycholic acid 10-15 mg/kg body weight should be administered.

In *autoimmune cirrhosis* – corticosteroid therapy and/or azathioprine (Imuran), if there are signs of activity and cirrhosis is compensated.

Pathogenic treatment

Corticosteroid therapy. In compensated autoimmune cirrhosis, with signs of activity, the administration of prednisone 40 – 60 mg can lead to significant improvements. Therapy is then continued with azathioprine. Corticosteroid treatment can also be effective in alcoholic cirrhosis, with over added acute alcoholic hepatitis.

Ursodeoxycholic acid (10-15 mg/kg body weight/day) is indicated in primary biliary cirrhosis, but it can also improve in alcoholic and viral cirrhosis with cholestatic form.

Hepatoprotective or hepatic trophic medication does not alter the evolution of the disease.

Vitamin supplementation is justified in the case of deficiencies. Thus, vitamin K is not highly effective, while vitamins B6, B12 are useful in patients with neuropathy. In megaloblastic anaemias, folic acid can be administered.

The treatment of complications, previously discussed at length for each complication, is the basis of the therapy of these patients.

Liver transplantation remains, in situations where there is an indication, the therapy that addresses all phenomena and complications that occur in liver cirrhosis (see the dedicated chapter).

To note:

- Cirrhosis of the liver is the final stage of chronic liver diseases, characterized by extensive fibrosis that leads to the destruction of normal liver architecture, with a tendency to form regenerative nodules (which are however devoid of the centrilobular vein).

- The most common causes of liver cirrhosis are hepatitis B, C, and D viruses, ethanolic aetiology, primary biliary cholangitis, autoimmune hepatitis, MASLD.

- The paraclinical investigations necessary for the diagnosis of liver cirrhosis are biological tests, abdominal ultrasound, upper digestive endoscopy, morphological evaluation (laparoscopy or liver biopsy sometimes), elastographic evaluation.

- The evolution of liver cirrhosis is generally long, with initially a compensated phase (without ascites or jaundice, a situation in which cirrhosis is often discovered by chance, at surgery or at necropsy) and then the vascular decompensation phase (ascites, edema) or parenchymal decompensation (jaundice), the evaluation of liver functional reserve can be performed using the Child Pugh, MELD or MELD-Na scores.

- The occurrence of complications is the rule in the evolution of liver cirrhosis, which obscures the prognosis of patients. The main complications that can occur are ascites, upper gastrointestinal haemorrhage, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocarcinoma (HCC), hepato-renal syndrome and hepatopulmonary syndrome.

- Considering that HCC is a frequent complication, cirrhotic patients should undergo the screening program for its early detection. Screening is done by abdominal ultrasound and alpha-fetoprotein determination every 6 months.

- The hygienic-dietary treatment, applicable to all cirrhotic patients, includes a quasi-normal diet in terms of caloric intake, proteins, lipids, carbohydrates, but more dietarily cooked. Highly restrictive diets are not recommended, especially in terms of protein intake, considering the risk of malnutrition and sarcopenia. Fluid consumption should not exceed 1.5–2 Liters/day. Salt intake should be reduced to 5-6.5 g/day, as the first step of treatment in patients with ascites. Alcohol is prohibited in any form of cirrhosis.

- Etiological treatment, when possible, is essential in liver cirrhosis (suppression of viral replication in viral cirrhosis, definitive interruption of alcohol consumption in alcoholic cirrhosis, etc.) because it leads to stabilization of the disease, slowing down or even stopping progression, improvement of the Child-Pugh class, improvement of survival.

- The treatment of complications, when they occur, must be quick and energetic.

26. LIVER TRANSPLANTATION

Definition

Liver transplantation is a curative treatment for acute liver failure, end-stage liver cirrhosis, and certain stages of hepatocarcinoma. The goal of liver transplantation is to prolong the duration and quality of life. It consists of replacing the diseased liver with a healthy liver from a brain-dead donor, or with a fragment of liver from a living donor. More than 450,000 liver transplants have been performed worldwide. In Romania, so far, >1100 liver transplant procedures have been performed, about 200-250 transplants annually, far below the needs.

