МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ

**УЧРЕЖДЕНИЕ ОБРАЗОВАНИЯ
«ГОМЕЛЬСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»**

Кафедра внутренних болезней № 1 с курсом эндокринологии

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ГАСТРОЭНТЕРОЛОГИЯ

**Допущено Министерством образования Республики Беларусь
в качестве учебного пособия для иностранных студентов
учреждений высшего образования по медицинским специальностям**

GASTROENTEROLOGY

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В учебном пособии изложены современные сведения об этиологии, патогенезе, основных клинических проявлениях, диагностических критериях и принципах лечения заболеваний пищевода, желудка, кишечника, поджелудочной железы, гепатобилиарной системы. Отражены дифференциальная диагностика заболеваний желудочно-кишечного тракта, принципы оказания неотложной помощи при ургентных состояниях, клиническая фармакология лекарственных средств.

Материал подготовлен в соответствии с типовой программой для высших учебных заведений по специальности «Лечебное дело».

Предназначено для студентов 3, 4, 6 курсов, обучающихся английском языке, медицинских вузов.

CONTENTS

ABBREVIATIONS

AASLD   — American Association for the Study of Liver Diseases
AIDS   — acquired immune deficiency syndrome
ALP   — alcaline phosphatase
ALT   — alanine aminotransferase
AMA   — anti-mitochondrial antibodies
ANA   — antinuclear antibodies
anti-HCV   — anti-hepatitis C virus antibodies
AST   — aspartate aminotransferase
bid   — bis in die (Latin), two times a day (English)
CCK   — cholecystokinin
COX   — cyclo-oxygenase
CT   — computed tomography
DU   — duodenal ulcer
EASL   — European Association for the Study of the Liver
EGD   — esophagogastroduodenoscopy
ERC   — endoscopic retrograde cholangiography
ERCP   — endoscopic retrograde cholangiopancreatography
FISH   — fluorescent in situ hybridization
GERD   — gastroesophageal reflux disease
GGT   — gamma glutamyl transferase
GI   — gastrointestinal
GU   — gastric ulcers
H. pylori — *Helicobacter pylori*
H_2 blockers — histamine 2-receptor antagonists
HBsAg   — hepatitis B surface antigen
HFE   — hereditary hemochromatosis gene
HIV   — human immunodeficiency virus
ICU   — intensive care unit
IL   — interleukin
INR   — international normalization ratio
IU   — international unit
IV   — intravenous
LES   — lower esophageal sphincter
LKM   — liver kidney membrane
MALT   — mucosal-associated lymphoid tissue
MARS   — molecular adsorption recirculating system
MELD   — model for end stage liver disease
MRCP   — magnetic resonance cholangiopancreatography
MRI   — magnetic resonance imaging
MRS   — proton magnetic resonance spectroscopy

NAFLD — nonalcoholic fatty liver disease
NASH — nonalcoholic steatohepatitis
NSAID — non-steroidal anti-inflammatory drug
NUD — nonulcer dyspepsia
p-ANCA — perinuclear anti-neutrophil cytoplasmatic antibodies
PG — prostaglandin
PPI — proton pump inhibitor
PSC — primary sclerosing cholangitis
PUD — peptic ulcer disease
qid — quater in die (Latin), four times a day (English)
SAAG — serum ascitic albumin gradient
SBP — spontaneous bacterial peritonitis
SLA — soluble liver antigen
SMA — smooth-muscle antibodies
TIPSS — transjugular intrahepatic porto-systemic shunt
TNF-α — tumor necrosing factor-α
UDCA — ursodesoxycholic acid
UDE — upper digestive endoscopy
pANCA — perinuclear neutrophil cytoplasmic antigen
CD — Crohn's disease
UC — ulcerative colitis
IBD — inflammatory bowel disease
TNF — tumor necrosis factor

1. DISEASES OF THE ESOPHAGUS

Diseases of esophagus are common in gastroenterology practice. The human esophagus is a 25 to 35 cm long muscular tube. The contractions of the esophagus propel food into the stomach and also help to clear refluxed acid back to the stomach. The lower esophageal sphincter (LES) remains tonically contracted preventing reflux of acid from stomach to the esophagus. LES relaxes during swallowing, vomiting and belching to allow foods and gastric contents to pass into and out of the stomach. Improvement in diagnosis and better understanding in pathophysiology of diseases of esophagus have been possible recently of due to advancement in technology. Tests of esophageal function evaluate contraction of its muscle and the movement of the food bolus and refluxate resulting from it. It also evaluates exposure of the esophagus to acid. These tests include contrast radiography, manometry, 24-h ambulatory pH-metry and impedance monitoring, radionuclide esophageal transit studies.

1.1. Functional esophageal disorders

Functional gastrointestinal disorders represent a common and important class of disorders within gastroenterology. The large number of patients suffering from the functional gastrointestinal disorders. Functional disorders are labeled when any investigations, including EGD, fail to identify an obvious organic explanation of symptoms. Functional disorders are important because it is not only highly prevalent but also impairs quality of life, work performance and family relationships and incurs a high healthcare cost worldwide.

Several mechanisms have been proposed for the pathogenesis of non-erosive reflux disease patients, including visceral hypersensitivity, prolonged contraction of the esophagus and psychological factors.

Classification of functional esophageal disorders (according to Rome IV criteria — point **A**):
- A1 — Functional chest pain
- A2 — Functional heartburn
- A3 — Reflux hypersensitivity
- A4 — Globus
- A5 — Functional Dysphagia

A1. Functional chest pain

Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week.

The criteria must include all of the following.

1. Retrosternal chest pain or discomfort; cardiac causes should be ruled out.

2. Absence of associated esophageal symptoms, such as heartburn and dysphagia.

3. Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis are the cause of the symptom.

4. Absence of major esophageal motor disorders (achalasia/ esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

A2. Functional heartburn

Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least twice a week. Must include all of the following.

1. Burning retrosternal discomfort or pain.

2. No symptom relief despite optimal antisecretory therapy.

3. Absence of evidence that gastroesophageal reflux (abnormal acid exposure and symptom reflux association) or eosinophilic esophagitis is the cause of symptoms.

4. Absence of major esophageal motor disorders (achalasia/ esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

A3. Reflux Hypersensitivity

Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least twice a week.

Must include all of the following.

1. Retrosternal symptoms including heartburn and chest pain.

2. Normal endoscopy and absence of evidence that eosinophilic esophagitis is the cause for symptoms.

3. Absence of major esophageal motor disorders (achalasia/esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

4. Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH–impedance monitoring (response to antisecretory therapy does not exclude the diagnosis).

A4. Globus:

Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week.

Must include all of the following.

1. Persistent or intermittent, nonpainful, sensation of a lump or foreign body in the throat with no structural lesion identified on physical examination, laryngoscopy, or endoscopy.

a. Occurrence of the sensation between meals.

b. Absence of dysphagia or odynophagia.

c. Absence of a gastric inlet patch in the proximal esophagus.

2. Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis is the cause of the symptom.

3. Absence of major esophageal motor disorders (achalasia/ esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

A5. Functional Dysphagia

Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week.

Must include all of the following.

1. Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus.

2. Absence of evidence that esophageal mucosal or structural abnormality is the cause of the symptom.

3. Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis is the cause of the symptom.

4. Absence of major esophageal motor disorders (achalasia/ esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

Management of functional esophageal disorders

Treatment patients with the functional gastrointestinal disorders include lifestyle changes, symptomatic agents (PPI, prokinetics), antidepressive drugs, psychotherapy. Antidepressants modulate both peripheral and central hyperalgesia independent of mood, and these agents should be considered as first-line medical treatment of functional chest pain. Different categories of antidepressants have been used, including tricyclic antidepressants, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, and trazodone. However, their side-effect profile and social stigma limit their utilization, prompting study of alternate agents, such as gabapentin, pregabalin, and theophylline. In all instances, clinical use of these neuromodulators should be weighed against potential side effects.

KEY MESSAGES

• Functional esophageal disorders are labeled when any investigations are fail to identify an obvious organic explanation of symptoms.

• Alarm or "red flags" symptoms - symptoms and findings suggestive of an organic diseaseare: overt gastrointestinal bleeding, anemia, unexplained weight loss, fever, leukocytosis, progressive dysphagia, odynophagia, recurrent vomiting, family history of gastrointestinal cancer, presence of an abdominal mass and/or lymphadenopathy.

• Symptoms of functional esophageal disorders may be heartburn, chest pain, dysphagia, globus.

• Farmacological and non-farmacological methods management are necessary for patients with functional esophageal disorders.

1.2. Gastroesophageal reflux disease

Gastroesophageal reflux disease is a common disease with a prevalence as high as 10–20 % in the western world. The disease can manifest in various symptoms which can be grouped into typical, atypical and extra-esophageal symptoms. Those with the highest specificity for GERD are acid regurgitation

and heartburn. In the absence of alarm symptoms, these symptoms can allow one to make a presumptive diagnosis and initiate empiric therapy. Whereas most patients can be effectively managed with medical therapy, others may go on to require anti-reflux surgery after undergoing a proper pre-operative evaluation.

GERD is chronic symptoms or mucosal damage caused by stomach acid coming up from the stomach into the esophagus GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms (i.e., at least two heartburn episodes per week) and/or complications.

Pathophysiology gastroesophageal reflux disease

GERD results from failure of the reflux barrier. This barrier has three components: (1) an intra-abdominal esophagus of adequate length, (2) an extrinsic sphincter, the esophageal hiatus, and (3) an intrinsic sphincter, LES.

Relaxation of the LES and crura are normal physiological processes occurring during swallowing and also during gas venting. Relaxations not initiated by a swallow are known as transient lower esophageal relaxations. The transient lower esophageal relaxations reflex is initiated by tension receptors in the stomach and mediated by a vagovagal pathway via the brainstem leading to simultaneous relaxation of the crura, LES and inhibition of peristalsis.

Reflux occurs more frequently when the pressure in the LES is < 10 mm Hg, and free reflux only occur if the LES pressure is < 4 mm Hg.

Factors which relax the LES, such as caffeine, fat, smoking, drugs (calcium channel antagonists and nitrates) and gastric distention, will increase the likelihood of reflux.

Symptomatology gastroesophageal reflux disease

The most common symptoms of GERD are:
- heartburn;
- regurgitation;
- trouble swallowing (dysphagia).

Less common symptoms include:
- pain with swallowing (odynophagia);
- increased salivation (also known as water brash);
- nausea;
- chest pain.

Atypical GERD symptoms are:
- cough;
- asthma;
- laryngitis;
- sore throat;
- chest pain;
- abdominal pain;
- bloating.

These symptoms in the absence of typical GERD symptoms point to diseases other than GERD. Careful investigation of alternative causes of atypical symptoms is necessary. Sophisticated testing, including impedance/pH monitoring, must be performed if GERD is believed to be the cause of atypical symptoms and surgery is being considered.

Los Angeles classification gastroesophageal reflux disease is now the most commonly used.

Grade extent of esophageal inflammation:

A: mucosal breaks < 5mm not extending between folds;

B: mucosal breaks > 5mm not extending between folds;

C: mucosal breaks extending between folds;

D: mucosal breaks extending between > 2 folds, involving > 75 % of the circumference.

Complications of gastroesophageal reflux disease:

• reflux esophagitis — necrosis of esophageal epithelium causing ulcers near the junction of the stomach and esophagus;

• esophageal strictures — the persistent narrowing of the esophagus caused by reflux-induced inflammation;

• Barrett's esophagus — intestinal metaplasia (changes of the epithelial cells from squamous to intestinal columnar epithelium) of the distal esophagus;

• esophageal adenocarcinoma — a rare form of cancer.

Diagnostic approach of gastroesophageal reflux disease

The signs and symptoms are insufficient to establish a conclusive diagnosis of GERD.

• The *empiric treatment PPI* — if patients have classic GERD symptoms with no alarm symptoms (overt gastrointestinal bleeding, anemia, unexplained weight loss, fever, leukocytosis, progressive dysphagia, odynophagia, recurrent vomiting, family history of gastrointestinal cancer, presence of an abdominal mass and/or lymphadenopathy).

• The *24-hour esophageal pH-metry* is the most important resource for a definite diagnosis of acid reflux, which constitutes most of reflux episodes. Quantification of reflux can be achieved either by measuring acid exposure to the distal esophagus (pH studies) or movement of liquid in the distal esophagus (*impedance studies*). Combined *impedance and pH measurement* characterizes all acid and non-acid reflux episodes.

• *Upper endoscopy* improves the diagnostic accuracy and also establishes a differential diagnosis with other diseases, such as cancer. Indicate to PPI unresponsive patients, with the alarm symptoms, high risk for Barrett's esophagus.

• *Esophageal manometry* excludes unsuspected motility disorders or motility disorders masquerading as GERD.

• *Esophageal biopsies* in patients with suspected GERD for the analysis of basal cell proliferation allow, in absence of the latter, ruling out the diagnosis or active disease.

• If dysphagia is the predominant symptom and the diagnosis is in question, the examination should start as a timed *barium esophagram*.

Management gastroesophageal reflux disease

The aim of GERD treatment is to effectively control symptoms and prevent GERD associated complications.

1. Lifestyle changes

Simple manoeuvres may have a marked effect on symptoms. These are outlined below:

• dietary changes. Some substances influence oesophageal physiology favouring increased acid reflux (fat, caffeine and alcohol).

• Avoiding late meals. Acid reflux episodes are prolonged when asleep as a result of both gravity, and also reduced peristalsis and acid clearance.

• Weight loss is suggested as part of GERD management.

2. Antacids/alginate combinations

Antacids consist of calcium carbonate, magnesium and aluminum salts in various compounds or combinations. The effect of antacids is due to partial neutralization of gastric hydrochloric acid and inhibition of the proteolytic enzyme, pepsin.

Alginate mechanism of action is due to the formation of a gel in the presence of gastric acid. Alginate-based reforming formulations usually contain sodium or potassium bicarbonate; in the presence of gastric acid, the bicarbonate is converted to carbon dioxide, which becomes entrapped within the gel precipitate, converting it into a foam which floats on the surface of the gastric contents, much like a raft on water.

Antacids and alginates have been shown to improve reflux symptoms, however, they do not heal esophagitis. They are indicated for very mild symptoms, where step-up treatment is not necessary. There is no role for antacids/alginates in the maintenance of GERD.

3. Histamine antagonists

H2 antagonists are very good for relieving the symptoms of GERD, particularly heartburn. However, they are not very good for healing the inflammation (esophagitis) that may accompany GERD.

4. Proton pump inhibitors

Five different PPIs are approved for the treatment of GERD:

• omeprazole 20/40 mg/day;
• lansoprazole 30 mg/day;
• rabeprazole 20 mg/day;
• pantoprazole 40 mg/day;
• esomeprazole 20/40 mg/day.

5. Pro-motility drugs

Pro-motility drugs work by stimulating the muscles of the gastrointestinal tract, including the esophagus, stomach, small intestine, and/or colon. Pro-

motility drugs increase the pressure in the lower esophageal sphincter and strengthen the contractions (peristalsis) of the esophagus.

One pro-motility drug — metoclopramide — is approved for GERD.

6. Foam barriers

Foam barriers provide a unique form of treatment for GERD.

Foam barriers are tablets that are composed of an antacid and a foaming agent. As the tablet disintegrates and reaches the stomach, it turns into foam that floats on the top of the liquid contents of the stomach. The foam forms a physical barrier to the reflux of liquid. At the same time, the antacid bound to the foam neutralizes acid that comes in contact with the foam. The tablets are best taken after meals (when the stomach is distended) and when lying down, both times when reflux is more likely to occur. Foam barriers are not often used as the first or only treatment for GERD. Rather, they are added to other drugs for GERD when the other drugs are not adequately effective in relieving symptoms.

There is only one foam barrier, which is a combination of aluminum hydroxide gel, magnesium trisilicate, and alginate.

7. Surgery

When the diagnosis of reflux is objectively confirmed, surgical therapy should be considered in individuals who:

• have failed medical management (inadequate symptom control, severe regurgitation not controlled with acid suppression, or medication side effects);

OR

• need for surgery despite successful medical management (due to quality of life considerations, lifelong need for medication intake, expense of medications, etc.);

OR

• have complications of GERD (e. g., Barrett's esophagus, peptic stricture);

OR

• have extra-esophageal manifestations (asthma, hoarseness, cough, chest pain, aspiration).

KEY MESSAGES

• Smoking, caffeine, fat, calcium channel antagonists and nitrates increase the likelihood of reflux.

• Typical GERD symptoms are heartburn, regurgitation, trouble swallowing.

• Atypical GERD symptoms are cough, asthma, laryngitis, sore throat, chest pain, abdominal pain, and bloating.

• GERD complications include erosive esophagitis, peptic stricture, Barrett's esophagus, esophageal adenocarcinoma and pulmonary disease.

• Management of GERD may involve lifestyle modification, medical therapy and surgical therapy. Lifestyle modifications including weight loss and/or head of bed elevation have been shown to improve esophageal pH and/or GERD symptoms. Medical therapy involves acid suppression which can be achieved with antacids, histamine-receptor antagonists or PPIs.

Eosinophilic esophagitis

Eosinophilic esophagitis is a worldwide chronic allergic disease of the esophagus. In the last decade, there is an epidemic of this entity in the western world. Mostly seen in children and young adults, patients present with dysphagia or food impaction in the emergency room. Characteristic endoscopic findings, esophageal eosinophilia and non-responsiveness to PPIs help make the diagnosis. Avoidance of food allergens, administration of steroidal anti-inflammatory medications and dilation of the esophagus are the mainstays of treatment. Investigations are ongoing for mucosal healing and optimum maintenance treatment.

Eosinophilic esophagitis also known as "asthma of the esophagus" is a chronic immune/antigen mediated disorder of the esophagus affecting both children and adults.

Epidemiology of eosinophilic esophagitis

The disease is more common in Caucasian population with a male to female ratio of 3:1. Eosinophilic esophagitis has also been seen in African Americans, Asians and Hispanic population. The disease is increasingly has been recognized over the last few decades. The disease can affect both children and adults. In adults, it mostly affects middle-aged men between the age of 30 and 50. Most of the patients with eosinophilic esophagitis have personal history of allergic disorders like bronchial asthma, allergic rhinitis, allergic conjunctivitis or food allergy.

Pathogenesis of eosinophilic esophagitis

Exposure of the esophagus to food and aeroallergens in genetically predisposed individuals may initiate the process of eosinophilic esophagitis although the exact mechanism is currently unknown.

Foods most commonly implicated in eosinophilic esophagitis are:
- milk;
- egg;
- wheat;
- soy;
- peanuts;
- beans;
- rye;
- beef.

The environmental pollen counts (grass, trees and weeds) as aeroallergens play an important role in the pathogenesis of eosinophilic esophagitis.

IL-5 is responsible for eosinophilic infiltration, growth and survival. Eosinophils secrete various inflammatory cytokines and chemokines including macrophage migration inhibitory factor, tumor necrosis factor, granulocyte-monocyte colony stimulating factors and toxic granules. Transforming growth factor β1 is a profibrotic molecule and helps in remodeling of the esophagus in

eosinophilic esophagitis. This may explain esophageal luminal narrowing, stricture formation and dysmotility.

Symptomatology of eosinophilic esophagitis

The major symptoms of eosinophilic esophagitis are:

• solid food dysphagia;

• esophageal food impaction requiring endoscopic removal of food bolus as an emergency case;

• heartburn and chest pain mimicking GERD (less commonly).

The diagnosis is suspected after a first episode of esophageal food impaction and biopsy showing esophageal eosinophilia.

Men presented with dysphagia and esophageal food impaction more commonly than women. Women presented with heartburn and chest pain more commonly than men.

The highest percentage of eosinophilic esophagitis occurred in the spring and the lowest percentage in the winter.

Diagnostic approach of eosinophilic esophagitis

Lab tests

Mild peripheral eosinophilia may be present.

Endsocopy

The five major endoscopic features of eosinophilic esophagitis are:

• edema (is identified by loss of vascular markings and mucosal pallor);

• rings (transient concentric rings or trachealization may indicate esophageal longitudinal muscle contraction and fixed rings may indicate fibrous stricture formation due to tissue remodeling);

• exudates or white spots or white plaques may mimic candida esophagitis (histologically they are eosinophilic microabscesses);

• furrows (are vertical lines running parallel to the axis of the esophagus probably due to epithelial edema);

• strictures long or short segment of esophagus.

Current recommendation is to take at least 2 to 4 biopsies both proximal and distal halves of esophagus (5 cm above gastroesophageal junction) and also to take targeted biopsies from abnormal mucosa, i. e., exudates, rings, edema, furrows and strictures. Gastric and duodenal biopsies should also be taken to evaluate eosinophilic gastroenteritis.

Barium swallow

Barium swallow may show normal esophagus. Sometimes featureless narrow-caliber esophagus, ringed esophagus, and isolated esophageal stricture are seen, but none is pathognomonic of eosinophilic esophagitis.

1.3. Esophageal manometry

Generally normal peristalsis is seen in eosinophilic esophagitis. Prolonged esophageal manometry and pH-metry showed ineffective esophageal peristalsis in children with eosinophilic esophagitis. Twenty-four hours pH study would be normal in eosinophilic esophagitis unless there is coexistent GERD.

Echoendoscopy may show hypoechogenesity and thickening of all the layers of the esophageal wall due to inflammation and edema.

Management eosinophilic esophagitis

Diet

Dietary therapy is very effective in the management of eosinophilic esophagitis.

The ways of dietary modification include:

• elemental diet: amino acid based formula to remove food allergens. This therapy when given for a minimum of 6 week did both symptomatic and histologic improvement;

• six-food group elimination diet: milk, egg, wheat, soy, peanuts/ tree nuts and sea food (fish/shellfish).

• *Topical corticosteroids*

The first line medications for the treatment of eosinophilic esophagitis. The maximal anti-inflammatory effect is found in proximal esophagus. Topical steroid is generally given for 8 week. If that fails, prolonged or higher doses of topical steroids or systemic steroids or dietary treatment or esophageal dilation should be tried to get symptomatic improvement.