The most common type of liver transplant is the transplantation from a brain-dead donor: *OLT (Orthotopic Liver Transplantation).* The number of transplants from living donors (living related transplantation) has increased lately due to the shortage of brain-dead donors.

Indications for liver transplantation

The main indications for liver transplantation are diseases leading to acute liver failure, liver cirrhosis of various etiologies, as well as selected cases of malignant conditions

1. Acute liver failure caused by:

- acute viral hepatitis: acute hepatitis A – rarely, acute hepatitis B, HDV superinfection in a patient with chronic liver disease, acute hepatitis E (fulminant forms being more common in pregnant women)

- post-medications: paracetamol, isoniazid, tetracycline, cocaine, etc. Acute hepatitis induced by the consumption of high doses of paracetamol (over 10 g) induces irreversible liver failure, the only treatment of which is transplantation.

- acute autoimmune hepatitis

- HELLP syndrome – acute hepatic steatosis in pregnancy

- poisoning with fungi (Amanita phalloides)

- Wilson's disease – rarely the onset may be with acute fulminant hepatitis

- acute Budd-Chiari syndrome (thrombosis of suprahepatic veins)

- acute alcoholic hepatitis (selected cases that do not respond to corticosteroid therapy)

2. End-stage liver cirrhosis of various causes (viral, ethanolic, autoimmune, fatty liver associated with metabolic dysfunction, primary biliary cirrhosis, Wilson's disease, hemochromatosis, glycogenosis, alpha 1 antitrypsin deficiency, cryptogenetic cirrhosis, etc.).

The situations that require liver transplantation in patients with cirrhosis are: irreversible hepatic encephalopathy, ascites refractory to diuretics, spontaneous bacterial peritonitis, repeated variceal bleeding, endoscopically uncontrollable, hepato-renal syndrome, severe coagulopathy, hypoalbuminemia and severe hyperbilirubinemia.

3. Malignant diseases. In these cases, the indications are limited, being conditioned by the lack of metastases and vascular invasion

- Fibrolamellar carcinoma
- Hepatocarcinoma – Milan criteria (with a single tumor of maximum 5 cm or maximum three tumors of no more than 3 cm each, without macrovascular invasion and without metastases)
- Hemangioendothelioma epithelioid
- Patients with primary sclerosing cholangitis and cholangiocarcinoma – according to the Mayo criteria: unresectable perihilar cholangiocarcinoma <3 cm, after neoadjuvant chemotherapy, in the absence of intra- and extrahepatic secondary determinations.

4. Other indications are: Non-malignant Budd-Chiari syndrome, polycystic liver disease, familial amyloidosis, biliary atresia, etc.

Contraindications to liver transplantation

Absolute contraindications are represented by:

- Sepsis or uncontrolled active infections except those of the hepato-biliary system.
- Multiple organ and system failure
- Brain death or cerebral hernia in patients with acute liver failure
- Severe cardio-respiratory conditions, with severe pulmonary hypertension
- Active addiction to alcohol, drugs. A weaning period of at least 6 months is required for the transplant.
- Acquired immunodeficiency syndrome (AIDS)
- Extrahepatic malignancies
- Inability to comply with the medical regimen, non-compliance
- Lack of minimum psycho-social and economic support to ensure the patient's connection and periodic visits to the transplant center.

Relative contraindications

- Advanced age, generally over 65-70 years old
- Cardio-vascular disorders: severe valvulopathies, NYHA II heart failure, moderate pulmonary hypertension, right-left intracardiac shunts
- HIV infection
- SARS COV2 infection
- Extensive portal vein thrombosis and/or superior mesenteric vein
- Metastatic intrahepatic disorders

Listing and evaluation of patients on the transplant waiting list

Liver transplantation, like any other organ transplant, is done in chronological order of registration on the waiting lists of transplant centers, except for emergencies, which can be prioritized according to the vital risk and the availability of transplantable organs.

In the case of patients with decompensated liver cirrhosis, they may be placed on the transplant waiting list if their Child-Pugh score is greater than 7 (Class B), but they must be listed on if their Child-Pugh score is greater than 10.

Once it is determined that a patient should be placed on the waiting list for OLT, an extensive clinical-biological and imaging evaluation begins to identify possible contraindications to the transplant. The evaluation of the socio-economic conditions in which the patient lives, as well as the psychological factors, are also very important. The patient must be fully aware that the treatment decision has been made and must give informed consent for the transplant. Psychological testing is mandatory to confirm the patient's ability to follow post-transplant therapy and the psychological impact it can have.

Patients proposed for liver transplantation must undergo a thorough cardiological and pneumological evaluation (ECG, cardiac ultrasound, +/- coronary angiography), lung radiography, respiratory function, evaluation of the degree of pulmonary hypertension (if any).

The hepatological evaluation must include biological tests: HBs Ag, anti-HCV, antibodies against cytomegalic virus, grayscale liver ultrasound and hepatic Doppler. It is necessary to perform a liver CT or MRI for the volumetric evaluation of the liver lodge, but also for the diagnosis of a possible hepatocarcinoma.

Patients on the waiting list should be evaluated monthly by the hepatologist. The final evaluation will take place a few hours before the OLT, taking into account modern liver preservation options that allow the preservation of graft quality for periods of 12 to 16 hours after collection.

A few hours before the transplant, the recipients undergo a thorough clinical and biological examination and note the changes that have occurred since the last examination.

Donor Assessment

Organ donors are people who are brain dead (post-road accident, serious stroke) established by a series of complex neurological tests and repeated lack of brain activity on EEG. The Romanian legislation in force on transplantation regulates that organ donation can be done only with the written consent of the closest relatives or if the person's option to become an organ donor is legally documented. In addition to establishing the diagnosis of brain death, the potential donor must be evaluated in terms of infectious status and possible liver damage (e.g. for the presence of severe steatosis with fibrosis lesions – which make the graft unsuitable for transplantation).

The most important requirement in the case of liver transplantation is that there is compatibility in the ABO system. Another need is that of compatibility in size of the donated liver with the size of the recipient. In the case of a large graft and a small recipient, only one liver lobe can be transplanted - *"Split Liver Transplantation"* – the other lobe can be transplanted to a child.

Due to a low number of cadaveric donors and the increasing number of recipients on the waiting list, a new type of transplant has emerged: "*living related transplantation"* - donation of a liver lobe, usually the left one, from a living donor. It is generally a donation from a parent to the child or between first- and second-degree relatives.

Transplant technique

As soon as a potential brain-dead donor presents itself, after obtaining consent for donation from the family, the harvesting team travels to the donor's location and extracts the selected organs under strict conditions of surgical asepsis. The liver graft is covered with ice and preserved using a preservation solution (Wisconsin solution), being transported to the transplant site in a refrigerated crate.

In the meantime, the transplant team notifies the recipient and carries out the final evaluation of the recipient. The liver can be preserved in good conditions for up to 12-16 hours. The transplant team explants the recipient's liver during an anhepatic period of a few minutes using a venous extracorporeal circulation pump. After the donated liver is prepared (preparation of vascular anastomoses, the main bile duct) it is used to replace the diseased explanted liver (OLT). The surgeon will restore the vascular anastomoses with the inferior vena cava, with the portal vein and the hepatic artery, as well as the biliary anastomosis (end-to-end choledocian or choledoco-jejunal anastomosis).

The duration of a liver transplant surgery is 3-7 hours, and depends on the local anatomical situation of the recipient, but also on the experience of the surgical team. After the intervention, the transplant patient is monitored in the intensive care unit, where strict antisepsis conditions are observed, in order to avoid intra-hospital infections in a patient who will be immunocompromised by post-transplant therapy.

Post-transplant medication

The administration of post-transplant medication aims to avoid acute or chronic rejection of the transplanted liver (association of corticosteroid therapy with one or more immunosuppressants) and to combat possible graft infections. In general, standard immunosuppressive medication includes

- *Corticosteroids* - immediately post-transplant, as an attack therapy, the doses then being progressively decreased

- *Calcineurin inhibitors* (cyclosporine, tacrolimus) – which can be dosed in the plasma, are also used as an attack treatment and for maintenance

- *Antimetabolites* (azathioprine and mofetil mycophenolate) – used as maintenance medication

- *mTOR* inhibitors (sirolimus and everolimus) – as maintenance treatment

Treatment regimens for maintenance are standardized and include the use of tacrolimus with or without steroids, with or without mofetil mycophenolate or mTor inhibitors.