Systemic steroids

Oral methylprednisolone induced marked clinical and histological improvement in pediatric eosinophilic esophagitis patients. Because of systemic side effects, this therapy is reserved when other therapeutic interventions fail. But recurrence of the eosinophilic esophagitis occurs after withdrawal of the steroids.

Immunomodulators

Azathiopurine and 6-mercaptopurine induced and maintained clinical and histological remission in steroid dependent eosinophilic esophagitis patients in a case series. They are not currently recommended for routine clinical use in eosinophilic esophagitis.

Mast cell stabilizers

Cromolyn sodium failed to show any clinical or histologic improvement in eosinophilic esophagitis patients.

Leukotrien inhibitors

Montelukast is an eosinophil stabilizing agent. It improved clinical symptoms but there was no histological improvement.

IL-5 antibody

Mepolizumab significantly reduced esophageal eosinophilia but there was minimum symptomatic improvement, reslizumab also improved esophageal eosinophilia but there was no difference in clinical improvement in comparison to placebo.

Endoscopic treatment

Esophageal dilation is indicated if the patients do not respond to pharmacological or dietary therapy. It is also very effective in symptomatic esophageal

stricture (esophageal diameter < 10 mm), long segment narrowing and narrow caliber esophagus. This modality of treatment improves dysphagia and quality of life but does not reduce esophageal eosinophilia.

Either hydrostatic balloon dilation or wire guided bougie dilation can be done. There is an increased risk of mucosal tear causing post-dilation chest pain for several days.

KEY MESSAGES

• Eosinophilic esophagitis is a clinicopathologically disease characterized clinically by dysphagia and pathologically by esophageal eosinophilia.

• Esophageal diameter should be 15 to 18 mm to relieve dysphagia.

• Diagnosis is made by 3 criteria: (1) symptoms of esophageal dysfunction; (2) presence of ≥ 15 eosinophils/high power field in at least 1 esophageal biopsy with few exceptions; and (3) eosinophilia limited to the esophagus, with exclusion of other possible causes of esophageal eosinophilia, including PPI responsive esophageal eosinophilia.

• Patients with endoscopic findings of edema, exudates and furrows should be given topical corticosteroids for 6 to 8 week. If there is no clinicopathological improvement, esophageal dilation should be offered.

1.4. Acid-suppressing drugs

Antacids

Antacids may be aluminum, magnesium, or calcium based. Calcium-based antacids (usually calcium carbonate), unlike other antacids, stimulate the release of gastrin from the stomach and duodenum. Gastrin is the hormone that is primarily responsible for the stimulation of acid secretion by the stomach. Therefore, the secretion of acid rebounds after the direct acid neutralizing effect of the calcium carbonate is exhausted.

Standart dose of antacids is 100–140 meq/l 1 and 3 h after meals.

Aluminum hydroxide (*phosphalugel*) can produce constipation and phosphate depletion; magnesium hydroxide may cause loose stools. Many of the commonly used antacids (e. g., *almagel, maalox*) have a combination of both aluminum and magnesium hydroxide in order to avoid these side effects. The magnesium-containing preparation should not be used in chronic renal failure patients because of possible hypermagnesemia, and aluminum may cause chronic neurotoxicity in these patients.

Calcium carbonate and sodium bicarbonate are potent antacids with varying levels of potential problems. The long-term use of calcium carbonate (converts to calcium chloride in the stomach) can lead to milk-alkali syndrome (hypercalcemia, hyperphosphatemia with possible renal calcinosis and progression to renal insufficiency). Sodium bicarbonate may induce systemic alkalosis.

H_2 Receptor Antagonists

Four of these agents are presently available (*cimetidine, ranitidine, famotidine, and nizatidine*), and their structures share homology with histamine. Al-

though each has different potency, all will significantly inhibit basal and stimulated acid secretion to comparable levels when used at therapeutic doses. Moreover, similar ulcer-healing rates are achieved with each drug when used at the correct dosage.

Cimetidine was the first H_2 receptor antagonist used for the treatment of acid peptic disorders. Cimetidine may have weak antiandrogenic side effects resulting in reversible gynecomastia and impotence, primarily in patients receiving high doses for prolonged periods of time (months to years), confusion and elevated levels of serum aminotransferases, creatinine, and serum prolactin.

Ranitidine, famotidine, and nizatidine are more potent H_2 receptor antagonists than cimetidine.

Standard dosing of cimetidine is 400 mg bid, ranitidine is 300 mg, famotidine is 40 mg, and nizatidine is 300 mg.

Anticholinergics, designed to inhibit activation of the muscarinic receptor in parietal cells, met with limited success due to their relatively weak acid-inhibiting effect and significant side effects (dry eyes, dry mouth, urinary retention).

Proton Pump (H^+, K^+-ATPase) Inhibitors

Omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole are substituted benzimidazole derivatives that covalently bind and irreversibly inhibit H^+, K^+-ATPase.

Standard dosing of omeprazole is 20 mg/d, esomeprazole is 20 mg/d, lansoprazole is 30 mg/d, rabeprazole is 20 mg/d, and pantoprazole is 40 mg/d.

Esomeprazole, the newest member of this drug class, is the S-enantiomer of omeprazole, which is a racemic mixture of both S- and R-optical isomers. These are the most potent acid inhibitory agents available.

Omeprazole and lansoprazole are the PPIs that have been used for the longest time. Both are acid-labile and are administered as enteric-coated granules in a sustained-release capsule that dissolves within the small intestine at a pH of 6.

Lansoprazole is available in an orally disintegrating tablet that can be taken with or without water, an advantage for individuals who have significant dysphagia. Absorption kinetics are similar to the capsule. In addition, a lansoprazole-naproxen combination preparation that has been made available is targeted at decreasing NSAID-related gastrointestinal injury.

Omeprazole is available as non-enteric-coated granules mixed with sodium bicarbonate in a powder form which can be administered orally or via gastric tube. The sodium bicarbonate has two purposes: to protect the omeprazole from acid degradation and to promote rapid gastric alkalinization and subsequent proton pump activation, which facilitates rapid action of the PPI.

Pantoprazole and rabeprazole are available as enteric-coated tablets. Pantoprazole is also available as a parenteral formulation for intravenous use. These agents are lipophilic compounds; upon entering the parietal cell, they are protonated and trapped within the acid environment of the tubulovesicular and canalicular system.

PPI potently inhibit all phases of gastric acid secretion. Onset of action is rapid, with a maximum acid inhibitory effect between 2 and 6 h after administration and duration of inhibition lasting up to 72–96 h. With repeated daily dosing, progressive acid inhibitory effects are observed, with basal and secretagogue-stimulated acid production being inhibited by > 95 % after 1 week of therapy. The half-life of PPIs is ~18 h; thus, it can take between 2 and 5 days for gastric acid secretion to return to normal levels once these drugs have been discontinued. Because the pumps need to be activated for these agents to be effective, their efficacy is maximized if they are administered before a meal (except for the immediate-release formulation of omeprazole) (e. g., in the morning before breakfast).

Mild to moderate hypergastrinemia has been observed in patients taking these drugs. Serum gastrin levels return to normal levels within 1–2 weeks after drug cessation.

Carcinoid tumors developed in some animals given the drugs preclinically; however, extensive experience has failed to demonstrate gastric carcinoid tumor development in humans.

Intrinsic factor production is also inhibited, but vitamin B12-deficiency anemia is uncommon, probably because of the large stores of the vitamin.

As with any agent that leads to significant hypochlorhydria, PPIs may interfere with absorption of drugs such as ketoconazole, ampicillin, iron, and digoxin.

Hepatic cytochrome P450 can be inhibited by the earlier PPIs (omeprazole, lansoprazole). Rabeprazole, pantoprazole, and esomeprazole do not appear to interact significantly with drugs metabolized by the cytochrome P450 system. The overall clinical significance of this observation is not definitely established. Caution should be taken when using warfarin, diazepam, atazanavir, and phenytoin concomitantly with PPIs.

Long-term acid suppression, especially with PPIs, has been associated with a higher incidence of community-acquired pneumonia. This observation requires confirmation but should alert the practitioner to take caution when recommending these agents for long-term use, especially in elderly patients at risk for developing pneumonia.

Two new formulations of acid inhibitory agents are being developed. Tenatoprazole is a PPI containing an imidazopyridine ring instead of a benzimidazole ring, which promotes irreversible proton pump inhibition. This agent has a longer half-life than the other PPIs and may be beneficial for inhibiting nocturnal acid secretion, which has significant relevance in GERD. A second new class of agents is the potassium-competitive acid pump antagonists. These compounds inhibit gastric acid secretion via potassium competitive binding of the H^+, K^+-ATPase.

1.5. Cytoprotective agents
Sucralfate
Sucralfate is a complex sucrose salt in which the hydroxyl groups have been substituted by aluminum hydroxide and sulfate. This compound is inso-

luble in water and becomes a viscous paste within the stomach and duodenum, binding primarily to sites of active ulceration. Sucralfate may act by several mechanisms: serving as a physicochemical barrier, promoting a trophic action by binding growth factors such as EGF, enhancing prostaglandin synthesis, stimulating mucous and bicarbonate secretion, and enhancing mucosal defense and repair. Toxicity from this drug is rare, with constipation being most common (2–3 %). It should be avoided in patients with chronic renal insufficiency to prevent aluminum-induced neurotoxicity. Hypophosphatemia and gastric bezoar formation have also been reported rarely. Standard dosing of sucralfate is 1 g qid.

Bismuth-containing preparations

The resurgence in the use of these agents is due to their effect against *H. pylori*. Colloidal bismuth subcitrate and bismuth subsalicylate are the most widely used preparations.

The mechanism by which these agents induce ulcer healing is unclear. Potential mechanisms include ulcer coating; prevention of further pepsin/HCl-induced damage; binding of pepsin; and stimulation of prostaglandins, bicarbonate, and mucous secretion.

Adverse effects with short-term usage include black stools, constipation, and darkening of the tongue.

Long-term usage with high doses, especially with the avidly absorbed colloidal bismuth subcitrate, may lead to neurotoxicity.

Prostaglandin analogues

Prostaglandin analogues enhance mucous bicarbonate secretion, stimulate mucosal blood flow, and decrease mucosal cell turnover. Standard dosing of *misoprostol* is 200 g qid.

The most common toxicity noted with this drug is diarrhea (10–30% incidence). Other major toxicities include uterine bleeding and contractions; misoprostol is contraindicated in women who may be pregnant, and women of child-bearing age must be made clearly aware of this potential drug toxicity.

KEY MESSAGES

• PPI inhibit the parietal cell H^+/K^+ adenosine triphosphatase, the enzyme of canalicular membrane of gastric parietal cells which is responsible for the last step in gastric acid secretion.

• PPI with anti-secretory effect declines the acid production from stomach, which allows the damaged tissues to heal.

• The half-life of PPIs is ~18 h; thus, it can take between 2 and 5 days for gastric acid secretion to return to normal levels once these drugs have been discontinued.

• The efficacy of PPI is maximized if they are administered before a meal (e. g., in the morning before breakfast), except for the immediate-release formulation of omeprazole.

• H2-receptor antagonists competitively inhibit histamine binding to its G-protein coupled receptor on the basolateral membrane of gastric parietal cells, which results in a reduction in acid production and an overall decrease in gastric secretions.

• PPI is more efficient than H_2-receptor antagonists in suppressing gastric acid secretion.

• Sucralfate acts by adhering to epithelial cells forming a physical cytoprotective barrier at the ulcer site, thereby protecting the gastric mucosa from the effects of acid and pepsin.

1.6. Differential diagnosis of dysphagia

Dysphagia is defined as difficulty or inability to transfer food from the oral cavity to the stomach.

Dysphagia is sub classified into two types depending on the location of the lesion:

• oropharyngeal dysphagia — inability or difficulty in transferring food from oral cavity to upper esophagus;

• esophageal dysphagia — inability or difficulty in transferring food from upper esophageal region to stomach

A careful history is vital in identifying the type and underlying cause of dysphagia. Difficulty in initiating a swallow suggests oropharyngeal dysphagia. This may be accompanied by sensation of food getting stuck above suprasternal notch, choking sensation, nasal regurgitation of food, aspiration, dysarthria and dysphonia. When swallow is initiated but a few seconds later the patient feels food is getting stuck in esophagus (below suprasternal notch), esophageal dysphagia is likely.

Dysphagia may occur due to structural lesions in the pathway of food bolus transit (*mechanical dysphagia*) or neuromuscular dysfunction (*motor dysphagia*). Difficulty in swallowing liquids and solids from the onset of dysphagia suggests motor dysphagia while difficulty in swallowing solids alone at the onset of illness indicates mechanical dysphagia. A short duration of progressive symptoms with significant weight loss is suggestive of malignancy. Presence of pain during swallowing (odynophagia) may occur in infective lesions (*Candida, Cytomegalovirus*, etc.) or acute ulcerating lesions (pill esophagitis). History of gastroesophageal reflux symptoms, systemic illness (stroke, Parkinson's disease, myasthenia gravis, muscular dystrophy, scleroderma, AIDS, etc.), drug/corrosive ingestion, exposure to radiation and surgeries in past may provide further clues to the diagnosis. Clinical examination for thyromegaly, cervical lymph nodes, oral cavity lesions and central nervous system function may be helpful. Hence, a careful history usually enables a physician to narrow down the list of differentials.

Table 1 shows the differential diagnosis of dysphagia.

Table 1 — Differential diagnosis of dysphagia

Oropharyngeal	Esophageal
Mechanical	
Oropharyngeal malignancy	Esophageal tumours
Upper esophageal web	Corrosive stricture
Zenker's diverticulum	Peptic stricture
Cervical osteophytes	Post radiation stricture
Thyromegaly	Anastomotic stricture
Retropharyngeal abscess	Food bolus impaction
Oropharyngeal infection	Foreign body impaction
	Esophageal webs and rings
	Diverticula
	Mediastinal mass lesion
	Vascular compression
Motor	
Cerebrovascular accident	Achalasia cardia
Myasthenia Gravis	Nutcracker esophagus
Parkinson's disease	Diffuse esophageal spasm
Intracranial Tumour	Hypertensive lower esophageal sphincter
Polymyositis or Dermatomyositis	Scleroderma
Muscular Dystrophy	
Rabies	
Cricopharyngeal achalasia	

Prevention and counselling of dysphagia

As dysphagia is a symptom resulting from various disease entities rather than a single disease, preventive measures are feasible in only certain situations. Diseases resulting from specific inciting agents may be prevented if awareness is improved among the general population.

1. Esophageal cancers have been associated with alcohol consumption, obesity and smoking and counselling about avoiding these risk factors might be useful.

2. Appropriate labelling of corrosive substances and keeping them away from the reach of children may prevent corrosive injuries of esophagus.

3. Swallowing pills in upright position with plenty of fluid may prevent pill esophagitis.

4. Prompt therapy of gastroesophageal reflux disease with PPI may heal esophageal ulcers and prevent development of peptic stricture.

5. Adequate chewing of food reduces the chance of food bolus impaction.

6. Counselling patients that dysphagia is an alarm symptom which requires prompt medical attention may help in early diagnosis and management of malignancy of esophagus.

Diagnostic approach of dysphagia

Prior to investigations for oropharyngeal/esophageal lesions, systemic illnesses causing dysphagia (stroke, Parkinson's disease, myasthenia gravis, etc.) should be considered and appropriately evaluated.

For structural oropharyngeal dysphagia, a nasopharyngeal endoscopy is appropriate. Specimen from lesions should be obtained for histopathology and/or microbiological evaluation. For motor oropharyngeal dysphagia, videofluoroscopic swallowing study is the best modality.

In patients with structural esophageal dysphagia, upper gastrointestinal endoscopy is appropriate as it enables better characterisation of lesion and collection of specimen for histopathology and/or microbiological evaluation. In suspected esophageal motility disorder, barium swallow study may be the appropriate initial test. For further characterisation of the motility disorder, patient may be referred to a higher center for esophageal manometry (Figure 1).
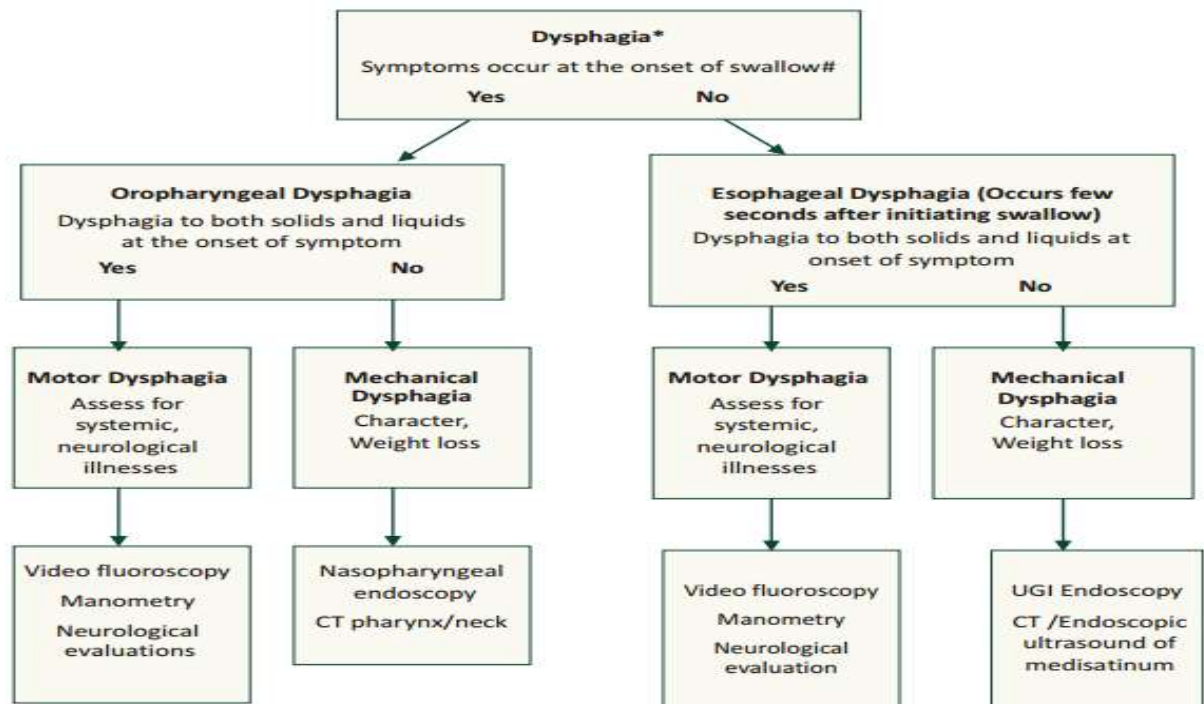
Figure 1 — Diagnostic algorithm of dysphagia

Management dysphagia
Oropharyngeal dysphagia:

1. Treatment of neuromuscular causes is difficult but in conditions like myasthenia gravis and Parkinson's disease medical therapy may be useful.

2. Adequate nutrition is crucial. Thick fluids or soft solids are better tolerated.

3. If risk of aspiration is high, feeding through nasogastric tube may be considered or surgical gastrostomy/jejunostomy may be performed for feeding.

4. For infective lesions, antibiotics may be used.

5. Malignant lesions require a multidisciplinary approach at a higher center.

Esophageal dysphagia:

1. Both structural and motor lesions require therapeutic endoscopic procedures or surgery and, hence, are better managed at a higher center.

2. Calcium channel blockers provide some relief in achalasia cardia or diffuse esophageal spasm.

3. PPI may be given for peptic strictures.

4. Soft foods should be recommended in case of esophageal webs and rings.

KEY MESSAGES

• Dysphagia may be accompanied by sensation of food getting stuck above suprasternal notch, choking sensation, nasal regurgitation of food, aspiration, dysarthria and dysphonia.

• Dysphagia can include difficulty in swallowing liquids and/or solids; paradoxal dysphagia — difficulty in swallowing only solids.

• Odynophagia — presence of pain during swallowing.

2. DISEASES OF THE STOMACH

The stomach is traditionally regarded as a hollow muscular sac that initiates the second phase of digestion. Hormones regulate several important physiological functions within the stomach, including secretion and motility. The control of gastric acid secretion depends on the central and peripheral effects of neuroendocrine hormones mediated directly and via vagal activity on the stomach. Several hormones (gastrin, somatostatin and ghrelin) and regulatory peptides are produced by cells within the stomach itself. Several other hormones that are secreted in the more distal portions of the GI tract (eg, cholecystokinin, glucose-dependent insulinotropic peptide) also regulate gastric function. The abnormal production of some of these hormones is associated with the development of various gastric diseases.

Gastric acid plays a role in regulating gastric function, protects against GI pathogens, facilitates the digestion and absorption of certain nutrients and may modulate feeding behavior. Acid secretion from gastric parietal cells facilitates protein and lipid digestion (essential amino and fatty acids — tryptophan, tyrosine and arachidonic acid). Tryptophan is a precursor of serotonin and in hypochlorhydric patients decrease digestion of tryptophan has been suggested as a precipitating factor for depression. Continuous acid-suppression therapy can lead to bacterial overgrowth in the small intestine, reducing calcium, iron and another nutrients absorption.

2.1. Functional gastroduodenal disorders

Functional gastroduodenal disorders are classified into 4 categories: functional dyspepsia (comprising postprandial distress syndrome and epigastric pain syndrome), belching disorders (comprising excessive gastric and supragastric

belching), chronic nausea and vomiting disorders (comprising chronic nausea vomiting syndrome, cyclic vomiting syndrome, and cannabinoid hyperemesis syndrome), and rumination syndrome. Postprandial distress syndrome and epigastric pain syndrome are increasingly accepted as valid clinical entities, based on new insights into the pathophysiology and the results of clinical trials. Diagnosis is based on the clinical history, and exclusion of peptic ulcer and cancer by endoscopy. The causes of functional dyspepsia remain to be established, but accumulating data suggest infections and possibly food may play an important role in subsets. The pathophysiology of functional dyspepsia involves many factors such as gastric motility, hypersensitivity, psychological factors and genetics. These factors interactively contribute to the manifestation of functional dyspepsia symptoms. Understanding of the underlying pathogenetic mechanisms might lead to better targeting of treatment in these patients with functional dyspepsia.