Post-transplant complications

Early complications. They can be the consequence of technical deficiencies of the procedure (hemorrhage, hepatic artery thrombosis/stenosis, portal vein thrombosis/stenosis, biliary stenosis or biliary fistula) or of graft deficiencies (graft dysfunction, rejection).

Clinical signs of *acute rejection* are asthenia, fever, pain in the right hypochondrium, jaundice, and early biological signs are increased transaminases, and the appearance of cholestasis. Confirmation is made by liver biopsy.

Late complications. The most common are

- *Chronic rejection,* which usually occurs more than 6 months post-transplant. The causes may be an inadequate dosage of immunosuppressive medication, hepatic ischemia due to partial thrombosis of the hepatic artery, cytomegalic virus infection. Diagnostic confirmation is made by liver biopsy.

- *Appearance/recurrence of neoplasms*. The risk of developing de novo extrahepatic neoplasms is 2-4 times higher in transplant patients compared to the general population of the same age and sex. Of these, the most common are skin cancers, followed by lymphoproliferative diseases.

- *Metabolic complications* (hypertension, diabetes, ischemic coronary artery disease, hyperlipidemia, chronic renal failure), mainly related to the side effects of corticosteroid therapy and immunosuppressive treatment.

- *Post-transplant infections (bacterial, viral, fungal).* In the first weeks after transplantation, in the absence of antiviral prophylaxis, reactivation of herpes infection (oral or genital), cytomegalovirus infection or varicella-zoster virus infection may occur.

- *Recurrence of the initial post-transplant condition* (in case of B or C virus infection, in autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hepatocarcinoma, alcoholic cirrhosis and non-alcoholic steatohepatitis). In the case of HBV infection, in the absence of treatment, infection is the rule. It is recommended to administer specific HBV immunoglobulins a la longue. In the case of HCV infection, therapy with direct antiviral agents is highly effective, with cure rates above 50%. Before this medication was available, graft reinfection was the rule, with rapid evolution to cirrhosis, within 4-5 years.

With all these complications, **Liver transplant survival**, in experienced centers, it is about 90% at one year and 80-85% at 5 years, with a much improved quality of life and acceptable costs.

To note

- Liver transplantation is the only curative treatment of chronic liver failure from cirrhosis of the liver, in some cases of acute failure, as well as in some cases of hepatocarcinoma.

- The transplant procedure involves replacing the diseased liver with a healthy liver from a brain-dead donor (most commonly performed), or with a liver fragment from a living donor, close relative (procedure with a certain degree of risk to the donor).

- Donor-recipient compatibility involves blood compatibility in system A,B,0 and volume compatibility of the transplanted organ.

- Post-transplant, the patient must undergo long-term immunosuppressive treatment to avoid rejection.

- in patients whose etiology of cirrhosis was chronic infection with hepatitis viruses, it is mandatory post-transplant to maintain viral suppression (HBV) or eradicate the infection (HCV), otherwise superinfection of the graft with rapid evolution to cirrhosis is the rule.

27. ARTIFICIAL INTELLIGENCE IN GASTROENTEROLOGY, HEPATOLOGY AND ULTRASONOGRAPHY

Introduction: From CAD to Artificial Intelligence (AI)

In the last decade, modern medicine has witnessed an important transition: from *Computer Assisted Diagnosis (CAD)* to *Artificial Intelligence (AI).* In ultrasound, CAD has been used for over 10 years ago, especially for ***the quantification of hepatic steatosis***. Subsequently, the technology was extended to the evaluation of circumscribed liver lesions, by means ***of contrast ultrasound (CEUS).*** An early example of the Timisoara group - in 2013 a paper was published on the use of CAD for the quantification of hepatic steatosis, marking the beginning of this research direction.

The emergence and expansion of the concept of AI. The term "Artificial Intelligence" began to be used intensively in medical imaging starting about 7-8 years ago, being popularized at international events such as the European Congress of Radiology in Vienna. In the last three to four years, developments in this field have accelerated considerably, with the number of publications has rapidly accelerated.

AI has become a central topic in medical research and practice, and its applications in gastroenterology, hepatology, and imaging are increasingly varied.