Classification of functional gastroduodenal disorders (according to Rome IV criteria — point **B**)

[a]Must fulfill criteria for B1a Postprandial Distress Syndrome and/or B1b. Epigastric Pain Syndrome.

[b]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

B1. Functional dyspepsia

diagnostic criteria[b] must include:

1. one or more of the following:

a. bothersome postprandial fullness;

b. bothersome early satiation (inability to finish a normal sized meal);

c. bothersome epigastric pain;

d. bothersome epigastric burning;

AND

2. no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

B1a. Postprandial distress syndrome

Diagnostic criteria must include one or both of the following at least 3 days per week:

1. Bothersome postprandial fullness (ie, severe enough to impact on usual activities).

2. Bothersome early satiation (ie, severe enough to prevent finishing a regular-size meal).

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive remarks

● Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present.

- Vomiting warrants consideration of another disorder.
- Heartburn is not a dyspeptic symptom but may often coexist.
- Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia.

Other individual digestive symptoms or groups of symptoms, eg, from gastroesophageal reflux disease and the irritable bowel syndrome may coexist with postprandial distress syndrome.

B1b. Epigastric pain syndrome

Diagnostic criteria[a] must include at least 1 of the following symptoms at least 1 day a week:

1. Bothersome epigastric pain (ie, severe enough to impact on usual activities).
AND/OR
2. Bothersome epigastric burning (ie, severe enough to impact on usual activities).

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy).

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive remarks

1. Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting.
2. Postprandial epigastric bloating, belching, and nausea can also be present.
3. Persistent vomiting likely suggests another disorder.
4. Heartburn is not a dyspeptic symptom but may often coexist.
5. The pain does not fulfill biliary pain criteria.
6. Symptoms that are relieved by evacuation of feces or gas generally should not be considered as part of dyspepsia.

Other digestive symptoms (such as from gastroesophageal reflux disease and the irritable bowel syndrome) may coexist with epigastric pain syndrome.

B2. Belching Disorders

Diagnostic criteria[a] must include all of the following:

bothersome (ie, severe enough to impact on usual activities) belching from the esophagus or stomach more than 3 days a week.

B2a: Excessive supragastric belching (from esophagus)
B2b: Excessive gastric belching (from stomach)

Supportive remarks:

- supragastric belching is supported by observing frequent, repetitive belching;
- gastric belching has no established clinical correlate;
- objective intraluminal impedance measurement can be used to distinguish supragastric from gastric belching.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

B3. Nausea and vomiting disorders

B3a: Chronic Nausea and Vomiting Syndrome

Must include all of the following:

1. Bothersome (ie, severe enough to impact on usual activities) nausea, occurring at least 1 day per week and/or 1 or more vomiting episodes per week.

2. Self-induced vomiting, eating disorders, regurgitation, or rumination are excluded.

3. No evidence of organic, systemic, or metabolic diseases that is likely to explain the symptoms on routine investigations (including at upper endoscopy).

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

B3b: Cyclic Vomiting Syndrome

Must include all of the following:

stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week).

1. At least e discrete episodes in the prior year and 2 episodes in the past 6 months, occurring at least 1 week apart.

2. Absence of vomiting between episodes, but other milder symptoms can be present between cycles.

Supportive remarks:

• history or family history of migraine headaches.

B3c: Cannabinoid Hyperemesis Syndrome

Diagnostic criteria[a] must include all of the following:

1. stereotypical episodic vomiting resembling cyclic vomiting syndrome in terms of onset, duration, and frequency.

2. Presentation after prolonged excessive cannabis use.

3. Relief of vomiting episodes by sustained cessation of cannabis use.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive remarks:

• may be associated with pathologic bathing behavior (prolonged hot baths or showers).

B4. Rumination syndrome

Diagnostic Criteria[a] for Rumination Syndrome must include all of the following:

1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing.

2. Regurgitation is not preceded by retching.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive remarks:

• effortless regurgitation events are usually not preceded by nausea;

• regurgitant contains recognizable food that might have a pleasant taste;

• the process tends to cease when the regurgitated material becomes acidic.

Diagnostic approach of functional gastroduodenal disorders

Functional dyspepsia is a diagnosis of exclusion; therefore, physicians should focus on excluding serious or specifically treatable diseases, without spending too much time investigating symptoms.

Dyspepsia has a broad and diverse differential diagnosis (table 2), including functional dyspepsia, peptic ulcer disease, reflux esophagitis, and gastric or esophageal malignancy. Functional dyspepsia is the most prevalent diagnosis, making up 70 percent of dyspepsia cases.

Table 2 — Differential diagnosis of dyspepsia

Diagnostic category	Approximate prevalence
Functional (nonulcer) dyspepsia	Up to 70 percent
Peptic ulcer disease	15 to 25 percent
Reflux esophagitis	5 to 15 percent
Gastric or esophageal cancer	< 2 percent
Abdominal cancer, especially pancreatic cancer	rare
Biliary tract disease	rare
Carbohydrate malabsorption (lactose, sorbitol, fructose, mannitol)	rare
Gastroparesis	rare
Hepatoma	rare
Infiltrative diseases of the stomach (Crohn's disease, sarcoidosis)	rare
Intestinal parasites (*Giardia species, Strongyloides species*)	rare
Ischemic bowel disease	rare
Medication effects	rare
Metabolic disturbances (hypercalcemia, hyperkalemia)	rare
Pancreatitis	rare
Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease)	rare

The physician should perform a detailed history and physical examination at the initial presentation, noting any findings that point to a diagnosis other than functional dyspepsia (e. g., right upper-quadrant pain with cholelithiasis, exercise association with coronary artery disease, radiation to the back with pancreatitis).

Agents commonly associated with dyspepsia:

• alcohol;

• oral antibiotics (e. g., erythromycin);

- bisphosphonates;
- corticosteroids (e. g., prednisone);
- herbs (e. g., garlic, ginkgo, saw palmetto, feverfew, chaste tree berry, white willow);
- iron;
- metformin;
- NSAID, including cyclooxygenase-2 inhibitors;
- opiates;
- orlistat;
- potassium chloride;
- theophylline.

Management functional dyspepsia

- Dietary change: smaller regular meals and reduced fat intake (fat can slow gastric emptying).
- *H. pylori* eradication.

H. pylori eradication may be beneficial as an initial strategy for management of uninvestigated dyspepsia before endoscopy.

- PPI (in epigastric pain syndrome).
- H_2-receptor antagonists (in epigastric pain syndrome).

The effect may have been overestimated, especially in comparison with PPI.

- Prokinetics (in postprandial distress syndrome).

The only available prokinetic agents in the United States are metoclopramide and erythromycin, for which the evidence is sparse. Metoclopramide may cause tardive dyskinesia and parkinsonian symptoms in elderly people, limiting its use. Erythromycin has some prokinetic effects and is used to treat gastroparesis. However, erythromycin has not been studied as a treatment for functional dyspepsia, so its effectiveness is unknown.

There is some initial evidence to suggest that herbal formulations containing peppermint improve functional dyspepsia symptoms, possibly through effects on the smooth muscle of the intestines. However, peppermint formulations available in the United States have not been well studied, and more research is needed.

- Antidepressants prescribe because of the high rate of coexisting depression and psychiatric illness in patients with refractory functional dyspepsia occur.

KEY MESSAGES

- Physicians should proceed directly to endoscopy in patients with dyspepsia who have warning signs (e. g., unintended weight loss, progressive dysphagia, persistent vomiting, evidence of gastrointestinal bleeding, family history of cancer) or who are older than 55 years.
- In patients with isolated dyspepsia who do not exhibit warning signs, a test-and-treat strategy for *H. pylori* infection is effective and less expensive than initial endoscopy.

• Histamine H_2 blockers and PPI reduce functional dyspepsia symptoms, although the effect is small.

• The prokinetic agent metoclopramide may be effective in treating functional dyspepsia, although the data are limited.

• Eradication of *H. pylori* is somewhat effective in reducing symptoms of endoscopically confirmed functional dyspepsia, although it may not be cost-effective.

• Gum chewing increases the flow of saliva, the frequency of saliva swallowing, but also could increase the frequency of air swallowing, worsening the discomfort caused by gastric and/or supragastric belching.

2.2. *Helicobacter pylori* infection

H. pylori is spiral in shape with a flagellum, gram-negative, micro aerophilic bacterium which colonizes in the human gastric mucosa, and the infection may last for decades. It is thought *H. pylori* infection to be the most common bacterial infection, and influence approximately 50–75 % of the population all over the world. *H. pylori* is the main reason for the upper gastrointestinal diseases, including peptic ulcer disease (gastric and duodenal), chronic gastritis, gastric cancer and gastric mucosal-associated lymphoid tissue lymphoma (Figure 2).
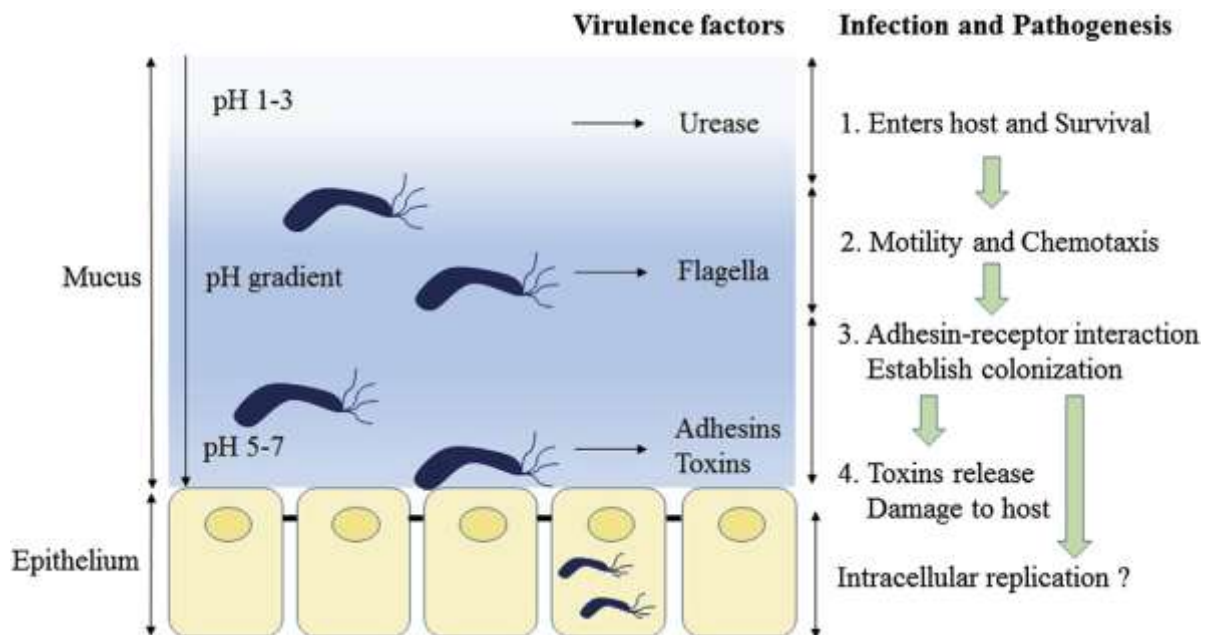
Figure 2 — Schematic diagram of *Helicobacter pylori* infection and pathogenesis

The urease activity and flagella-mediated motility of *H. pylori* facilitate its survival and movement toward the lower mucus gel above the epithelium, followed by several adhesins, including blood-antigen binding protein A, sialic acid-binding adhesin, and other outer membrane proteins interacting with receptors on the host epithelium cells. After successful colonization, toxins, including cytotoxin-associated gene A, and vacuolating cytotoxin A, are involved in damage of host tissue and intracellular replication.

Along with upper gastrointestinal tract problems, *H.pylori* caused chronic and low-grade inflammation in the gastric mucosa that could lead to some metabolic disorders. *H. pylori* infection may be correlated with insulin resistance, increased total and low density lipoprotein cholesterol and decrease of high density lipoprotein in infected peoples. Also, *H. pylori* has a critical role in the other extragastric diseases such as chronic urticaria.

Although *H. pylori*-associated diseases commonly present with dyspepsia (e. g., peptic ulcer and gastric cancer), the infection itself may cause dyspepsia without obvious gross structural changes. *H. pylori* infection causes progressive functional and structural gastroduodenal damage that unpredictably may progress to peptic ulcer disease and its complications such as atrophic gastritis or gastric cancer as follows.

Clinical outcomes related to H. pylori infection are as follows:
- active chronic gastritis:
  ➢ impaired acid production;
  ➢ impaired drug absorption.
- Atrophic gastritis:
  ➢ impaired B12 vitamin absorption.
- Transmission of the infection to others especially family.
- Dyspepsia (nonulcer).
- Iron deficiency anaemia.
- Autoimmune thrombocytopenia.
- Peptic ulcer:
  ➢ peptic ulcer complications.
- MALT lymphoma.
- Gastric adenocarcinoma.

Diagnostic approach of *H. pylori* infection
Noninvasive tests for H. pylori infection include the following:
- serology:
  ➢ blood Ig G serology;
  ➢ salivary assay;
  ➢ urinary Ig G assay.
- Urea breath test:
  ➢ ^{13}C-urea breath tests is the best approach to the diagnosis of H. pylori infection, with high sensitivity and specificity, and excellent performances.
  ➢ ^{14}C-urea breath tests.
- Urea blood test:
  ➢ ^{13}C-urea blood test.
- Stool antigen test:
  ➢ polyclonal stool antigen tests;
  ➢ monoclonal stool antigen tests;
  ➢ rapid stool antigen tests.

According to the Maastricht V/Florence Consensus Report (2016) Urea breath test is the most investigated and best recommended non-invasive test in the context of a 'test-and-treat strategy'. Monoclonal stool antigen test can also be used. Serological tests can be used only after validation. Rapid ('office') serology tests using whole blood should be avoided in this regard.

Invasive tests for H. pylori infection requiring endoscopy include the following:

- biopsy urease testing (rapid urease test);
- histology:
  ➢ immunostaining;
  ➢ FISH;
  ➢ molecular testing for susceptibility;
  ➢ molecular tests for virulent factors (VacA-CagA).
- Brush cytology.
- Bacterial culture:
  ➢ susceptibility tests.

In clinical practice when there is an indication for endoscopy, and there is no contraindication for biopsy, the rapid urease test is recommended as a first-line diagnostic test. In the case of a positive test, it allows immediate treatment. One biopsy should be taken from the corpus and one from the antrum. The rapid urease test is not recommended as a test for *H. pylori* eradication assessment after treatment (the Maastricht V/Florence Consensus Report). For assessment of *H. pylori* gastritis, a minimum standard biopsy setting is two biopsies from the antrum (greater and lesser curvature 3 cm proximal to the pyloric region) and two biopsies from the middle of the body. Additional biopsy from the incisura is considered for detection of precancerous lesions.

The choice of test depends on clinical setting, local availability, and cost and use of medications (e. g., use of PPIs, bismuth, or antibiotics) that reduce the density of *H. pylori* and thus reduce the accuracy of tests for active infection. The presence of such potentially interfering agents is not an absolute contraindication for testing as testing can generally be delayed for a time during which those drugs are discontinued. The choice of a test is also influenced by the pretest probability of the infection.

H. pylori eradication

H. pylori eradication may be beneficial as an initial strategy for management of uninvestigated dyspepsia before endoscopy.

All patients with peptic ulcer disease, gastric cancer, and MALT lymphoma should be tested for *H. pylori*. Recommend testing in first degree relatives to patients with gastric cancer, in NSAID-naive patients, who need long-term NSAID therapy, and in patients presenting with dyspepsia and no alarm symptoms.

Non-endoscoped patients can be tested with a urea-breath test or a faecal antigen test. Endoscoped patients can be tested with a rapid urease test.

PPI therapy should be stopped at least 1 week prior to *H. pylori* testing. All infected patients should be offered *H. pylori* eradication therapy.

The optimal treatment for *H. pylori* infection are usually triple or quadruple antibiotic therapies. The most commonly used antibiotics are imidazole (metronidazole or tinidazol), macrolide (clarithromycin or azithromycin), tetracycline, amoxicillin, rifabutin and furazolidon (table 3).

Table 3 — Regimens recommended for eradication of *H. pylori* infection

Drug	Dose
Triple therapy	
Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin *plus*	500 mg bid
Metronidazole *or*	500 mg bid
Amoxicillin	1 g bid
Quadruple Therapy	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

PPI-based triple therapy — first- line therapy — includes PPIs in combination with several antibiotics such as amoxicillin plus clarithromycin or metronidazole. Standard dose (amoxicillin 1 g, clarithromycin 500 mg and rabeprazole 20 mg, all two times per day). It is recommended to perform clarithromycin susceptibility testing when a standard clarithromycin-based treatment is considered as the first-line therapy, except in populations or regions with well documented low clarithromycin resistance (< 15 %). This test can be performed either by a standard method (antibiogram) after culture or by a molecular test directly on the gastric biopsy specimen. In areas of high (> 15 %) clarithromycin resistance, bismuth quadruple or non-bismuth quadruple, concomitant (PPI, amoxicillin, clarithromycin and a nitroimidazole) therapies are recommended.

After failure of a PPI clarithromycin-containing treatment for *H. pylori* infection, either a bismuth-containing quadruple therapy or levofloxacin-based triple therapy is recommended as second-line treatment or rescue therapy.

Ten-days sequential regime: amoxicillin plus a PPI for 5 days, then continue by clarithromycin, metronidazole and a PPI for more 5 days.

H. pylori treatment involves combination of antimicrobial and antisecretory agents for 7 to 14 days. The dosage and duration of treatment of PPIs for adults correspond to those that are able to suppress gastric acid secretion. Long-term omeprazole therapy in *H. pylori* positive patients induced changes in mucosal inflammation and glandular atrophy.

H. pylori testing should be offered to all patients after eradication therapy but is mandatory in patients with ulcer disease, noninvasive gastric cancer or

MALT lymphoma. Testing after eradication should not be done before 4 weeks after treatment has ended.

Adjuvant therapy with the probiotics (live microorganisms mostly within *Lactobacillus, Bifido* bacterium and *Saccharomyces*) is recommended due to immunomodulation, stimulation of mucin production and inhibition of colonization and survival of *H.pylori*.

Potential options such as medicinal plants, photodynamic therapy and vaccine are still in the experimental phase.

KEY MESSAGES

• *H. pylori* is an important major cause of chronic gastritis, peptic ulcer disease and gastric malignancies such as mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma.

• *H. pylori* has a role in the extragastric diseases such as insulin resistance, dyslipidemia, chronic urticaria, anemia.

• Multiple drugs have been evaluated in the therapy of *H. pylori*. No single agent is effective in eradicating the organism. Combination therapy for 14 days provides the greatest efficacy. A shorter course administration (7–10 days), although attractive, has not proved as successful as the 14-day regimens. The agents used with the greatest frequency include amoxicillin, metronidazole, tetracycline, clarithromycin, and bismuth compounds.

• The Maastricht IV/Florence Consensus Report proposed a standard triple therapy consisting of two antibiotics and a PPI as the first-line regimen.Levofloxacin containing triple treatment are recommended as rescue treatment for infection of *H. pylori* after defeat of first-line therapy.Bismuth containing quadruple treatment, sequential treatment or a non-bismuth quadruple treatment are an alternative therapy.

• Adjuvant therapy with the probiotics (live microorganisms mostly within *Lactobacillus, Bifido* bacterium and *Saccharomyces*) is recommended.

2.3. Chronic gastritis

The term "gastritis" defines any histologically confirmed inflammation of the gastric mucosa. It is usually classified as acute or chronic, a clinical distinction that does not imply a different profile of the inflammatory cell population.

Chronic gastritis is a multistep, progressive and lifelong inflammation. It begins usually in childhood as a simple chronic ("superficial") mononuclear inflammation with co-existence of an acute ("active") neutrophilic inflammation of varying degree. Gastritis progresses stepwise, within years and decades, to atrophic gastritis that is characterized by a loss of normal mucosal glands either in antrum or corpus (and fundus), or in both.

Proposed classification of gastritis in the Kyoto consensus conference (2015):

• Autoimmune gastritis.
• Infectious gastritis:
  ➤ *H. pylori*-induced gastritis;

➢ bacterial gastritis other than *H. pylori (Helicobacter heilmannii* gastritis; *Enterococcus* gastritis; *Mycobacteria* gastritis; secondary syphilitic gastritis);

➢ gastric phlegmone;

➢ viral gastritis (enteroviral gastritis; *Cytomegalovirus* gastritis);

➢ fungal gastritis (due to mucormycosis; gastric candidiasis; gastric histoplasmosis);

➢ parasitic gastritis (*Cryptosporidium* gastritis; gastric *strongyloides stercorale*; gastric *anisakiasis*).

• Gastritis due to external causes:

➢ drug-induced gastritis;

➢ alcoholic gastritis;

➢ radiation gastritis;

➢ chemical gastritis;

➢ gastritis due to duodenal reflux;

➢ gastritis due to other specified external cause.

• Gastritis due to specified causes:

➢ lymphocytic gastritis;

➢ Ménétrier disease;

➢ allergic gastritis;

➢ eosinophilic gastritis.

• Gastritis due to other diseases classified elsewhere:

➢ gastritis due to sarcoidosis;

➢ gastritis due to vasculitis;

➢ gastritis due to Crohn's disease.

Pathology chronic gastritis

The most aggressive forms of chronic gastritis are those which result most likely in advanced stages of atrophic gastritis, i.e., are forms of *H. pylori* gastritis with highest likelihood to progress to the end-stage atrophy. Along the progression of chronic non-atrophic gastritis to atrophic phenotypes, manifold coincidental pathogenetic processes, even carcinogenic ones, are potentially triggered on, which phenomena in sc. "Correa cascade" may finally contribute to processes that link the chronic gastritis with such extreme sequelae as cancer (Figure 3).

Corpus atrophy leads ultimately to failures in the secretion of hydrochloric acid and intrinsic factor. In acid-free and atrophic stomach, due to the impairment in secretion of intrinsic factor, absorption of the essential vitamins are failed. In acid-free stomach dietary metabolism and absorption of micronutrients, like iron, calcium, magnesium and zinc, or absorption of some medicines (e.g., dipyridamol, some iron formulations and anti-fungal medicines like fluconazole or itraconazole, thyroxin and atazanovir) are impaired.
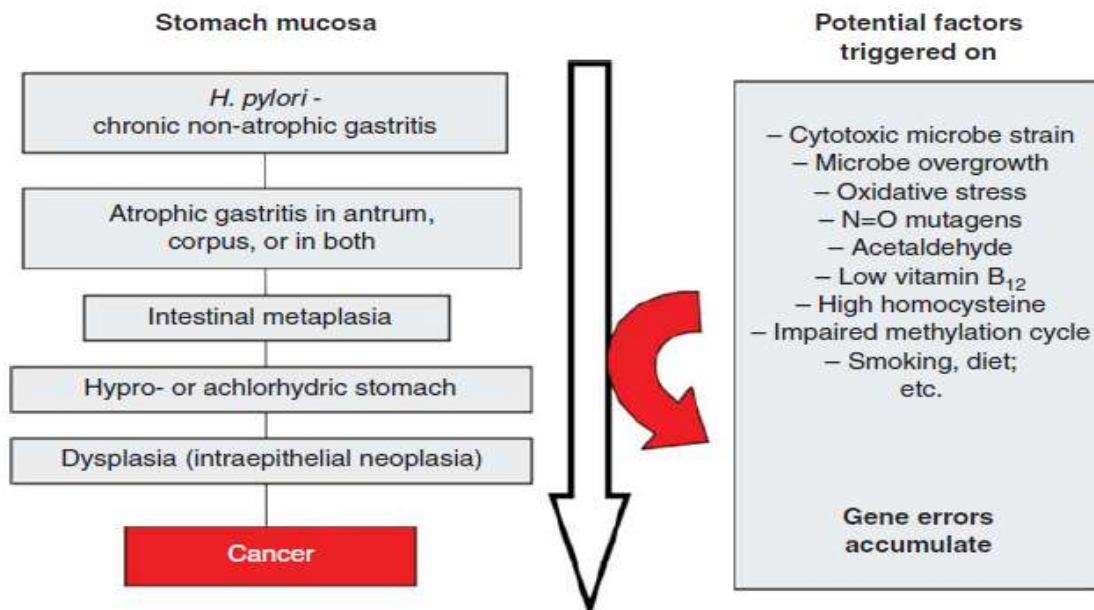
Figure 3 — Scheme on natural course and progression of *Helicobacter pylori* gastritis from a non-atrophic form to gastric malignancy (sc. "Correa cascade") (modified from a paper of P. Sipponen et al.)

Several potentially pathogenetic factors and mechanisms, linked with carcinogenesis, play a role and are triggered stepwise on during the course and progression of the cascade.

Diagnostic approach of chronic gastritis

Atrophic mucosa and intestinal metaplasia can be accurately detected by image-enhanced endoscopy (includes chromoendoscopy, high-resolution magnification endoscopy and image-enhanced endoscopy combined with magnification) after appropriate training. Conventional endoscopy is an inadequate tool for diagnosing atrophy and intestinal metaplasia and therefore it remains mandatory that a biopsy is carried out, allowing histomorphological assessment of the gastric mucosa according to the Sydney classification.

The Sydney System and its updating are the guidelines for interpretation of the morphological appearances (degree of atrophy, inflammation, activity, metaplasia, HP) in biopsy specimens in endoscopy practice.

The OLGA/OLGIM staging (Operative Link on Gastritis/Intestinal Metaplasia Assessment) of atrophic gastritis is a practical scheme for the categorization of the patients to low-, medium- and high-risk groups for stomach cancer (Figure 4).

Modified from a paper of Rugge et al. The staging is a practical tool for the delineation of patients to high (stages III–IV) and low (stages 0–II) risk groups for cancer, for gastric cancer of the intestinal type in particular. The staging requires endoscopy and proper biopsy practice but can also be done non-invasively by a blood test with applying specific biomarkers (pepsinogen I and II, gastrin-17 and *H. pylori* serology) that reflect the function (acid secretion) and the structure of both antral and corpus mucosa in the blood plasma/serum.

Atrophy score Antrum	Corpus			
	No atrophy (score 0)	Mild atrophy (score 1)	Mod atrophy (score 2)	Severe atrophy (score 3)
No atrophy (score 0) (incl incisura angularis)	STAGE 0	STAGE I	STAGE II	STAGE III
Mild atrophy (score 1) (incl incisura angularis)	STAGE I	STAGE I	STAGE II	STAGE III
Mod atrophy (score 2) (incl incisura angularis)	STAGE II	STAGE II	STAGE III	STAGE IV
Severe atrophy (score 3) (incl incisura angularis)	STAGE III	STAGE III	STAGE IV	STAGE IV

Figure 4 — OLGA staging for risk of stomach cancer

The prognostic value of gastritis staging, already recognised by the Maastricht IV Consensus Conference, was recently confirmed at the Kyoto Global Consensus Meeting on *H. pylori* gastritis (2015).

In diagnosis and screening of atrophic gastritis can use the plasma biomarkers – pepsinogen 1, pepsinogen 2, gastrin-17, *H. pylori* serology test.

Antral atrophic gastritis (loss of antral glands) is accompanied with a loss of antral G cell and low plasma levels of both fasting and stimulated gastrin-17 (after a drink with protein powder, stimulation with bombesin (gastrin releasing peptide) or PPI. A low fasting plasma G-17 (1 pmol/l or less) indicates two options in practice. Either there is an advanced atrophic gastritis in the antrum (OLGA class III–IV) or the low G-17 is a result of a high intragastric acidity (low pH). Both options are indications for upper gastrointestinal endoscopy.

Management chronic gastritis

Treatment of chronic gastritis depends on the etiology. *H. pylori* infected individuals should be offered eradication therapy.

KEY MESSAGES

• Chronic gastritis is a morphological diagnosis.

• A life-long and aggressive inflammation in gastritis results in destruction (atrophic gastritis) of stomach mucosa with time (years and decades). "Correa cascade" may contribute to processes that link the chronic gastritis to cancer.

• The progressive worsening of atrophic gastritis results subsequently in dysfunctions of stomach mucosa. Atrophic gastritis will finally end up in a permanently acid-free stomach in the most extreme cases.

• Image-enhanced endoscopy (includes chromoendoscopy, high-resolution magnification endoscopy and image-enhanced endoscopy combined with magnification) allow to detect atrophic mucosa and intestinal metaplasia.

• In diagnosis and screening of atrophic gastritis can use the plasma biomarkers — pepsinogen 1, pepsinogen 2, gastrin-17, *H. pylori* serology test.

● The risk for development of gastric cancer correlates with the extent and severity of atrophic gastritis.

● Autoimmune gastritis can be detected by the presence of antiparietal cell antibodies.

● In addition to the risks of malignancy and peptic ulcer, acid-free stomach and severe forms of atrophic gastritis may associate with failures in absorption of essential vitamins, like vitamin B_{12}, micronutrients (like iron, calcium, magnesium and zinc), diet and medicines.

2.4. Peptic ulcer disease

Peptic ulcer disease is one of the most commonly encountered diseases in gastroenterology clinics. After the discovery of *H. pylori* by Warren and Marshall, it has been identified as the most important cause of peptic ulcer. Eradication of *H. pylori* markedly reduces the post-treatment recurrence rate of peptic ulcer.

PUD encompasses both gastric and duodenal ulcers.

Ulcers are defined as breaks in the mucosal surface > 5 mm in size, with depth to the submucosa.

Duodenal ulcers (DUs) and gastric ulcers (GUs): share many common features in terms of pathogenesis, diagnosis, and treatment, but several factors distinguish them from one another.

Epidemiology of peptic ulcer disease
Duodenal ulcers

DUs are estimated to occur in 6–15 % of the Western population. The incidence of DUs declined steadily from 1960 to 1980 and has remained stable since then. The death rates, need for surgery, and physician visits have decreased by > 50 % over the past 30 years. The reason for the reduction in the frequency of DUs is likely related to the decreasing frequency of *H. pylori*. Before the discovery of *H. pylori*, the natural history of DUs was typified by frequent recurrences after initial therapy. Eradication of *H. pylori* has greatly reduced these recurrence rates.

Gastric ulcers

GUs tend to occur later in life than duodenal lesions, with a peak incidence reported in the sixth decade. More than half of GUs occur in males and are less common than DUs, perhaps due to the higher likelihood of GUs being silent and presenting only after a complication develops. Autopsy studies suggest a similar incidence of DUs and GUs.

Pathology of peptic ulcer disease
Duodenal ulcers

DUs occur most often in the first portion of duodenum (> 95 %), with ~ 90 % located within 3 cm of the pylorus. They are usually 1 cm in diameter but can occasionally reach 3–6 cm (giant ulcer). Ulcers are sharply demarcated, with depth at times reaching the muscularis propria. The base of the ulcer often consists of a zone of eosinophilic necrosis with surrounding fibrosis. Malignant DUs are extremely rare.

Gastric ulcers

In contrast to DUs, GUs can represent a malignancy.

Benign GUs are most often found distal to the junction between the antrum and the acid secretory mucosa. Benign GUs are quite rare in the gastric fundus and are histologically similar to DUs. Benign GUs associated with *H. pylori* are also associated with antral gastritis. In contrast, NSAID-related GUs are not accompanied by chronic active gastritis but may instead have evidence of a chemical gastropathy, typified by foveolar hyperplasia, edema of the lamina propria and epithelial regeneration in the absence of *H. pylori*. Extension of smooth-muscle fibers into the upper portions of the mucosa, where they are not typically found, may also occur.

Pathophysiology of peptic ulcer disease
Duodenal ulcers

H. pylori and NSAID-induced injury account for the majority of DUs. Many acid secretory abnormalities have been described in DU patients. Of these, average basal and nocturnal gastric acid secretion appears to be increased in DU patients as compared to controls; however, the level of overlap between DU patients and control subjects is substantial. The reason for this altered secretory process is unclear, but *H. pylori* infection may contribute. Accelerated gastric emptying of liquids has been noted in some DU patients, but its role in DU formation, if any, is unclear. Bicarbonate secretion is significantly decreased in the duodenal bulb of patients with an active DU as compared to control subjects. *H. pylori* infection may also play a role in this process

Gastric ulcers

As in DUs, the majority of GUs can be attributed to either *H. pylori* or NSAID-induced mucosal damage. GUs that occur in the prepyloric area or those in the body associated with a DU or a duodenal scar are similar in pathogenesis to DUs. Gastric acid output (basal and stimulated) tends to be normal or decreased in GU patients. When GUs develop in the presence of minimal acid levels, impairment of mucosal defense factors may be present.

Abnormalities in resting and stimulated pyloric sphincter pressure with a concomitant increase in duodenal gastric reflux have been implicated in some GU patients. Although bile acids, lysolecithin, and pancreatic enzymes may injure gastric mucosa, a definite role for these in GU pathogenesis has not been established. Delayed gastric emptying of solids has been described in GU patients but has not been reported consistently.

H. pylori and acid peptic disorders

Gastric infection with the bacterium *H. pylori* accounts for the majority of PUD. This organism also plays a role in the development of gastric mucosal-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma. Although the entire genome of *H. pylori* has been sequenced, it is still not clear how this organism, which resides in the stomach, causes ulceration in the duodenum, or whether its eradication will lead to a decrease in gastric cancer.

The final effect of *H. pylori* on the gastrointestinal tract is variable and determined by microbial and host factors. The type and distribution of gastritis correlate with the ultimate gastric and duodenal pathology observed.

Pathogenetic factors unrelated to *H. pylori* and NSAIDs in acid peptic disease

Cigarette smoking has been implicated in the pathogenesis of PUD. Not only have smokers been found to have ulcers more frequently than do nonsmokers, but smoking appears to decrease healing rates, impair response to therapy, and increase ulcer-related complications such as perforation.

Genetic predisposition may play a role in ulcer development. First-degree relatives of DU patients are three times as likely to develop an ulcer; however, the potential role of *H. pylori* infection in contacts is a major consideration. Increased frequency of blood group O and of the nonsecretor status have also been implicated as genetic risk factors for peptic diathesis. However, *H. pylori* preferentially binds to group O antigens. The role of genetic predisposition in common PUD has not been established.

Psychological stress has been thought to contribute to PUD, but studies examining the role of psychological factors in its pathogenesis have generated conflicting results. Although PUD is associated with certain personality traits (neuroticism), these same traits are also present in individuals with nonulcer dyspepsia (NUD) and other functional and organic disorders. Although more work in this area is needed, no typical PUD personality has been found.

Diet has also been thought to play a role in peptic diseases. Certain foods can cause dyspepsia, but no convincing studies indicate an association between ulcer formation and a specific diet. This is also true for beverages containing alcohol and caffeine. Specific chronic disorders have been associated with PUD.

Multiple factors play a role in the pathogenesis of PUD. The two predominant causes are *H. pylori* infection and NSAID ingestion.

Risk factors of idiopathic ulcer disease:
- demographic risk factors (e. g., white race and older age);
- psychoactive substance use (e. g., tobacco use and alcohol);
- genetic risk factors (e. g., mucin genes and HLA-DQA1);
- comorbid diseases (e. g., liver cirrhosis, end-stage renal disease, diabetes mellitus, cerebrovascular accident, and malignancy);
- chronic mesenteric ischemia;
- higher psychological stress.

Clinical features of peptic ulcer disease

History

Abdominal pain is common to many gastrointestinal disorders, including DU and GU, but has a poor predictive value for the presence of either DU or GU. Up to 10 % of patients with NSAID-induced mucosal disease can present with a complication (bleeding, perforation, and obstruction) without antecedent

symptoms. Despite this poor correlation, a careful history and physical examination are essential components of the approach to a patient suspected of having peptic ulcers.

Epigastric pain described as a burning or gnawing discomfort can be present in both DU and GU. The discomfort is also described as an ill-defined, aching sensation or as hunger pain. The typical pain pattern in DU occurs 90 min to 3 h after a meal and is frequently relieved by antacids or food. Pain that awakes the patient from sleep (between midnight and 3 a.m.) is the most discriminating symptom, with two-thirds of DU patients describing this complaint. Unfortunately, this symptom is also present in one-third of patients with NUD. The pain pattern in GU patients may be different from that in DU patients, where discomfort may actually be precipitated by food. Nausea and weight loss occur more commonly in GU patients. Endoscopy detects ulcers in < 30 % of patients who have dyspepsia.

The mechanism for development of abdominal pain in ulcer patients is unknown. Several possible explanations include acid-induced activation of chemical receptors in the duodenum, enhanced duodenal sensitivity to bile acids and pepsin, or altered gastroduodenal motility.

Variation in the intensity or distribution of the abdominal pain, as well as the onset of associated symptoms such as nausea and/or vomiting, may be indicative of an ulcer complication. Dyspepsia that becomes constant, is no longer relieved by food or antacids, or radiates to the back may indicate a penetrating ulcer (pancreas). Sudden onset of severe, generalized abdominal pain may indicate perforation. Pain worsening with meals, nausea, and vomiting of undigested food suggest gastric outlet obstruction. Tarry stools or coffee-ground emesis indicate bleeding.

Physical examination

Epigastric tenderness is the most frequent finding in patients with GU or DU. Pain may be found to the right of the midline in 20 % of patients. Unfortunately, the predictive value of this finding is rather low. Physical examination is critically important for discovering evidence of ulcer complication. Tachycardia and orthostasis suggest dehydration secondary to vomiting or active gastrointestinal blood loss. A severely tender, boardlike abdomen suggests a perforation. Presence of a succussion splash indicates retained fluid in the stomach, suggesting gastric outlet obstruction.

PUD-related complications

Gastrointestinal bleeding

Gastrointestinal bleeding is the most common complication observed in PUD. It occurs in ~ 15 % of patients and more often in individuals > 60 years old. The higher incidence in the elderly is likely due to the increased use of NSAIDs in this group. Up to 20 % of patients with ulcer-related hemorrhage bleed without any preceding warning signs or symptoms.

Perforation

The second most common ulcer-related complication is perforation, being reported in as many as 6–7 % of PUD patients. As in the case of bleeding, the incidence of perforation in the elderly appears to be increasing secondary to increased use of NSAIDs. *Penetration* is a form of perforation in which the ulcer bed tunnels into an adjacent organ. DUs tend to penetrate posteriorly into the pancreas, leading to pancreatitis, whereas GUs tend to penetrate into the left hepatic lobe. Gastrocolic fistulas associated with GUs have also been described.

Gastric outlet obstruction

Gastric outlet obstruction is the least common ulcer-related complication, occurring in 1–2 % of patients. A patient may have relative obstruction secondary to ulcer-related inflammation and edema in the peripyloric region. This process often resolves with ulcer healing. A fixed, mechanical obstruction secondary to scar formation in the peripyloric areas is also possible. The latter requires endoscopic (balloon dilation) or surgical intervention. Signs and symptoms relative to mechanical obstruction may develop insidiously. New onset of early satiety, nausea, vomiting, increase of postprandial abdominal pain, and weight loss should make gastric outlet obstruction a possible diagnosis.

Differential diagnosis of peptic ulcer disease

The list of gastrointestinal and nongastrointestinal disorders that can mimic ulceration of the stomach or duodenum is quite extensive. The most commonly encountered diagnosis among patients seen for upper abdominal discomfort is NUD (functional dyspepsia or essential dyspepsia) — a group of heterogeneous disorders typified by upper abdominal pain without the presence of an ulcer.

Several additional disease processes that may present with "ulcer-like" symptoms include proximal gastrointestinal tumors, gastroesophageal reflux, vascular disease, pancreaticobiliary disease (biliary colic, chronic pancreatitis), and gastroduodenal Crohn's disease.

Etiologies to be excluded for the diagnosis of idiopathic peptic ulcer:

• *H.pylori* infection;

• usage of ulcerogenic medications (e. g., NSAIDs, aspirin, and other ulcerogenic drugs — steroids, potassium chloride, nitrogen-containing bisphosphonates, some immunosuppressive medications);

• systemic diseases with upper gastrointestinal tract manifestations (e. g., Crohn's disease, mastocytosis, sarcoidosis, amyloidosis, eosinophilic gastroenteritis, and vasculitis);

• hyperacidity of the stomach (i. e., Zollinger-Ellison syndrome)

• other infections (e. g., *Helicobacter heilmanii, cytomegalovirus, herpes simplex virus*, tuberculosis, syphilis, and fungal infection).

Diagnostic approach of peptic ulcer disease

Documentation of an ulcer requires either a radiographic (barium study) or an endoscopic procedure.

- *Barium studies*
  - ➢ A DU appears as a well-demarcated crater, most often seen in the bulb.
  - ➢ A GU may represent benign or malignant disease.

Typically, a benign GU also appears as a discrete crater with radiating mucosal folds originating from the ulcer margin.

Ulcers >3 cm in size or those associated with a mass are more often malignant.

The sensitivity of older *single-contrast barium meals* for detecting a DU is as high as 80 %, with a *double-contrast study* providing detection rates as high as 90 %.

Sensitivity for detection is decreased in small ulcers (< 0.5 cm), presence of previous scarring, or in postoperative patients.

Radiographic studies that show a GU must be followed by endoscopy and biopsy.

- *Endoscopy* provides the most sensitive and specific approach for examining the upper gastrointestinal tract.

Endoscopic examination is particularly helpful in identifying lesions too small to detect by radiographic examination, for evaluation of atypical radiographic abnormalities, or to determine if an ulcer is a source of blood loss.

- *Tissue biopsy.*

Management peptic ulcer disease

- *H. pylori eradication* should be done in patients with documented PUD.

- *Acid-suppressing therapy* with acid neutralizing/inhibitory drugs (antacids, H_2 receptor antagonists, PPI) remains the mainstay of treatment PUD. PPIs administration for 4 to 8 weeks is recommended, and a longer duration of therapy may be needed for complicated ulcer (e. g., bleeding or perforated).

- *Bismuth-containing compounds* for treating PUD due to their effect against *H. pylori* and inducing ulcer healing. Potential mechanisms include ulcer coating; prevention of further pepsin/HCl-induced damage; binding of pepsin; and stimulation of prostaglandins, bicarbonate, and mucous secretion.

- *Prostaglandin analogues* were developed for the treatment of PUD in view of their central role in maintaining mucosal integrity and repair.

Endoscopic approaches for the treatment of of peptic ulcer disease

For peptic ulcer bleeding various endoscopic hemostatic methods are available, including injection therapy, mechanical therapy, and thermal coagulation. Newly developed methods, such as Hemospray powder and over-the-scope clips, may provide additional options. Appropriate decisions and specific treatment are needed depending upon the conditions.

Surgical therapy of peptic ulcer disease

Surgical intervention in PUD can be use for treatment of medically refractory disease, or as urgent/emergent, for the treatment of an ulcer-related complication.

Refractory ulcers are an exceedingly rare occurrence. Surgery is more often required for treatment of an ulcer-related complication. Gastrointestinal bleed-

ing, perforation, and gastric outlet obstruction are the three complications that may require surgical intervention.

Hemorrhage is the most common ulcer-related complication, occurring in ~15–25 % of patients. Bleeding may occur in any age group but is most often seen in older patients (sixth decade or beyond). The majority of patients stop bleeding spontaneously, but endoscopic therapy is necessary in some. Parenterally and orally administered PPIs also decrease ulcer rebleeding in patients who have undergone endoscopic therapy. Patients unresponsive or refractory to endoscopic intervention will require surgery (~ 5 % of transfusion-requiring patients).

Free peritoneal perforation occurs in ~2–3 % of DU patients. As in the case of bleeding, up to 10 % of these patients will not have antecedent ulcer symptoms. Concomitant bleeding may occur in up to 10 % of patients with perforation, with mortality being increased substantially. Peptic ulcer can also penetrate into adjacent organs, especially with a posterior DU, which can penetrate into the pancreas, colon, liver, or biliary tree.