Applications of artificial intelligence

1. Applications of AI in Endoscopy and Gastroenterology

a. Colonoscopy and colorectal cancer screening

- Studies already published in 2022 have shown that ***AI used in colonoscopy reduces the rate of omission of adenomas (colon polyps)*** by almost 50%, compared to standard colonoscopy.
- ***AI helps detect colon polyps***, leading to much more effective colon cancer screening. AI is also used for planning screening colonoscopies in various categories of patients, but also for generating colonoscopy results.
- ***Prediction of remission in ulcerative colitis.***

b. Upper Digestive Endoscopy

- AI is used to
    - ***Detection of endoscopic lesions in the stomach;***
    - ***Differentiation of benign ulcers from malignant ones;***
    - ***Diagnosing atrophic gastritis;***
    - ***Endoscopic diagnosis of intestinal metaplasia.***

- There is already an ***official position of ESGE (European Society of Gastrointestinal Endoscopy***) that supports the integration of AI in endoscopy, to streamline endoscopic evaluation and increase performance.
- Apart from the use of AI in endoscopy, this method can be used in gastroenterology for ***the prediction of mortality in acute pancreatitis, for the diagnosis of pancreatic cancer, for improving the diagnosis of acute appendicitis, etc.***

2. Applications of AI in Hepatology

a. For the diagnosis of MASLD (metabolic dysfunction associated with steatotic liver);

b. Morphopathological diagnosis of MASH

- AI is used in histological analysis for ***the diagnosis of metabolic dysfunction-associated steatohepatitis (MASH).*** A meta-analysis published in *2023* confirms the usefulness of AI in identifying subtle histological changes.

c. Assessment of prognosis in liver disease

- AI is used to estimate the evolution of patients with:
  - ***MASLD (metabolic dysfunction associated with stetotic liver);***
  - ***Evaluation of the evolution of the disease in patients with chronic hepatitis B;***
  - ***Cirrhosis and portal hypertension;***
  - ***Risk of rupture of esophageal varices;***
  - ***Diagnosis and prognosis of hepatocellular carcinoma (HCC).***

3. Applications of AI in Ultrasonography

a. *Quantification of hepatic steatosis*

- An article published in *2022* presents AI as an effective tool for ***the automatic detection and quantification of hepatic steatosis*** on ultrasound images.

b. *Differential diagnosis of focal liver lesions*, both in standard ultrasound and in contrast ultrasound (CEUS). Special efforts are being made to integrate into high-performance ultrasound devices modules for the automatic detection of liver lesions, but also for the characterization of these lesions, using AI.

c. *Ultrasound diagnosis of gallbladder pathology*

- AI is being used for imaging evaluation of the gallbladder, with promising results, according to an article published in 2023

d. *Image-guided therapy of liver lesions*

- AI plays an emerging role in **guiding percutaneous ultrasound therapy**, including by ***integrating virtual reality for sonographer training***.

It should be emphasized that AI is currently used a lot in medical imaging, for various pathologies, making the work of the radiologist easier.

Ethical perspectives of AI

A study in *Scientific Reports (2022)* looked at perceptions related to AI. ***62.5% of gastroenterologic patients*** were familiar with AI. Both patients and gastroenterologists believe that AI will *improve the quality of medical care; reduce patient waiting times; speed up diagnosis and therapy of the disease.*

The main concern of patients is *the loss of personal contact with the doctor,* with the development of AI. Another issue raised is that *of responsibility for a medical case*, which will continue to belong to the doctor.

What is certain at this point is that by using AI, the diagnosis made by the novice doctor increases in performance, approaching that of the experienced doctor, and this represents an important step in medical practice. The effects of AI for the evolution of the novice doctor, in the long term, will have to be evaluated.

Possible future: ChatGPT in medicine?

A new possibility opens up: ***the use of language models, such as ChatGPT****,* in the writing of scientific articles, the development of clinical protocols and medical training.

Conclusion (challenging)

AI is not a fad. It is a ***revolutionary tool*** that transforms the way we learn, diagnose and treat. AI is not a tool for the future, but is already used in medical practice in some fields (such as in endoscopy for the detection of polyps). All that remains is for us to **understand, validate and integrate** these technologies into our daily clinical practice.

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