Pyloric channel ulcers or DUs can lead to gastric outlet obstruction in ~2–3 % of patients. This can result from chronic scarring or from impaired motility due to inflammation and/or edema with pylorospasm. Patients may present with early satiety, nausea, vomiting of undigested food, and weight loss. Conservative management with nasogastric suction, intravenous hydration/nutrition, and antisecretory agents is indicated for 7–10 days with the hope that a functional obstruction will reverse. If a mechanical obstruction persists, endoscopic intervention with balloon dilation may be effective. Surgery should be considered if all else fails.

KEY MESSAGES

• *H.pylori* infection and NSAIDs are common causes of peptic ulcer disease.

• Multiple factors play a role in the pathogenesis of PUD: cigarette smoking, genetic predisposition, psychological stress, diet, usage of ulcerogenic medications: NSAIDs, aspirin, steroids, potassium chloride, nitrogen-containing bisphosphonates, some immunosuppressive medications; systemic diseases: Crohn's disease, mastocytosis, sarcoidosis, amyloidosis, eosinophilic gastroenteritis, and vasculitis.

• In contrast to duodenal ulcers, gastric ulcers can represent a malignancy.

• The physician's goal in treating PUD is to provide relief of symptoms (pain or dyspepsia), promote ulcer healing, and ultimately prevent ulcer recurrence and complications.

• The common conclusion arrived at by multiple consensus conferences around the world is that *H. pylori* should be eradicated in patients with documented PUD. Failure of *H. pylori* eradication with triple therapy in a compliant patient is usually due to infection with a resistant organism. Quadruple therapy should be the next step.

2.5. NSAID-induced gastrointestinal damage

NSAIDs are among the widely used prescription and over-the-counter medications. They are used to treat the symptoms of a variety of inflammatory conditions, most notably osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and gout. By inhibiting the activity of COX, NSAIDs prevent the formation of PG H_2, which is the precursor for the production of all other PG and thromboxane subtypes. Inhibition of COX is central to the major anti-inflammatory actions of NSAIDs. By inhibiting the production of PGs (particularly PGE_2 and PGI_2), NSAIDs reduce two key elements of inflammation: vasodilation and pain. By reducing blood flow to a damaged and inflamed site, NSAIDs also contribute to a reduction of edema.

Pathophysiology NSAID-induced gastrointestinal damage

PGs do not only contribute to the cardinal signs of inflammation. They also play important roles in many physiological processes.

In the gastrointestinal tract, PGs are very important mediators of mucosal defence and repair. Inhibition of their synthesis renders gastrointestinal tissues much more susceptible to damage induced by luminal irritants (including gastric acid and bile), and less able to restore mucosal structure and function after injury. Suppression of PG synthesis is the key effect of NSAIDs that leads to gastro-duodenal ulceration and bleeding.

NSAID-enteropathy has largely been ignored as a result of the focus on NSAID-gastropathy. The prevalence and clinical significance of NSAID-enteropathy continues to be greatly underrecognized.

Diagnostic approach drug-induced damage

NSAID-induced enteropathy and bleeding occur more frequently that NSAID-induced gastropathy. Significant small intestinal damage and bleeding can be observed in about 70 % of chronic NSAID users, and in the majority of patients the injury is sub-clinical.

Iron-deficient anemia is a common first presentation of NSAID-enteropathy, and serious complications can include massive bleeding, perforation and strictures.

Diagnostic of NSAID-gastropathy is EGD, NSAID-enteropathy are video capsule endoscopy and double-balloon enteroscopy which allow directly visualize of NSAID-induced damage and bleeding throughout the small intestine.

Aspirin and NSAIDs frequently cause gastric erosions which are defined as superficial mucosal breaks with a diameter of 3–5 mm.

Management and prevention drug-induced damage

PPIs provide upper GI protection against NSAIDs but worsen NSAID-enteropathy.

Misoprostol, metronidazole and sulfasalazine have all been suggested to be beneficial in treatment or prevention of NSAID-enteropathy in humans, but the studies suggesting this had significant limitations. Studiing the potential value of

probiotics (*Lactobacillus acidophilus* and *Bifidobacteria adolescentis)* for treatment or prevention of NSAID-enteropathy.

KEY MESSAGES

• Prostaglandins protect the gastric mucosa from damage, diminished synthesis in elderly subjects and after using NSAIDs makes their mucosa more susceptible to aggressive factors, followed by the ulcerogenic process.

• Any way using of NSAIDs (per os, IV, per rectum, transdermal) can lead to gastro- and enteropathy (erosions, ulcers).

• Erosion is a superficial mucosal breaks with a diameter of 3–5 mm.

• NSAIDs can cause not only NSAID-gastropathy, but enteropathy, which can manifest with complications - gastrointestinal bleeding, perforation.

3. DISEASES OF THE BILIARY TRACT

The basic role of the gallbladder is to enhance the digestive power of bile through a concentrating mechanism, drive the flow of bile salt. The gallbladder has a motor function, with 20–30 % emptying at 1- to 2-h intervals during the fasting state and 70–80 % emptying after stimulation by cholecystokinin during a meal. The interplay between gallbladder contraction and relaxation has an important role in driving the flow of bile salts in enterohepatic circulation and facilitating the absorption of lipids and fat-soluble vitamins.

3.1. Functional gallbladder and sphincter of Oddi disorders

Motility disorders of the biliary tree (biliary dyskinesia, including both gallbladder dysfunction, and sphincter of Oddi dysfunction) are difficult to diagnose and to treat.

It has been almost 130 years since the muscular structure at the terminal end of the biliary and pancreatic ducts was first described by a young anatomist and physiologist Rugero Oddi. His subsequent studies demonstrated that this sphincter muscle was under physiologic regulation. Disorders of the sphincter could result in clinical syndromes such as abdominal pain.

Sphincter of Oddi dysfunction has been defined as an abnormality of either the biliary and/or pancreatic sphincter causing intermittent or fixed obstruction to flow of bile or pancreatic juice, respectively, associated with episodic biliary-type pain, recurrent pancreatitis, abnormal liver chemistry tests, or ductal dilatation. The etiology and pathogenesis of these disorders are poorly understood, and diagnostic criteria have been historically controversial.

Classification of functional gallbladder and sphincter of Oddi disorders (according to Rome IV criteria — point **E)**

E1. Diagnostic Criteria for Biliary Pain

Pain located in the epigastrium and/or right upper quadrant and all of the following:

1. Builds up to a steady level and lasting 30 minutes or longer.

2. Occurring at different intervals (not daily).

3. Severe enough to interrupt daily activities or lead to an emergency department visit.

4. Not significantly (< 20 %) related to bowel movements.

5. Not significantly (< 20 %) relieved by postural change or acid suppression.

Supportive Criteria

The pain may be associated with:

1. Nausea and vomiting.

2. Radiation to the back and/or right infrasubscapular region.

3. Waking from sleep.

E1a. Diagnostic Criteria for Functional Gallbladder Disorder

1. Biliary pain.

2. Absence of gallstones or other structural pathology.

Supportive Criteria

1. Low ejection fraction on gallbladder scintigraphy.

2. Normal liver enzymes, conjugated bilirubin, and amylase/lipase.

E1b. Diagnostic Criteria for Functional Biliary Sphincter of Oddi Disorder

1. Criteria for biliary pain.

2. Elevated liver enzymes or dilated bile duct, but not both.

3. Absence of bile duct stones or other structural abnormalities.

Supportive Criteria

1. Normal amylase/lipase.

2. Abnormal sphincter of Oddi manometry.

3. Hepatobiliary scintigraphy.

E2. Diagnostic Criteria for Pancreatic Sphincter of Oddi Disorder

All of the following:

1. Documented recurrent episodes of pancreatitis (typical pain with amylase or lipase > 3 times normal and/or imaging evidence of acute pancreatitis).

2. Other etiologies of pancreatitis excluded.

3. Negative endoscopic ultrasound.

4. Abnormal sphincter manometry.

Pathology biliary dyskinesia

Biliary dyskinesia is a controversial group of functional disorders of the biliary system. The exact pathogenesis of gallbladder dysfunction is unknown, but it is presumed that the pain associated with biliary dyskinesia might be related to a functional obstruction of the bile flow out from the gallbladder, due perhaps to a non-occluding narrowing of the cystic duct. Gallbladder dysfunction has been associated with altered motility in other gastrointestinal organs. For example, impaired gallbladder emptying has been observed more commonly in adults suffering from slow-transit constipation and achalasia.

Diagnostic approach of biliary dyskinesia

• Transabdominal ultrasound — to exclude the sludge, stones, or microlithiasis in the gallbladder.

- Endoscopic ultrasound — for better visualization of the gallbladder to detect stones not visualized by transabdominal ultrasound.
- The microscopic evaluation of bile samples looking for microlithiasis and biliary sludge.
- CCK cholescintigraphy with radioactive bile tracer to quantitatively study gallbladder evacuation.
- MRI cholangiography.
- The morphine-prostigmine provocation test (has low specificity) — a positive test is defined by a fourfold rise in serum amylase or lipase along with reproduction of abdominal pain after intramuscular introduction of 10 mg of morphine and 1 mg of prostigmine.

Management biliary dyskinesia

- Centrally acting antidepressants such as amitriptyline and desipramine have been found to be effective in patients with functional gastrointestinal disorders in general.
- The antibiotic and motilin agonist erythromycin induces gallbladder contraction and reduces fasting and postprandial gallbladder volumes.
- Overall, no good medical therapy exists for gallbladder dysfunction.
- Cholecystectomy.

KEY MESSAGES

- Biliary dysfunction should be considered in patients presenting with recurrent right-upper-quadrant abdominal pain in the absence of visualized gallstones on abdominal ultrasound, meeting the Rome III criteria.
- Sphincter of Oddi dysfunction may be associated with episodic biliary-type pain, recurrent pancreatitis, abnormal liver chemistry tests (transaminases, alkaline phosphatase, conjugated bilirubin, amylase/lipase).
- Cholecystectomy may offer partial or complete symptomatic relief in more than 85 % of patients.

3.2. Gallstone disease

Gallstone disease is one of the most common biliary tract diseases worldwide in which both genetic and environmental factors have roles in its pathogenesis.

Gallstone disease is the term used to refer to the presence of stones in the gallbladder or common bile duct and the symptoms and complications they cause.

Gallstones are hardened deposits of the digestive fluid bile, that can form within the gallbladder. They vary in size and shape from as small as a grain of sand to as large as a golf ball.

Gallstones occur when there is an imbalance in the chemical constituents of bile that result in precipitation of one or more of the components. Biliary cholesterol supersaturation from metabolic defects in the liver is traditionally seen as the main pathogenic factor. Gallstones are composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials.

There are three types of gallstones:
- pure cholesterol stones, which contain at least 90 % cholesterol;
- pigment stones either brown or black, which contain at least 90% bilirubin;
- mixed composition stones, which contain varying proportions of cholesterol, bilirubin and other substances such as calcium carbonate, calcium phosphate and calcium palmitate.

Factors influencing gallstone disease:
- *age:* increasing age associate with an increased prevalence of gallstones;
- *gender, parity, and oral contraceptives*: women during their fertile years are almost twice as likely as men to experience cholelithiasis; increased levels of the hormone estrogen, as a result of pregnancy or hormone therapy, or the use of combined (estrogen-containing) forms of hormonal contraception, may increase cholesterol levels in bile and also decrease gallbladder movement, resulting in gallstone formation;
- *genetics:* cholesterol gallstone prevalence varies widely, from extremely low (< 5 %) in Asian and African populations, to intermediate (10–30 %) in European and Northern American populations, and to extremely high (30–70 %) in populations of Native American ancestry (Pima Indians in Arizona, Mapuche Indians in Chile);
- *obesity and body fat distribution*: lithogenic risk of obesity is strongest in young women, and slimness protects against cholelithiasis;
- *rapid weight loss* is associated with occurrence of sludge and gallstones in 10–25 % of patients in a few weeks of initiating the slimming procedures;
- *diet: n*utritional exposure to western diet, i. e., increase intake of fat, refined carbohydrates and decrease in fibre content is a potent risk factor for development of gallstones;
- *physical activity*: regular exercise, in addition to facilitating weight control, alone or in combination with dieting, improves several metabolic abnormalities related to both obesity and cholesterol gallstones;
- *drugs:*
  - ➢ all fibric acid derivatives (clofibrate, etc) increase biliary cholesterol saturation while lowering serum cholesterol;
  - ➢ prolonged use of PPIs has been shown to decrease gallbladder function, potentially leading to gallstone formation;
  - ➢ ceftriaxone has a lithogenic role;
- *diabetes*:
  - ➢ people with diabetes generally have high levels of fatty acids (triglycerides), which may increase the risk of gallstones;
  - ➢ gallbladder function is impaired in the presence of diabetic neuropathy, and regulation of hyperglycaemia with insulin seems to raise the lithogenic index;

➢ a lack of melatonin could significantly contribute to gallbladder stones, as melatonin inhibits cholesterol secretion from the gallbladder, enhances the conversion of cholesterol to bile, and is an antioxidant, which is able to reduce oxidative stress to the gallbladder.

The following aspects of gallstone disease are important:

• asymptomatic gallbladder stones;
• symptomatic gallbladder stones, including:
➢ biliary colic;
➢ acute cholecystitis;
➢ Mirrizi syndrome;
➢ xanthogranulomatous cholecystitis;
• common bile duct stones, including:
➢ biliary colic;
➢ cholangitis;
➢ obstructive jaundice;
➢ gallstone pancreatitis;
➢ other complications of gallstones (such as gastric outlet obstruction, or gallstone ileus);
➢ other conditions related to the gallbladder (such as gallbladder cancer, or biliary dyskinesia).

Clinical manifestation of gallstone disease

The symptoms of gallstone disease range from mild, non-specific symptoms that can be difficult to diagnose, to severe pain and/or complications which are often easily recognised as gallstone disease.

Most patients with gallstones have no symptoms. These gallstones are called "silent stones".

Patients with symptomatic stones most often present with:

• recurrent episodes of right-upper-quadrant or epigastric pain, probably related to the impaction of a stone in the cystic duct;

• intense pain in the upper-right side of the abdomen, often accompanied by nausea and vomiting, that steadily increases for approximately 30 min to several hours;

• referred pain between the shoulder blades or below the right shoulder region (Boas' sign).

Often, attacks occur after a particularly fatty meal and almost always happen at night.

People with mild, non-specific symptoms of gallstone disease may attribute their symptoms to other conditions, or may be misdiagnosed and undergo unnecessary investigations and treatment.

Some patients with gallstones present with acute cholecystitis, and often secondary infection by intestinal microorganisms, predominantly *Escherichia coli* and Bacteroides species. Inflammation of the gallbladder wall causes severe

abdominal pain, especially in the right upper quadrant, with nausea, vomiting, fever, and leukocytosis. This condition may remit temporarily without surgery, but it sometimes progresses to gangrene and perforation.

Less commonly, gallstones can become lodged in the common bile duct (choledocholithiasis), sometimes with obstruction of the common bile duct and symptoms of cholestasis. Obstruction leading to jaundice though commonly caused by a stone migrating into the common bile duct, can be due to compression of the common hepatic duct by a stone in the neck of the gall bladder or cystic duct (Mirrizi syndrome).

Infection in the bile ducts (cholangitis) can occur even with a seemingly minor degree of obstruction to bile flow. Stones in the common bile duct usually cause pain in the epigastrium or right upper quadrant, but may be painless. The passage of common-bile-duct stones can provoke acute pancreatitis, probably by transiently obstructing the main pancreatic duct where it passes near the common bile duct at the ampulla of Vater.

Gallstones may fistulate directly into the duodenum from the gallbladder during a period of silent inflammation. This stone can impact in the duodenum leading to duodenal obstruction (Bouveret's syndrome) Alternatively, gallstones can impact at the narrowest portion of healthy small, bowel causing an obstruction termed gallstone ileus.

Diagnostic approach of gallstone disease

• history of recurrent episodes of right-upper-quadrant or epigastric pain, suggesting biliary colic and Boas' sign;

• may be fever, tender right upper quadrant with or without Murphy's sign, tenderness when the hand taps the right costal arch (Ortner's sign);

• ultrasonography;

• nuclear scanning (cholescintigraphy);

• oral cholecystography;

• endoscopic retrograde cholangiopancreatography;

• magnetic resonance cholangiopancreatography;

• endoscopic ultrasound.

Algorithm of diagnosing symptomatic gallstone disease

• Step 1: offer liver function tests and ultrasound to people with suspected gallstone disease, and to people with abdominal or gastrointestinal symptoms which have been unresponsive to previous management.

• Step 2: consider magnetic resonance cholangiopancreatography if ultrasound has not detected common bile duct stones but the bile duct is dilated or liver function test results are abnormal.

• Step 3: consider using endoscopic ultrasound if MRCP does not allow a diagnosis to be made.

Management gallstones disease

Management gallstones disease depends on available the symptoms disease, localization the stones, sizes of gallbladder and biliary tree.

Information for patients/ carers:

• advise people to avoid food and drink that trigger their symptoms until they have their gallbladder or gallstone(s) removed;

• advise people that they should not need to avoid food and drink that triggered their symptoms after they have their gallbladder or gallstone(s) removed.

Asymptomatic gallbladder stones found in a normal gallbladder and normal biliary tree do not need treatment unless they develop symptoms.

Chenodeoxycholic acid and ursodeoxycholic acid are known to dissolve gallstones, but chenodeoxycholic acid causes diarrhoea and abnormal aminotransferase levels, while ursodeoxycholic acid does not.

Managing symptomatic gallbladder stones

• Offer laparoscopic cholecystectomy to people diagnosed with symptomatic gallbladder stones.

• Offer day case laparoscopic cholecystectomy for people having it as an elective planned procedure, unless their circumstances or clinical condition make an inpatient stay more appropriate.

• Offer early laparoscopic cholecystectomy (to be carried out within 1 week of diagnosis) to people with acute cholecystitis.

• Offer percutaneous cholecystostomy to manage gallbladder empyema when:
   ➢ surgery is not appropriate at presentation and
   ➢ conservative management is unsuccessful.

• Reconsider laparoscopic cholecystectomy for people who have had percutaneous cholecystostomy once they are well enough for surgery.

Managing common bile duct stones

• Offer bile duct clearance and laparoscopic cholecystectomy to people with symptomatic and asymptomatic common bile duct stones.

• Clear the bile duct may be:
   ➢ surgically, at the time of laparoscopic cholecystectomy or
   ➢ with ERCP before or at the time of laparoscopic cholecystectomy.

• Use the lowest-cost option suitable for the clinical situation when choosing between day-case and inpatient procedures for planned, elective ERCP.

• If the bile duct cannot be cleared at ERCP use biliary stenting to achieve biliary drainage only as a temporary measure until definitive endoscopic or surgical clearance.

KEY MESSAGES

• Most people with gallstone disease have asymptomatic gallbladder stones.

• The symptoms of gallstone disease range from mild, non-specific symptoms that can be difficult to diagnose, to severe pain and/or complications.

• Attacks of pain occur after a particularly fatty meal and almost always happen at night.

• There are a range of endoscopic, surgical and medical treatments available of gallstone disease.

• There is uncertainty about the timing of cholecystectomy, and whether it should take place during the acute presentation of the disease, or if it should be delayed until after the acute symptoms have subsided.

• People with asymptomatic *gallbladder stones* found in a normal gallbladder and normal biliary tree do not need treatment unless they develop symptoms; people with asymptomatic *bile duct stones* need treatment to prevent complications.

• Offer early laparoscopic cholecystectomy (to be carried out within 1 week of diagnosis) to people with acute cholecystitis.

• Clear the bile duct may be surgically at the time of laparoscopic cholecystectomy or with endoscopic retrograde cholangiopancreatography.

3.3. Primary sclerosing cholangitis

PSC is a rare but significant disease, which commonly affects males with a median age at diagnosis of 35 years. There is a significant association with IBD, hepatobiliary malignancies and colorectal cancer.

PSC is a chronic autoimmune cholestatic disorder characterised by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts, resulting in multifocal biliary strictures.

The pathogenesis of PSC remains unclear but hypotheses include:
• genetic factors;
• lymphocyte recruitment and activation;
• portal bacteraemia;
• bile salt toxicity.

Diagnostic approach of primary sclerosing cholangitis
• Symptoms patients may have include:
  ➢ fatigue;
  ➢ pruritis;
  ➢ right upper quadrant pain or discomfort;
  ➢ jaundice;
  ➢ weight loss.

• Physical examination may reveal hepatomegaly and/or splenomegaly, but otherwise there are few signs.

• Elevated cholestatic liver enzymes (GGT, AP) and a normal bilirubin over at least a 6-month time period.

• ANA and/ or SMA to be positive, usually in low titres.

• ANCA are detected in 80 % of patients with PSC, but not specific.

• ERCP: diffuse multifocal strictures and irregularities, with normal or minimally dilated segments in between giving rise to the characteristic beaded pattern.

• Cholangioscopy: dilated and tortuous vessels.

• Liver biopsy: portal tract inflammation with lymphocytes, progressing to obliterative concentric fibrosis (so-called "onion skinning") and bile duct de-

struction ("ductopenia"). The basement membrane of the bile duct is often thickened, and there is usually copper deposition present, indicating chronic cholestasis.

• Colonoscopy with biopsies is recommended as part of the diagnostic work-up in any new diagnosis of PSC (to exclude IBD).

Differential diagnosis from other cholangiopathies, in particular immunoglobulin G4 related sclerosing cholangitis (table 4).

Table 4 — Differential diagnosis of primary sclerosing cholangitis

Vascular	Hepatic artery thrombosis
	Portal hypertension bilopathy
	Portal cavernoma associated cholangiopathy
	Intra-arterial chemotherapy
	Sickle cell disease related cholangiopathy
Trauma	Trauma post cholecystectomy
	Abdominal trauma
Infections	AIDS related cholangiopathy
	Recurrent pyogenic cholangitis
Benign	Intraductal stone disease
Malignancy	Cholangiocarcinoma
Autoimmune	Autoimmune sclerosing cholangitis
	IgG_4 related sclerosing cholangitis
	Systemic vasculitis
Other	Recurrent pancreatitis
	Sclerosing cholangitis in critically ill patient
	TPN related cholangiopathy
	Histocytosis X

Management of primary sclerosing cholangitis

• UDCA at standart doses 10–15 mg/kg and higher doses 17–23 mg/kg reduces liver enzymes but has not been shown to improve survival.

AASLD and EASL guidelines do not support the administration of UDCA, though moderate dose UDCA administration is widely practised by hepatologists around the world, despite the lack of robust evidence. There is some evidence that UDCA has a chemopreventive effect on cancer of the bowel.

• Pruritus may be treated with bile acid sequestrants, such as cholestyramine or colesevelam, or with rifampicin or naltrexone.

• Optimal biliary drainage of dominant biliary strictures. A dominant stricture is defined as a narrow biliary stricture which impedes normal bile flow, with a diameter < 15 mm in the choledoch-bile duct/choledoch-hepatic duct or < 10 mm in the hepatic duct.

• Liver transplantation.

KEY MESSAGES

• PSC affects mainly young males in association with inflammatory bowel

disease.

• Patients with PSC are almost always positive for antineutrophil cytoplasmic antibodies (ANA).

• UDCA is a hydrophilic bile acid which was studied in patients with PSC following the discovery of its efficacy in chronic cholestatic conditions, in particular primary biliary cirrhosis.

4. DISEASES OF THE LIVER

The liver is one of the most vital organs in the human body and has specific physiological functions and a unique anatomical architecture. Blood circulates through the liver via the hepatic artery and portal vein. The hepatic artery shares arterial functions with other organs, whereas the hepatic portal vein contains a myriad of absorbed nutrients, microbial products and drugs from the gastrointestinal tract and spleen. The liver is an organ engaged primarily in metabolic, nutrient storage and detoxification activities. The liver is also an immunologically complex organ, responsible for the production of acute phase proteins, complement components, cytokines and chemokines, and contains large, diverse populations of resident immune cells.

4.1. Nonalcoholic liver disease

The prevalence of NAFLD parallels that of obesity, which has steadily risen throughout the world over the past thirty years. The natural history of NAFLD in some individuals, is to progress to end-stage liver disease. Thus, NAFLD is projected to become the leading cause of liver related morbidity and mortality within 20 years and a leading indication for liver transplantation in the next few years.

Fatty liver, or hepatosteatosis, is characterized histologically by triglyceride accumulation within the cytoplasm of hepatocytes. When hepatosteatosis is present in the absence of excessive alcohol consumption, it is termed NAFLD, which is considered to be the hepatic manifestation of the metabolic syndrome, a constellation of frequent abnormalities involving insulin resistance, visceral obesity, dyslipidemia, diabetes, hypertension, plus additional factors.

NAFLD encompasses a spectrum of disorders ranging from simple steatosis to inflammatory NASH and cirrhosis.

NAFLD is the most common cause of elevated liver function tests results, after the commonly investigated causes have been excluded, and frequently coexists with type 2 diabetes mellitus because the conditions have common risk factors.

Clinical features nonalcoholic fatty liver disease

The majority of patients diagnosed with NAFLD are asymptomatic. When present, clinical symptoms and physical findings are nonspecific and unreliable for diagnosing and assessing disease severity in patients with NAFLD.

Patients might have:

- hepatomegaly;
- general malaise;
- abdominal discomfort;
- vague right upper quadrant abdominal pain;
- nausea;
- other nonspecific symptoms referred to the gastrointestinal tract.

Clinical examination of patients who present with NASH-related cirrhosis may reveal:

- ascites;
- splenomegaly;
- spider angiomas;
- palmar erythema
- caput medusae
- jaundice.

The features more consistently found to be associated with disease severity include obesity, older age, diabetes, and hypertension.

Diagnostic approach of nonalcoholic fatty liver disease

Common biomarkers

There is no single biochemical marker that can confirm a diagnosis of NAFLD or distinguish between steatosis, NASH, and cirrhosis.

Although mildly elevated serum aminotransferase levels are the primary abnormality seen in patients with NAFLD, liver enzymes may be normal in up to 78 % of patients with NAFLD. Liver enzyme levels are not sensitive for the diagnosis of NAFLD. The elevations in ALT and AST are typically mild when present and are usually not greater than four times the upper limit of normal. The ratio of AST/ALT is usually less than 1 in patients who have either no or minimal fibrosis, although this ratio may be greater than 1 with the development of cirrhosis.

GGT in the serum is frequently elevated in patients with NAFLD, and it has been reported to be associated with increased mortality. However, the diagnosis of NAFLD cannot be made using only GGT.

Fibrosis. During the evaluation of NAFLD, it is important to consider the level of fibrosis. Potential fibrosis biomarkers include type IV collagen 7S domain and hyaluronic acid.

Serum laminin was also shown for prediction of fibrosis in NAFLD.

Imaging. Although many imaging tools have been assessed in NAFLD subjects, their main focus has been the quantification of liver fat. The results of these imaging tests cannot be used to differentiate between the histological subtypes of simple steatosis or NASH, nor can they be used to stage the degree of fibrosis.

Ultrasonography is currently the most common method for screening asymptomatic patients with elevated liver enzymes and suspected NAFLD. Ul-

trasonography findings of fatty liver include hepatomegaly, diffuse increases in the echogenicity of the liver parenchyma, and vascular blunting. Nonsteatotic hepatic parenchyma exhibits an echotexture similar to that of renal parenchyma, but becomes "brighter" when infiltrated with fat. This hepatorenal contrast can be used for detecting hepatosteatosis.

Computed tomography allows for a more quantitative assessment with measurement of liver attenuation in Hounsfield units compared to ultrasonography, but the information about liver attenuation is not uniform when reported by radiologists. It appears that noncontrast CT scanning is more useful for detecting steatosis than contrastenhanced scans.

Magnetic resonance imaging and proton magnetic resonance spectroscopy. MRI has been shown to most accurately detect lower levels of steatosis than those detected by ultrasonography and CT.

Transient elastography (Fibroscan, others) is a non-invasive method of assessing liver fibrosis which can be performed at the bedside or in an outpatient clinic. It uses ultrasound-based technology to measure liver stiffness.

Histology. The histological spectrum of NAFLD ranges from simple steatosis through steatohepatitis to fibrosis and cirrhosis. Liver biopsy is the gold standard for diagnosis and has the additional benefit of distinguishing between NASH and simple steatosis, thus allowing for the staging of the degree of fibrosis, which also provides helpful information regarding prognosis and may influence the clinical management of NAFLD. Liver biopsies can also exclude other liver diseases, such as druginduced hepatotoxicity, Wilson disease and autoimmune hepatitis. Hence, although the diagnosis of NAFLD can usually be confirmed by only a combination of history, serological analyses, and abdominal imaging, liver tissue is needed to determine the severity of NAFLD and to rule out other possible liver diseases.

Management nonalcoholic fatty liver disease
- Lifestyle intervention.
- Calorie restriction.
- Exercise.
- Pharmacological therapy:
  - insulin sensitizers: metformin, thiazolidinediones, incretin-based therapies;
  - lipid-lowering agents: statins, fibrates, N-3 polyunsaturated fatty acids;
  - cytoprotective and antioxidant agents: ursodeoxycholic acid, vitamin E, silymarin, betaine;
  - anti-TNF-α agents: pentoxifylline, monoclonal antibodies.
- Phlebotomy.
- Surgical intervention and antiobesity drugs.
- Bariatric surgery.
- Orlistat.

KEY MESSAGES

- The components of metabolic syndrome are the risk factors for chronic liver disease, including NAFLD.
- NAFLD encompasses a spectrum of disorders ranging from simple steatosis to inflammatory steatohepatitis and cirrhosis.
- ALT is an indicator of hepatic inflammation, alkaline phosphatase and GGT are markers for cholestasis.
- Normal hepatic parenchyma exhibits an echotexture similar to that of renal parenchyma, but when infiltrated with fat becomes "brighter". Ultrasonography findings of fatty liver include hepatomegaly, diffuse increases in the echogenicity of the liver parenchyma, and vascular blunting.
- Potential fibrosis biomarkers include type IV collagen 7S domain, laminin and hyaluronic acid.
- Transient elastography is a non-invasive method to measure liver fibrosis according to liver stiffness.
- Liver biopsy is the gold standard for diagnosis liver diseases.

4.2. Alcoholic liver disease

ALD represents a spectrum of conditions ranging from reversible fatty liver (steatosis, steatohepatitis) to alcoholic hepatitis, and cirrhosis.

The pathogenesis of alcoholic hepatitis is multifactorial. Current evidence suggests that the damage is the end result of the complex interplay between ethanol metabolism, inflammation and innate immunity.

Clinical presentation and diagnostic alcoholic liver disease

Alcoholic hepatitis patients generally present with:
- the rapid onset of jaundice (the cardinal sign);
- ascites and/or hepatic encephalopathy;
- fever;
- hepatomegaly (the liver is usually enlarged and tender);
- malnutrition (indicate clinical status, hypoalbuminemia < 35 g/l, low blood urea nitrogen, zinc level);
- low blood pressure and tachycardia;
- macrocytic hyperchromic anemia: an elevated mean corpuscular erythrocyte volume is found frequently in those ingesting more than 50 g alcohol per day;
- leukocytosis (may be even higher with leukemoid reactions) and thrombocytopenia (transitory or persistent in those who have concomitant cirrhosis);
- serum levels of aspartate AST that are more than twice the upper limit of the normal range, although rarely above 300 IU per milliliter, whereas serum levels of ALT are lower; the ratio of the AST/ALT is usually greater than 2;
- elevation in the GGT level is more sensitive (70 %) but less specific (65–80 %) than elevation of AST or ALT for excessive alcohol consumption;
- other biochemical and hematologic parameters often seen during alcoholic hepatitis include hypokalemia, hypomagnesemia, hyperuricemia, hypertrigly-

ceridemia, and hyperferritinemia.

Liver biopsy normally shows ballooning degeneration, focal hepatocyte necrosis, and neutrophilic infiltration.

Several clinical scoring systems, the Child-Turcotte-Pugh score, the Maddrey discriminant function, the Lille Model, the model for end stage liver disease (MELD) scores, and the Glasgow alcoholic hepatitis score, have been derived to predict the clinical outcomes of patients with alcoholic hepatitis. The assessment of the disease severity becomes an important and practical issue for clinicians involved in the management of patients with alcoholic hepatitis.

Management alcoholic hepatitis:
- abstinence;
- corticosteroids;
- pentoxifylline;
- N-acetylcysteine;
- treatment of ascites by salt restriction and the use of diuretics;
- treatment of hepatic encephalopathy by lactulose and gut-cleansing antibiotics;
- infection should be treated with appropriate antibiotics, chosen according to the sensitivity of the organism isolated;
- a daily protein intake of 1.5 g/kg of body weight is recommended;
- administration of B-complex vitamins is required to prevent Wernicke encephalopathy;
- benzodiazepine should be used for acute alcoholic withdrawal syndrome with caution due to potential encephalopathy precipitated.

KEY MESSAGES
- Alcoholic liver disease represents a spectrum of conditions ranging from reversible fatty liver (steatosis, steatohepatitis) to alcoholic hepatitis, and cirrhosis.
- The rapid onset jaundice and ascites are universal signs of ALD.
- Patients with acute alcoholic hepatitis have AST and ALT levels that rise to several hundred units per liter. With alcohol-induced damage, the ratio of AST to ALT is usually greater than 2.
- Several clinical scoring systems, the Child-Turcotte-Pugh score, the Maddrey discriminant function, the Lille Model, the model for end stage liver disease (MELD) scores, and the Glasgow alcoholic hepatitis score, have been derived to predict the clinical outcomes of patients with alcoholic hepatitis.
- The main treatment ALD include abstinence, corticosteroids, pentoxifylline.
- For acute alcoholic withdrawal syndrome benzodiazepine should be used with caution.

4.3. Metabolic inherited disorders

Inherited liver diseases are a group of metabolic and genetic defects that

typically cause early chronic liver involvement. Most are due to a defect of an enzyme/transport protein that alters a metabolic pathway and exerts a pathogenic role mainly in the liver.

4.3.1. Wilson's disease

Wilson's disease, also known as hepatolenticular degeneration, is an autosomal recessive inherited disorder resulting from abnormal copper metabolism. Reduced copper excretion causes an excessive deposition of the copper in many organs such as the liver, central nervous system, cornea, kidney, joints, and cardiac muscle where the physiological functions of the affected organs are impaired.

Wilson's disease affects 1 in every 30000 live births. It is caused by mutations in the *ATP7B* gene (chromosome 13), which encodes the protein responsible for the metabolism, transport and biliary excretion of copper.

The clinical presentation of Wilson's disease involves:
- *the liver* is characterized by:
  - ➢ abnormal liver function tests (ALT, AST);
  - ➢ acute hepatitis;
  - ➢ liver failure;
  - ➢ portal hypertension;
  - ➢ gallstones;
  - ➢ liver cirrhosis.
- *Central nervous system* is characterized by:
  - ➢ a dystonic syndrome (the most common form of tremor is an irregular, and somewhat jerky, dystonic tremor — "wing-beating tremor" or "flapping tremor" in combination with dysarthria);
  - ➢ an ataxic syndrome;
  - ➢ a parkinsonian syndrome.
- *Psychiatric symptoms* (abnormal behaviour — typically increased irritability or disinhibition, personality changes, anxiety and depression).
- *Cornea* is characterized by the presence of Kayser-Fleischer rings.

Diagnostic approach of Wilson's disease
- Family screening, including assessment of both clinically unaffected siblings and their parents.
- Clinical manifestations.
- Liver function tests.
- Serum ceruloplasmin < 10 mg/dl.
- Copper in 24-hour urine sample > 100 µg per 24 hour in the absence of cholestatic liver disease.
- Ophthalmologic examination — the presence of Kayser-Fleischer rings.
- Liver biopsy, measurement of the hepatic parenchymal copper level. Hepatic copper values greater than 250 micrograms per gram of dry weight (normal 20–50) are characteristic of Wilson's disease.
- Hepatic imaging studies.
- Genetic testing — *ATP7B* mutation.

Management Wilson's disease

• Diet (elevated amounts of copper are naturally found in numerous food products, including chocolate, nuts, mushrooms, crustaceans, soy, and gelatin).

• Chelators of copper such as D-penicillamine and trientine.

• Zinc has been recommended as a maintenance drug for the treatment because prevent copper absorption from intestinal tract.

• Liver transplantation is choice for patients who have fulminant hepatic failure or the end stage of cirrhosis.

4.3.2. Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive disease characterized by iron overload that may cause liver cirrhosis, cardiomyopathy, diabetes, arthritis, and skin pigmentation that appear during the third to fifth decade. The incidence is about 1: 250. Men have a 24-fold increased rate of iron-overload disease compared with women. Persons who are homozygous for the *HFE* gene mutation C282Y comprise 85 to 90 percent of phenotypically affected persons.

The pathogenesis of liver damage in hereditary hemochromatosis is mainly due to the iron-induced lipid peroxidation that occurs in hepatocytes and causes hepatocellular injury or death. Kupffer cells become activated and produce cytokines, which in turn stimulate hepatic stellate cells to synthesize collagen, thereby leading to cirrhosis.

The clinical presentation of hereditary hemochromatosis

• Weakness;

• lethargy;

• arthralgias;

• impotence;

• osteoporosis;

• cirrhosis;

• hepatocellular cancer;

• cardiomyopathy;

• arrhythmia;

• diabetes mellitus;

• hypogonadism;

• bronze-colored skin.

Diagnostic approach of hereditary hemochromatosis

•Testing should be performed in first-degree relatives of patients with classical *HFE*-related hemochromatosis, those with evidence of active liver disease, and patients with abnormal iron study results.

• Clinical manifestations.

• Liver function tests.

• Enhanced serum ferritin.

• High transferrin saturation.

- Liver biopsy: iron liver overload, liver fibrosis and cirrhosis.
- Hepatic imaging studies.
- Genetic testing — p.C282Y in HFE gene associated with liver cirrhosis.

Management hereditary hemochromatosis

- Dietary modification is generally unnecessary.
- Phlebotomy for treatment of iron overload is the same as for classic HFE-associated hemochromatosis, i.e., phlebotomy of one unit of blood (~200 mg of iron) one to two times per week for up to two to three years to reduce iron stores to desired levels (serum ferritin concentration below 50 ng/mL and normal transferrin-iron saturation), followed by phlebotomies to maintain normal serum iron studies.
- Treatment of secondary complications, including hypogonadotropic hypogonadism, arthropathy, cardiac failure, liver disease, diabetes mellitus.
- Liver transplantation is a choice for patients who have the end stage of cirrhosis.

KEY MESSAGES

- Genetic testing in first-degree relatives of patients with hemochromatosis and Wilson's disease should be performed.
- Treatment of iron overload in hemochromatosis and copper overload in Wilson's disease is necessary.

4.4. Drug-induced liver injury

Drug-induced liver injury is a common adverse event encountered in clinical practice, since a vast number of compounds, including herbs and alternative medications, are metabolized in the liver microsomes. The most detrimental clinical presentation is fulminant liver failure, where patients without a history of liver disease present with hepatic encephalopathy and coagulopathy preceding jaundice. Both, natural and synthetic chemicals are foreign products to the body and need metabolic degradation to be eliminated. During this process, hepatotoxic metabolites may be generated causing liver injury in susceptible patients.

Factors influencing drug-related hepatotoxicity:

- dose and pattern of use (increase toxicity with acute, high doses);
- increase toxicity with chronic ethyl alcohol ingestion;
- age and genetic factors (increase toxicity with advancing age and impaired glucouronidation);
- nutritional status (increase toxicity in malnourished patients);
- chronic liver disease increase toxicity especially in chronic ethyl alcohol abuse.

Acetaminophen = APAP** (in the United States) = **paracetamol** (in Europe and other areas of the world) = **N-acetyl-p-aminophenol** — **the most of liver-toxity drug.

In the creation of LiverTox, drugs were divided into four different categories of likelihood for causing liver injury based on reports in the published litera-

ture. Category A with > 50 published reports, B with > 12 but less than 50, C with > 4 but less than 12, and D with one to three cases.

Drugs that have been associated with more than 100 cases of drug-induced liver injury (category A) : allopurinol, amiodarone, amoxicillin-clavulanate, anabolic steroids, atorvastatin, azathioprine/6-mercaptopurine, busulfan, carbamazepine, chlorpromazine, contraceptives, dantrolene, diclofenac, didanosine, disulfiram, efavirenz, erythromycin, floxuridine, flucloxacillin, flutamide, halothane, hydralazine, ibuprofen, infliximab, interferon alpha/peginterferon, interferon beta, isoniazid, ketoconazole, methotrexate, methyldopa, minocycline, nevirapine, nimesulide, nitrofurantoin, phenytoin, propylthiouracil, quinidine, pyrazinamide, rifampin, simvastatin, sulfamethoxazole/trimethoprim, sulfasalazine, sulindac, telithromycin, thioguanine, ticlopidine, valproate.

For some traditional Chinese medicine herbs known to cause liver injury, various toxic substances have been proposed and are listed as examples (table 5)

Table 5 — Some examples of suspected toxic compounds as suggested causes of hepatotoxicity by herbal traditional Chinese medicine

Chinese name	Scientific name	Tentative hepatotoxic components
Ai Ye	*Artemisia argyi*	Volatile oil
Bi Ma Zi	*Rhicinus communis*	Ricin, toxic proteins
Cang Shan	*Xanthium*	Glycosides (kaurene), diterpenoids
Chang Shan	*Dichor febrifuga Lour*	Alkaloids (dichroine)
He Huan Pi	*Albizia julibrissin*	Glycosides (saponine)
He Shou Wu	*Polygonum multiflorum*	Anthraquinones
Huang Yao Zi	*Discorea bulbifera L*	Glycosides (steroids, diosgenin), diterpenoids-lactones
Ku Lian Zi	*Melia azedarach*	Glycosides (tetranortriterpenoids)
Lei Gong Teng	*Tripterygium wilfordii hook F*	Glycosides (tripterygium), diterpenoid-lactones
Qian Li Guang	Senecio scandens	Pyrrolizidine alkaloids
Shan Lu	*Phytolacca acinosa Roxb.*	Alkaloids (phytolaccine)
Xiang Si Zi	*Abrus Precatorius*	Abrin

Diagnostic approach of drug-induced liver injury

Many patients have only minimal and non-specific symptoms:
- malaise;
- nausea with or without vomiting;
- abdominal pain.

Three different types of drug-induced liver injury are to be considered:
- hepatocellular (increase level of ALT, AST);
- cholestatic (increase level of GGT, AP);
- mixed type.

There are four established sequential stages of *acetaminophen hepatotoxicity:*
- Stage I (upon presentation to clinic) occurs within the first 24 hours of

ingestion and is characterized by:

➢ the non-specific symptoms of nausea, vomiting, malaise, lethargy and diaphoresis;

➢ AST and ALT values are usually normal, although in immense overdose, elevated values can be detected in as little as 8–12 hours.

- Stage II occurs within 24 to 72 hours and is characterized by:

➢ improvement or resolution of stage I symptoms (also known as the latent period);

➢ elevations of AST and ALT typically begin to occur;

➢ tender hepatomegaly (with right-upper quadrant pain);

➢ jaundice;

➢ coagulopathy;

➢ hepatic necrosis;

➢ acute tubular necrosis and renal failure (approximately 1~2 % of patients).

- Stage III occurs within 72 to 96 hours and is characterized by:

➢ marked AST and ALT elevations (possibly > 3000 IU/l);

➢ jaundice;

➢ encephalopathy;

➢ coagulopathy (prothrombin time to rise beyond 4 seconds);

➢ lactic acidosis;

➢ renal failure;

➢ pancreatitis;

➢ multi-organ failure.

- Stage IV occurs after 96 hours and is characterized by:

➢ the recovery during 1–2 weeks, but its duration can be prolonged; the histologic recovery period may take several months longer than the clinical recovery.

Poor prognostic signs include:

- multi-organ failure, which may involve cerebral edema, renal failure;
- profound hypoglycemia;
- lactic acidosis.

Management drug-induced liver injury

Initial therapy is:

- inhibit drug absorption (within 4 hours of the acute drug ingestion): activated charcoal can be effective.

- Remove the offending agent from the gastrointestinal tract by gastric lavage, and vomiting induced by ipececauanha.

- *N*-acetylcysteine within 24 hours of ingestion of acetaminophen.

- Intubation with mechanical ventilation are necessary in severe damage and multi-organ failure.

- Liver transplantation can be a lifesaving procedure when drug-induced liver injury has progressed to irreversible liver failure.

KEY MESSAGES

• Drugs (*acetaminophen*, also known as APAP (in the United States), *paracetamol* (in Europe and other areas of the world) or *N-acetyl-p-aminophenol*; antibiotics, antifungal drugs, oral contraceptives, chlorpromazine, and estrogenic or anabolic steroids, cytostatics) and herbal products can cause drug-induced liver injury and can evolve into acute liver failure in rare cases.

• All herbal products and herbal dietary supplements used as medicine should be under a more strict regulatory surveillance, considering these products as herbal drugs.

• Three different types of liver injury are to be considered: hepatocellular, cholestatic, and mixed.

• Chronic hepatitis has not been reported as a complication of acetaminophen overdose-associated acute liver failure.

• Liver transplantation is necessary in drug-induced acute liver failure.

4.5. Liver cirrhosis

Liver cirrhosis and its related complications remain a prominent global health concern despite advances in understanding and treating the disorder. At present, liver transplantation remains the only curative option for a selected group of patients, but pharmacological therapies that can halt progression to decompensated cirrhosis or even reverse cirrhosis are currently being developed.

Cirrhosis is an end-stage liver disease, has a multifactorial etiopathogenesis, and is usually the result of longstanding disease with development of regenerative nodules surrounded by fibrous bands, progressive fibrosis (ie, scarring) of the normal liver architecture which causes increased intrahepatic resistance and the development of portal hypertension, leading to diminished liver function and potentially life-threatening complications.

Pathogenesis and pathophysiology of cirrhosis

Fibrosis describes encapsulation or replacement of injured tissue by a collagenous scar. Liver fibrosis results from the perpetuation of the normal wound healing response resulting in an abnormal continuation of fibrogenesis (connective tissue production and deposition). Fibrosis progresses at variable rates depending on the cause of liver disease, environmental and host factors.

Cirrhosis is an advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature. It leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma, i. e., hepatocytes. The hepatic sinusoids are lined by fenestrated endothelia which rest on a sheet of permeable connective tissue (the space of Disse) which contains hepatic stellate cells and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes which execute most of the known liver functions. In cirrhosis the space of Disse is filled with scar tissue and endothelial fenestrations are lost, a process termed sinusoidal capillarization.

Histologically, cirrhosis is characterized by vascularized fibrotic septa that link portal tracts with each other and with central veins, leading to hepatocyte islands that are surrounded by fibrotic septa and which are devoid of a central vein.

The major clinical consequences of cirrhosis are impaired hepatocyte (liver) function, an increased intrahepatic resistance (portal hypertension) and the development of hepatocellular carcinoma.

The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are intimately linked to the hepatic vascular alterations and the resulting portal hypertension.

Cirrhosis and its associated vascular distortion are traditionally considered to be irreversible but recent data suggest that cirrhosis regression or even reversal is possible.

Causes of liver cirrhosis

• Viral infection (hepatitis B, C, D).

• Autoimmune disorders (autoimmune hepatitis, PBC, PSC, Ig G4 cholangiopathy).

• Fatty liver disease (NAFLD, alcoholic liver disease).

• Inherited metabolic diseases (Wilson's disease, hemochromatosis, α1-antitrypsin deficiency).

• Cardiovascular diseases (right heart failure, Badd-Chiari syndrome, Osler disease).

• Chronic biliary disease (reccurent bacterial cholangitis, bile duct stenosis).

• Rare causes (porphyria, medications).

• Mix causes (viral hepatitis C and alcohol abuse, etc).

Classification liver cirrhosis see table 6.

Table 6 — Child Pugh Turcotte classification

POINTS	1	2	3
Encephalopathy	absent	medically controlled	poorly controlled
Ascites	absent	medically controlled	poorly controlled
Bilirubin, μmol/l (mg/dl)	<34 (< 2)	34–50 (2–3)	>50 (> 3)
Albumin (g/dl)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.2	> 2.2
Class A — 5–6 points. Class B — 7–9 points. Class C — 10–15 points.			
Life expectancy (years)	Class A — 15–20	Class B — 4–14	Class C — 1–3

Clinical presentation liver cirrhosis

Cirrhosis is frequently asymptomatic and unsuspected until complications of liver disease present. The diagnosis of asymptomatic cirrhosis is usually made when incidental screening tests such as liver transaminases or radiologic findings suggest liver disease and patients undergo further evaluation and liver biopsy. Initial clinical presentation of patients with decompensated cirrhosis is still common and is characterized by the presence of dramatic and life-threatening

complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy.

Clinical features of cirrhosis:

• *Jaundice* — yellow discoloration of skin, cornea and mucous membranes — due to compromised hepatocyte excretory function, occurs when serum bilirubin > 2 mg/dl.

• *Spider angiomata* — central arteriole with tiny radiating vessels, mainly on trunk and face – due to elevated estradiol, decreased estradiol degradation in liver.

• *Nodular liver* — irregular, hard surface on palpation — due to fibrosis, irregular regeneration.

• *Splenomegaly* — enlarged on palpation or in ultrasound — due to portal hypertension, splenic congestion.

• *Ascites* — proteinaceous fluid in abdominal cavity, clinically detected when ≥ 1.5 L — due to portal hypertension.

• *Caput medusae* — prominent veins radiating from umbilicus — due to portal hypertension, reopening of the umbilical vein that shunts blood from the portal vein.

• *Cruveilhier Baumgarten syndrome* — epigastric vascular murmur — due to shunts from portal vein to umbilical vein branches, can be present without caput medusa.

• *Palmar erythema* — erythema sparing the central portion of the palm — due to elevated estradiol, decreased estradiol degradation in liver.

• *White nails* — horizontal white bands and/or proximal white nail plate — due to hypoalbuminemia.

• *Hypertrophic osteoarthropathy/finger clubbing* — painful proliferative osteoarthropathy of long bones — due to hypoxemia due to right-to-left shunting, porto-pulmonary hypertension.

• *Dupuytren's contracture* — fibrosis and contraction of the palmar fascia — due to enhanced oxidative stress, elevated hypoxanthine (alcohol exposure or diabetes).

• *Gynecomastia, loss of male hair pattern* — benign proliferation of glandular male breast tissue — due to enhanced conversion of androstenedione to estrone and estradiol, decreased estradiol degradation in liver.

• *Hypogonadism* — mainly in alcoholic cirrhosis and hemochromatosis — due to direct toxic effect of alcohol or iron.

• *Flapping tremor* (asterixis) — asynchronous flapping motions of dorsiflexed hands — due to hepatic encephalopathy, disinhibition of motor neurons.

• *Foetor hepaticus* — sweet, pungent smell — due to volatile dimethylsulfide, especially in portosystemic shunting and liver failure.

• *Anorexia, fatigue, weight loss, muscle wasting* — due to catabolic metabolism by diseased liver, secondary to anorexia.

• *Type 2 diabetes* — due to disturbed glucose utilization and/or decreased insulin removal by the liver

The common complications of liver cirrhosis

Variceal bleeding

According to the AASLD, all newly diagnosed cirrhotics should undergo screening EGD for the diagnosis of esophageal and gastric varices.

If EGD reveals no varices, then it should be repeated in 2–3 years. Small varices (< 5 mm) necessitate repeat screening every 1–2 years, and decompensated cirrhotics should have a yearly EGD.

Ascites

The pathophysiology behind formation of ascites is complex but three key factors are involved:
• portal hypertension;
• splanchnic and peripheral arterial vasodilation;
• neuro-humoral activation.

Cirrhotic ascites primarily develops due to impaired renal sodium excretion leading to a positive sodium balance and hence water retention, causing expansion of the extracellular fluid volume. The decreased sodium excretion is predominantly caused by arterial vasodilation, which triggers neuro-humoral responses such as the renin–angiotensin–aldosterone system and the sympathetic nervous system.

All patients with ascites should be screened for the presence of SBP and ascitic fluid investigations should at least include neutrophil cell count, albumin/protein concentration and ascitic fluid inoculation in blood culture bottles.

Clinical practice includes determination of the serum albumin ascites gradient (SAAG) (serum albumin concentration–ascites albumin concentration), which can help differentiate between ascites ascribed to portal hypertension and ascites due to other causes. If the SAAG is ≥1.1 g/dl (or 11 g/l), ascites is most likely due to portal hypertension.

Grading of ascites:
• grade 1 — mild ascites, only detectable by ultrasound;
• grade 2 — moderate ascites evident by moderate symmetrical distention of the abdomen;
• grade 3 — large ascites with marked abdominal distension;
• refractory ascites:
   ⇒ diuretic-resistant ascites – cannot be mobilized or the early recurrence of which cannot be prevented because of lack of response to sodium restriction and diuretic treatment;
   ⇒ diuretic-intractable ascites – cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage.

Spontaneous bacterial peritonitis

All patients with cirrhosis and ascites are at risk of developing SBP.

Symptoms of SBP include:
• abdominal pain;

• fever;

• vomiting;

• leukocytosis.

Diagnosis should also be suspected in patients with worsening of liver function, hepatic encephalopathy, renal failure and/or gastrointestinal bleeding but SBP is frequently asymptomatic.

An ascitic neutrophil cell count of 250 cells/mm^3 (0.25 × 109/l) is diagnostic criteria of SBP. Inoculation of ascitic fluid in blood culture bottles often display Escherichia coli and Streptococcus species.

Renal failure

Hepatorenal syndrome is functional renal failure that develops as a result of multiple pathophysiological derangements that occur in the cirrhotic patient.

Criteria for diagnosis of hepatorenal syndrome in cirrhosis (International ascites club):

• cirrhosis with ascites;

• serum creatinine > 1.5 mg/dl (133 μmol/l);

• absence of shock;

• asence of hypovolemia as defined by no improvement of renal function following at least 2 days of diuretic withdrawal (if on diuretics) and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day;

• no current or recent treatment with nephrotoxic drugs;

• absence of parenchymal renal disease as defined by absence of proteinuria (< 0.5 g/day), no microhematuria (< 50 red blood cells per high power field) and normal renal ultrasonography.

Hepatorenal syndrome is divided into:

• type 1 — is characterized by rapidly progressing renal failure, indicated by a rise in serum creatinine to a level greater than 2.5 mg/dl in less than 2 weeks.

• type 2 — is defined by gradually developing renal failure reflected by an increase of serum creatinine values to between 1.5 mg/dl and 2.5 mg/dl. This type is more likely to occur spontaneously and is often associated with refractory ascites.

Median survival of type 1 is 1 month, type 2–6 months.

Hepatic encephalopathy

Hepatic encephalopathy is a complex, reversible neuropsychiatric syndrome, complicating the course of liver disease.

Mechanisms for the pathophysiology of hepatic encephalopathy involves hyperammonemia, which occurs due to an impaired breakdown of primarily glutamine due to impaired liver function. Ammonia is able to cross the blood–brain barrier, and causes neuroinflammation, swelling of astrocytes and mild cerebral edema.

Hepatic encephalopathy associated with cirrhosis and portal hypertension or portal-systemic shunts — type C (type A — associated with acute liver failure, type B — associated with portal-systemic bypass and no intrinsic hepatocellular disease).

Type C hepatic encephalopathy is divided into episodic (precipitated, spontaneous, recurrent), persistent (mild, severe, treatment dependent), minimal.

Features of hepatic encephalopathy:
• disturbed consciousness:
  ⇒ reversal of sleep pattern;
  ⇒ drowsiness
  ⇒ coma (later stages).
• Personality changes:
  ⇒ irritability;
  ⇒ irrational behavior.
• Intellectual impairment:
  ⇒ reduced attention span;
  ⇒ impaired mental agility;
  ⇒ impaired working memory.
• Speech impairment:
  ⇒ slow;
  ⇒ slurred.
• Motor impairment:
  ⇒ asterixis/flapping tremor;
  ⇒ ataxic gait;
  ⇒ exaggerated tendon reflexes.

Hepatic encephalopathy is divided into 2 broad categories based on severity:

• *covert hepatic encephalopathy* ("sub-clinical", "latent", "minimal") is defined as patients with minimal hepatic encephalopathy and Grade I encephalopathy by West-Haven criteria;

• *overt hepatic encephalopathy* is defined as patients with grade II to IV by West-Haven criteria (table 7).

Table 7 — West Haven criteria for hepatic encephalopathy

Grade 0	No abnormality detected
Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impairment of addition or subtraction
Grade 2	Lethargy
	Disorientation for time
	Obvious personality change
	Inappropriate behavior
Grade 3	Somnolence to semistupor

	Responsive to stimuli
	Confused
	Gross disorientation, bizarre behavior
Grade 4	Coma, unable to test mental state

Diagnostic approach of hepatic encephalopathy:

• neuropsychometric tests;

• quantitative neurophysiological tools (electroencephalography) with mean dominant frequency and P300 auditory evoked potentials;

• high blood-ammonia level.

The differential diagnosis hepatic encephalopathy should include other conditions that can cause diffuse brain dysfunction and/or acute confusion, such as diabetes, alcohol, medications, metabolic disturbances, kidney disease, intracranial bleeding, stroke, delirium, dementia, and infection.

Risk factors for hepatocellular carcinoma:

• cirrhosis;

• decompensated cirrhosis;

• viral hepatitis B and C;

• NASH;

• type 2 diabetes;

• aflatoxin exposure;

• co-infection with multiple viruses; HBV, HCV and HIV (risk 2–6 fold);

• increasing age;

• male sex;

• positive family history of hepatocellular carcinoma;

• associated secondary alcohol abuse (risk 2–4 fold) or NASH as a co- factor.

Diagnostic approach of liver cirrhosis

Laboratory findings in cirrhosis

• *AST and ALT* — often normal or moderately elevated — leakage from damaged hepatocytes; AST to ALT ratio often above 1, especially in alcoholic cirrhosis (relative vitamin B6 deficiency).

• *ALP* — elevated < 3-fold, except for PBC and PSC — due to cholestasis.

• *GGT* — more specific for liver than ALP, high in active alcoholics — due to cholestasis.

• *Bilirubin* — elevated later than GGT and ALP, important predictor of mortality – due to cholestasis, decreased hepatocyte and renal excretory function (exacerbated by systemic inflammation).

• *Albumin* — decreased in advanced cirrhosis — due to decreased hepatic production, sequestration into ascites and interstitium (exacerbated in systemic inflammation). Differential diagnosis: malnutrition, protein losing enteropathy.

• *Prothrombin time* — decreased in advanced cirrhosis — due to decreased hepatic production of factor V/VII (While thrombin production is maintained). Differential diagnosis: vitamin K deficiency (e. g., due to mechanical biliary ob-struction).

• *Immune globulins* — increased (mainly Ig G) — due to shunting of portal venous blood carrying (intestinal) antigens to lymph tissues with resultant stimulation of plasma cells.

• *Sodium imbalance* — hyponatremia — due to unability to excrete free water via the kidneys due to increased activity of antidiuretic hormone (vasopressin 2 receptor effect).

• *Anemia* — macro-, normo- or microcytic anemia — due to folate deficiency, hypersplenism, direct toxicity (alcohol), gastrointestinal blood loss (e.g., via esophageal varices).

• Thrombocytes and leukocytes — thrombocytopenia (leukopenia) — due to hypersplenism, dysfibronogenemia, reduced hepatic thrombopoietin production.

Imaging of cirrhosis

Ultrasonography, CT and MRI are not sensitive to detect cirrhosis, and final diagnosis still relies on histology.

However, their specificity is high when an obvious cause is present and imaging reveals an inhomogeous hepatic texture or surface, rarefied hepatic central vein, an enlarged caudate lobe, splenomegaly or collateral veins. However, other etiologies such as portal vein thrombosis, parasitic diseases or hematological malignancies need to be excluded, and normal radiographic findings do not exclude compensated cirrhosis. The major role of radiography is for the detection and quantitation of complications of cirrhosis, i. e., ascites, hepatocellular carcinoma, and hepatic or portal vein thrombosis.

• Ultrasonography provides important information on hepatic architecture, is cheap and widely available.

⇒ Nodularity and increased echogenicity of the liver are often found in cirrhosis but are also present in steatosis.

⇒ There is typically atrophy of the right lobe and hypertrophy of the left and especially caudate lobes.

⇒ Ultrasonography and Doppler ultrasonography of portal and central vein diameters and velocities are useful screening tests for portal hypertension and vessel patency.

• *Contrast ultrasonography* examines the appearance of echogenic microbubbles in the hepatic vein. Their appearance after antecubital injection is correlated inversely with fibrosis.

Contrast ultrasonography is the first imaging modality for suspected hepatocellular carcinoma by improving visualization of abnormal vessels.

• *Elasticity measurement* (Fibroscan) is a promising technique based on the velocity of an elastic wave via an intercostally placed transmitter. Shear wave velocity is determined by pulse ultrasound and correlates with liver stiffness, i. e., fibrosis. The examination is limited by morbid obesity, ascites and small intercostal spaces.

Liver biopsy

Biopsy is considered the gold standard for diagnosis of cirrhosis, and sequential histological grading of inflammation and staging of fibrosis can assess risk of progression.

Biopsy confirmation of cirrhosis is not necessary when clear signs of cirrhosis, such as ascites, coagulopathy, and a shrunken nodular appearing liver are present.

Evaluation of patients with cirrhosis

• Age, sex, ethnicity.

• Family history: consanguinity, liver disease, autoimmune disease.

• Previous medical history: jaundice, hepatitis, drug use, blood transfusions, inflammatory bowel disease.

• Social behaviors (adolescence): use of alcohol or other drugs, tattoos, piercings.

• Pregnancy and birth data: adverse events during pregnancy, maternal serologies, birthweight, neonatal cholestasis, surgery.

• Adolescence: menstrual history.

• Signs and symptoms of systemic disease: anorexia, fatigue, muscle weakness, failure to thrive.

• Patient's complaints: dyspepsia, nausea, vomiting, abdominal pain, abdominal distension, diarrhea, discoloration of urine and feces, pruritus, bleeding from nose, gums, skin, gastrointestinal tract, bone pain, fractures, peripheral edema, daytime somnolence.

• Physical examination:

⇒ general: anthropometric data (malnutrition or obesity), fever;

⇒ skin and extremities: jaundice, edema, flushing or pallor, spider nevi, telangiectasias, palmar erythema, clubbing of the nails, xanthoma, Terry's nails;

⇒ abdomen: distension, prominent blood vessels, liver and spleen alterations (reduced liver size, splenomegaly);

⇒ neurological alterations: academic performance, sleep, asterixis, positive Babinski sign, mental status changes;

⇒ miscellaneous: pubertal delay, gynecomastia, testicular atrophy, feminization.

Management liver cirrhosis

Elimination of the triggers that lead to cirrhosis is likely to retard progression severity cirrhosis and to reduce the incidence of hepatocellular carcinoma.

There is evidence that causal treatment may even reverse cirrhosis.

Patients with *alcoholic cirrhosis* must abstain, since continued alcohol consumption drives hepatitis which favours hepatic fibrogenesis and decompensation. Liver function often worsens in the first 2–3 weeks of withdrawal, since alcohol has an immunosuppressive effect.

Patients with *compensated* replicating *HCV-cirrhosis* benefit from interferon-based antiviral treatment. Viral eradication and a consequently lowered risk of hepatic decompensation and hepatocellular carcinoma can be achieved in up to 40 and 70 % of patients with genotypes 1 and 2 or 3, respectively.

Longterm treatment with oral nucleoside and nucleotide inhibitors of HBV polymerase may not only retard or reverse cirrhosis but were also shown to prevent complications of end stage liver disease.

The data on reversibility and stabilization of other causes of cirrhosis is less well defined. Cohort studies showed that some cirrhotic patients with *autoimmune hepatitis* showed regression after long-term treatment with corticosteroids, and venesection of patients with hereditary hemochromatosis could decrease the development of complications of portal hypertension.

It is necessary to prevent and treat the complications of liver cirrhosis (table 8).

Table 8 — Prevention and treatment the complications of liver cirrhosis

Complication	Prevention	Treatment
Variceal bleeding	• Non selective beta blockers (nadolol, propranolol). • Variceal band ligation.	*Acute:* • Resuscitation. • Vasocontrictors (vasopressin, octreotide/somatostatin, terlipressin). • Sclerotherapy. • Band ligation. • TIPSS. • Surgical shunts
		Chronic: • Variceal obliteration. • TIPSS. • Surgical shunts
Ascites	Low Na diet	• Low Na diet < 2 g per day. • Diuretics. The typical starting regimen being 100 mg of spironolactone and 40 mg of furosemide daily. These doses can be titrated maintaining a 100 mg to 40 mg ratio up to a maximum of 400 mg of spironolactone and 160 mg of furosemide daily. • Large volume paracentesis. • TIPSS. • LeVeen / Denver shunts
Spontaneous bacterial peritonitis	Treat ascites	• Early diagnosic paracentesis: if neutrophils > 250/cells/mm^3 → antibiotics iv • Secondary prophylaxis with a po antibiotic such as levofloxacin
Renal failure	Avoid hypovolemia	• Discontinue diuretics. • Rehydration. • Albumin infusion

		Hepatorenal syndrome: • add terlipressin or midodrine (noradrena-line) and somatostatin (octreotide).
Encephalopathy	Avoid precipitants	• Treat precipitating factors: infection, bleeding, electrolyte imbalance, seda-tives, high protein intake. • Nonabsorbable disaccharides (prebio-tics) — lactulose. • Nonabsorbable antibiotics: neomycin, metronidazole, rifaximin.

Diuretic-induced complications:

• diuretic-induced hepatic encephalopathy: the development of encephalo-pathy in the absence of any other precipitating factor;

• diuretic-induced renal impairment: increase in serum creatinine by > 100 % to a value of >2 mg/dl (177 μmol/l) in patients with ascites responding to treatment;

• diuretic-induced hyponatremia: decrease of serum sodium by >10 mmol/l to a serum sodium level of <125 mmol/l;

• diuretic-induced hypo- or hyperkalemia: change in serum potassium to < 3 mmol/l or >6 mmol/l despite appropriate measures.

The liver transplantation is the ultimate therapy for liver cirrhosis patients.

KEY MESSAGES

• Liver cirrhosis is an end-stage liver disease.

• Cirrhosis is frequently asymptomatic and unsuspected until complications of liver disease present.

• The major clinical consequences of cirrhosis are impaired liver function, a portal hypertension and the development of hepatocellular carcinoma.

• If the serum albumin concentration–ascites albumin concentration is ≥ 1.1 g/dl (or 11 g/l), ascites is most likely due to portal hypertension.

• The restriction of sodium plays a larger role for preventing accumulation of ascites, as fluid always follows sodium.

• The typical starting regimen of diuretics in patients with ascites is 100 mg of spironolactone and 40 mg of furosemide daily.

• A high degree of suspicion in hepatocellular carcinoma in patients with an α-fetoprotein above 200 μg/l. Patients with cirrhosis should be screened for he-patocellular carcinoma every 6 to 12 months using imaging, with or without se-rum α-fetoprotein measurement.

• Cirrhosis and its associated vascular distortion are traditionally consi-dered to be irreversible but recent data suggest that cirrhosis regression or even reversal is possible.

4.5.1. Primary biliary cirrhosis

PBC is an autoimmune, slowly progressive, cholestatic liver disease characterized by a triad: of chronic cholestasis, circulating **AMA**, and characteristic liver biopsy findings.

Clinical manifestations primary biliary cirrhosis

• Pruritus.

The leading and early pathognomonic symptom of PBC is the appearance of skin itching that may be the only manifestation of the disease within a few months and even few years. The skin shows multiple scratched traces that further display hyperpigmentation portions. The itching is characterized by extension (local or systemic), degrees (moderate or severe), and duration (persistent or transient). Itching may be excruciating, may seriously impair quality of life and even induce suicidal ideation in the most severe cases. Itching is not relieved with symptomatic (antihistamine, sedative) agents; it often causes excruciating insomnia, emotional changes, and depression.

• Weakness, fatigue.

• Weight loss.

• Daytime somnolence.

• Xanthelasma.

Xanthelasmas vary in shape, may be solitary or multiple, flat, pale yellow color slightly raised above the skin.

• Skin hyperpigmentation — due to excessive melanin biosynthesis in the melanocytes.

• Jaundice develops in the end-stage disease — may be absent long (for 2 years or more).

• Hepatomegaly and less — splenomegaly.

• Malabsorption syndrome.

• Osteodystrophy, osteoporosis.

• Cholelithiasis.

• Extrahepatic manifestations of autoimmune nature:
  ➤ autoimmune hepatitis;
  ➤ Sjogren's syndrome;
  ➤ CREST syndrome;
  ➤ Raynaud's phenomenon;
  ➤ rheumatoid arthritis;
  ➤ autoimmune thyroiditis;
  ➤ scleroderma;
  ➤ pulmonary fibrosis;
  ➤ polymyositis;
  ➤ sarcoidosis;
  ➤ hemolytic anemia;
  ➤ celiac disease;
  ➤ IBD.

Complications of cirrhosis from advanced PBC include esophageal varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatoma formation.

Diagnostic approach of primary biliary cirrhosis

PBC is diagnosed provided two of the following three criteria are satisfied:

(1) AMA titer > 1:40;

(2) AP > 1.5 times the upper limit of normal for > 24 week;

(3) compatible liver histology, demonstrating nonsuppurative destructive cholangitis and interlobular bile duct destruction.

Management primary biliary cirrhosis

Ursodeoxycholic acid is the primary therapy.

Obtecholic acid and fibrate are promising new, but incompletely tested, therapies.

Liver transplantation is the definitive therapy for advanced disease, with about 70 % 10-year survival after transplantation.

KEY MESSAGES

• Patients with primary biliary cirrhosis are almost always positive for antimitochondrial antibody.

• The leading and early pathognomonic symptom of PBC is the appearance of skin itching that may be the only manifestation of the disease within a few months and even few years.

4.6. Liver transplantation

Liver transplantation offers the greatest hope for survival currently available for patients with severe acute and chronic liver diseases in whom other available forms of therapy have failed.

Three important questions must be addressed in a patient being considered for liver transplantation:

(1) when should the patient be referred for possible transplantation?

(2) When should the patient be listed for transplantation?

(3) When is the patient too sick to have a reasonable chance of surviving the perioperative period?

Tne patients should not be placed on the transplant waiting list until their predicted chance of surviving 1 year is 90 % or less.

The ideal timing of liver transplantation occurs when patients have less than a 50 % chance of surviving 1 to 2 years but before they develop multisystem disease.

Indications for orthotopic liver transplantion

• *Advanced chronic liver failure:*
  ➢ Child-Pugh-Turcotte score > 7;
  ➢ qualifying MELD score for organ allocation.

• *Acute liver failure:*
  ➢ unresectable hepatic malignancy;

- inherited metabolic disorders.
- *General:*
  - no alternative form of therapy;
  - no absolute contraindications;
  - willingness to comply with follow up care;
  - ability to provide for costs of orthotopic liver transplantion (for citizens of Belarus is free in Belarus).

Contraindications for orthotopic liver transplantion
- *Relative:*
  - HIV seropositivity;
  - methadone dependence;
  - stage 3 hepatocellular carcinoma.

Patients with cirrhosis and hepatocellular carcinoma may still qualify for transplant if only one tumor is identified and it is less than 5 cm in size, or if two or three tumors are identified and are 3 cm or less in size.
- *Absolute:*
  - extrahepatic malignancy;
  - AIDS;
  - Cholangiocarcinoma;
  - severe, uncontrolled systemic infection;
  - multiorgan failure;
  - advanced cardiopulmonary disease;
  - active substance abuse.

The major issues that remain in the care of the patient post liver transplantation are recurrent disease in the transplant, particularly HCV, and longterm consequences of immunosuppressive agents such as hypertension, hyperlipidemia and renal disease.

KEY MESSAGES
- Liver transplantation is indicated for acute or chronic liver failure from any cause.
- The best efficacy of liver transplantation assessed in primary biliary cirrhosis and primary sclerosing cholangitis.
- The timing of the surgery can have a profound impact on the mortality and morbidity of patients undergoing liver transplantation.
- Because of the long waiting lists for donor organs, the need to project far in advance when transplantation might be required in patients with end-stage liver disease.

4.7. Differential diagnosis of jaundice

Jaundice in an adult patient can be caused by a wide variety of benign or life-threatening disorders. Organizing the differential diagnosis by prehepatic, intrahepatic, and posthepatic causes may help make the work-up more manageable. The laboratory work-up should begin with a urine test for bilirubin, which indicates that conjugated hyperbilirubinemia is present. If the complete blood

count and initial tests for liver function and infectious hepatitis are unrevealing, the work-up typically proceeds to abdominal imaging by ultrasonography or computed tomographic scanning. In a few instances, more invasive procedures such as cholangiography or liver biopsy may be needed to arrive at a diagnosis.

Jaundice is a yellowish staining of the skin, sclera, and mucous membranes by bilirubin, a yellow-orange bile pigment. Bilirubin is formed by a breakdown product of heme rings, usually from metabolized red blood cells. The discoloration typically is detected clinically once the serum bilirubin level rises above 3 mg per dL (51.3 μmol per L).

Clinical presentation of jaundice

Patients with jaundice may present with no symptoms at all (i. e., the condition is found accidentally), or they may present with a lifethreatening condition. The wide range of possibilities is based on the variety of underlying causes and whether disease onset is quick or slow moving.

Patients presenting with acute illness, which is frequently caused by infection, may seek medical care because of fever, chills, abdominal pain, and flu-like symptoms. For these patients, the change in skin color may not be their greatest concern.

Patients with noninfectious jaundice may complain of weight loss or pruritus. Abdominal pain is the most common presenting symptom in patients with pancreatic or biliary tract cancers. Even something as nonspecific as depression may be a presenting complaint in patients with chronic infectious hepatitis and in those with a history of alcoholism.

Occasionally, patients may present with jaundice and some extrahepatic manifestations of liver disease.

Differential diagnosis of jaundice

Pseudojaundice can occur with excessive ingestion of foods rich in beta-carotene (e.g., squash, melons, and carrots). Unlike true jaundice, carotenemia does not result in scleral icterus or elevation of the bilirubin level.

Prehepatic causes of jaundice

Unconjugated hyperbilirubinemia results from a derailment of the necessary bilirubin conjugation in the hepatocyte. This problem may occur before bilirubin has entered the hepatocyte or within the liver cell. Excessive heme metabolism, from hemolysis or reabsorption of a large hematoma, results in significant increases in bilirubin, which may overwhelm the conjugation process and lead to a state of unconjugated hyperbilirubinemia.

Hemolytic anemias usually result in mild bilirubin elevation, to about 5 mg per dL (85.5 μmol per L), with or without clinical jaundice. Hemolytic anemias result from abnormal red blood cell survival times. These anemias may occur because of membrane abnormalities (e. g., hereditary spherocytosis) or enzyme abnormalities (e. g., glucose-6-phosphate dehydrogenase deficiency). Other etiologies of hemolysis include autoimmune disorders, drugs, and defects in he-

moglobin structure such as sickle cell disease and the thalassemias.

Intrahepatic causes of jaundice

Unconjugated hyperbilirubinemia. Several disorders of enzyme metabolism affect the conjugation process inside the hepatocyte, thereby impeding complete conjugation.

There are varying degrees of unconjugated hyperbilirubinemia, depending on the severity of enzyme inhibition with each disease.

Gilbert syndrome is a common, benign, hereditary disorder results in a mild decrease in the activity of the enzyme glucuronosyltransferase, causing an increase in the indirect fraction of serum bilirubin. Gilbert syndrome is typically an incidental finding on routine liver function tests, when the bilirubin level is slightly increased and all other liver function values are within normal limits. Jaundice and further elevation of the bilirubin level may occur during periods of stress, fasting, or illness. However, these changes are usually transient, and there is no need to pursue treatment or liver biopsy.

Conjugated hyperbilirubinemia. The predominant causes of conjugated hyperbilirubinemia are intrahepatic cholestasis and extrahepatic obstruction of the biliary tract, with the latter preventing bilirubin from moving into the intestines.

Intrahepatic causes of conjugated hyperbilirubinemia:
- hepatocellular disease;
- viral infections (hepatitis A, B, and C);
- chronic alcohol use;
- autoimmune disorders;
- drugs (**acetaminophen**, penicillins, oral contraceptives, chlorpromazine, and estrogenic or anabolic steroids);
- pregnancy;
- parenteral nutrition;
- sarcoidosis;
- Dubin-Johnson syndrome;
- Rotor's syndrome;
- primary biliary cirrhosis;
- primary sclerosing cholangitis.

Posthepatic causes of jaundice

Conjugated hyperbilirubinemia also may result from problems that occur after the bilirubin is conjugated in the liver. These posthepatic causes can be divided into intrinsic or extrinsic obstruction of the duct system.

Extrahepatic causes of conjugated hyperbilirubinemia:
- intrinsic to the ductal system;
- gallstones;
- surgical strictures;
- infection (*cytomegalovirus, Cryptosporidium* infection in patients with

acquired immunodeficiency syndrome);
- intrahepatic malignancy;
- cholangiocarcinoma;
- extrinsic to the ductal system;
- extrahepatic malignancy (pancreas, lymphoma);
- pancreatitis.

Physical examination of the patient with jaundice

The physical examination should focus primarily on signs of liver disease other than jaundice, including bruising, spider angiomas, gynecomastia, testicular atrophy, and palmar erythema. An abdominal examination to assess liver size and tenderness is important.

The presence or absence of ascites also should be noted.

Diagnostic approach of jaundice

The initial work-up of the patient with jaundice depends on whether the hyperbilirubinemia is conjugated (direct) or unconjugated (indirect).

A urinalysis that is positive for bilirubin indicates the presence of conjugated bilirubinemia. Conjugated bilirubin is water soluble and therefore able to be excreted in urine. The findings of urinalysis should be confirmed by measurements of the serum total and direct bilirubin levels.

Serum testing

First-line serum testing in a patient presenting with jaundice should include:
- complete blood count;
- bilirubin (total and direct fractions);
- AST, ALT, GGT, and ALP levels.

A complete blood count is useful in detecting hemolysis, which is indicated by the presence of fractured red blood cells (schistocytes) and increased reticulocytes on the smear.

AST and ALT are markers of hepatocellular injury. They can be less helpful in patients with chronic liver disease, because levels can be normal or only slightly elevated when there is little liver parenchyma left to damage. Acute viral hepatitis may cause the levels of ALT to rise several thousand units per liter. Levels greater than 10,000 U per L usually occur in patients with acute injury to the liver from another source (e.g., drugs or ischemia).

Patients with acute alcoholic hepatitis have AST and ALT levels that rise to several hundred units per liter. With alcohol-induced damage, the ratio of AST to ALT is usually greater than 1, whereas infectious causes of hepatitis typically cause greater elevation in ALT than in AST.

Alkaline phosphatase and GGT are markers for cholestasis. As bile obstruction progresses, the levels of these two markers rise several times above normal.

The second-line serum investigations may include tests for hepatitis A IgM

antibody, hepatitis B surface antigen and core antibody, hepatitis C antibody, and autoimmune markers such as antinuclear, smooth muscle, and liver-kidney microsomal antibodies.

Imaging

Ultrasonography and CT scanning are useful in distinguishing an obstructing lesion from hepatocellular disease in the evaluation of a jaundiced patient. Ultrasonography is typically the first test ordered, because of its lower cost, wide availability, and lack of radiation exposure, which may be particularly important in pregnant patients. While ultrasonography is the most sensitive imaging technique for detecting biliary stones, CT scanning can provide more information about liver and pancreatic parenchymal disease.

Further imaging includes endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography.

Liver biopsy

A liver biopsy provides information on the architecture of the liver and is used mostly for determining prognosis. It also may be useful for diagnosis if serum and imaging studies do not lead to a firm diagnosis. Liver biopsy can be particularly helpful in diagnosing autoimmune hepatitis or biliary tract disorders (e. g., primary biliary cirrhosis, primary sclerosing cholangitis).

KEY MESSAGES

• Pseudojaundice can occur with excessive ingestion of foods rich in beta-carotene (e. g., squash, melons, and carrots). Unlike true jaundice, carotenemia does not result in scleral icterus or elevation of the bilirubin level.

• The discoloration typically is detected clinically once the serum bilirubin level rises above 3 mg/dl (51.3 μmol/l).

• Prehepatic causes of jaundice include hemolysis and hematoma resorption, which lead to elevated levels of unconjugated (indirect) bilirubin.

• Intrahepatic disorders can lead to unconjugated or conjugated hyperbilirubinemia. The conjugated (direct) bilirubin level is often elevated by alcohol, infectious hepatitis, drug reactions, and autoimmune disorders.

• Gilbert syndrome is a common, benign, hereditary disorder results in a mild decrease in the activity of the enzyme glucuronosyltransferase

• Posthepatic disorders also can cause conjugated hyperbilirubinemia. Gallstone formation is the most common and benign posthepatic process that causes jaundice; however, the differential diagnosis also includes serious conditions such as biliary tract infection, pancreatitis, and malignancies.

4.8. Differential diagnosis of chronic liver diseases

Liver fibrosis is the common end-point of a variety of chronic liver diseases. The progression of liver fibrosis leads to cirrhosis, decompensation, liver failure, hepatocellular carcinoma and death. Accurate diagnosis of chronic liver disease (table 9) is essential for prognostication and for timely intervention to prevent negative outcome.

Table 9 — Diagnostic algorithm for chronic liver disease

Screening measures	Step 1: General laboratory testing	Step 2: Specific laboratory testing	Step 3: Molecular and invasive studies
History (identification of risk constellations)	ALT, AST, GGT, alkaline phosphatase, bilirubin	Hepatitis serology (HBsAg, anti-HCV)	Ceruloplasmin, copper in 24-hour urine sample, genetic testing for Wilson disease
Physical examination	Complete blood count, platelet, coagulation studies	Autoantibody testing (ANA, SMA, LKM, SLA, p-ANCA, AMA)	HFE mutation
Serum ALT and GGT	Total protein, albumin, serum electrophoresis	Quantitative immunoglobulins (Ig A, Ig G, Ig M)	α1-antitrypsin genotype
Ultrasonography	Cholesterol, triglycerides, glucose	Ferritin, transferrin saturation, iron	Liver biopsy, MRCP, ERC (for suspected PSC)

Investigation of chronic liver disease and cirrhosis (Tab. 10)

• Hematology (hemoglobin, leukocyte and platelet count, prothrombin time (INR), Coombs test, blood type, Rh factor).

• Biochemistry (bilirubins, transaminases, AP, GGT, albumin and globulin, urea, creatinine, calcium, phosphorus, magnesium, sodium, potassium, bicarbonate, chloride, uric acid, lactic acid, fasting blood glucose).

• 25-OH vitamin D.

• Parathyroid hormone.

• Serum transferrin and ferritin saturation.

• Serum ceruloplasmin and copper, 24 h urinary copper.

• Alpha-1-antitrypsin phenotype.

• If ascites present — paracentesis (cell count, albumin, total protein, neutrophil count, amylase, cytology, mycobacterial culture).

• Urinary sodium excretion.

• Immunology (smooth muscle, mitochondrial, anti-nuclear, anti- LKM-1 antibodies, HBsAg, anti-HCV, α-fetoprotein, immunoglobulins, HIV serology).

• Metabolic screen (urine and serum amino acids, urine organic acids).

• Genetic tests (if alpha-1-antitrypsin deficiency, Alagille syndrome, etc., suspected).

• Urine and serum analysis for bile acid and acid precursors (if progressive familial intrahepatic cholestasis suspected).

• Bone marrow examination and skin fibroblast culture (if glycogen storage disease suspected).

• Endoscopy (if prophylactic treatment is considered).

• Abdominal ultrasound (computed tomography or MRI in selected cases).

• Needle liver biopsy (if blood coagulation permits).

• EEG (if neuropsychiatric changes present).

Table 10 — Diagnostic tests in chronic liver disease

Etiology	Specific physical associations	Diagnostic parameters	Value of liver biopsy
HBV	Arthritis	HBsAg, (HBeAg), anti-HBc, HBV-DNA	+
HCV	Cryoglobulinemia	anti-HCV, HBV-RNA	+
Alcoholic		AST/ALT ≥2, carbohydrate deficient transferrin ↑, GGT↑	++ (Mallory bodies, steatosis, granulocytes > hepatocyte ballooning)
NASH	Overweight/obesity, metabolic syndrome, type 2 diabetes	Uric acid, fasting glucose/insulin/triglycerides	++ (Mallory bodies, steatosis, hepatocyte ballooning>granulocytes)
Autoimmune		Autoantibodies (ANA, anti-LKM, anti-SLA), γ-globulins↑↑	+++ (bridging necrosis)
Etiology	Specific physical associations	Diagnostic parameters	Value of liver biopsy
PBC	Sicca-syndrome, xanthelasma	AMA, ALP/GGT↑, cholesterol↑	++ (cholangitis, paucity of bile ducts, granuloma, ductopenia)
PSC	Ulcerative colitis (90 %)	Anti-pANCA (70%), ALP/GGT↑ imaging: beaded intra- (and extra-) hepatic bile ducts	+++ (concentric peri-bile ductular fibrosis, ductopenia)
Hemochromatosis	Arthritis, myocarditis, diabetes	Fasting transferrin saturation >60 % (♂), >50 % (♀), ferritin↑↑, HFE mutation	++ (periportal iron-loaded hepatocytes, quant. liver iron)
Wilson's	Neurological	Ceruloplasmin↓, urinary copper (24h) ↑, slit-lamp: corneal copper deposits	+++ (quant. liver copper)
α1-antitrypsin	Pulmonary fibrosis	α1- antitrypsin ↓, α1- antitrypsin subtyping	+++ (α1- antitrypsin - loaded hepatocytes)
Congenital			+++ (bile ductular plate malformations etc.)

KEY MESSAGES

• Chronic liver diseases have a multifactorial etiopathogenesis (congenital, autoimmune, metabolic, etc.) and complex investigations are necessary to reveal the main reason and to treat properly.

5. DISEASES OF THE PANCREAS

The pancreas is a composite organ and contains a distinctive combination of cell lineages. The exocrine tissue comprises acinar cells that secrete digestive fluid and a duct system by which the fluid drains into the intestine. The endocrine portion is arranged as discrete islets of Langerhans, which comprise mul-

tiple distinct cell types secreting (at least) five different hormones into the circulation (α-cells — glucagon; β-cells — insulin; δ-cells — somatostatin; ε-cells — ghrelin; and γ [or PP]-cells — pancreatic polypeptide).

5.1. Chronic pancreatitis

Chronic pancreatitis has a multifactorial etiology. The average age at diagnosis is 35 to 55 years. Because of advances in medical imaging and more inclusive definitions, the incidence of chronic pancreatitis has quadrupled in the past 30 years. Alcoholism plays a significant role in adults, whereas genetic and structural defects predominate in children. Morbidity and mortality are secondary to chronic pain and complications (e. g., diabetes, pancreatic cancer).

Chronic pancreatitis is the progressive and irreversible destruction of the pancreas as characterized by permanent loss of endocrine and exocrine function and, often, chronic disabling pain.

Pancreatitis is characterized by inflammation of the pancreas that progresses from acute (sudden onset; duration < 6 months) to recurrent acute (> 1 episode of acute pancreatitis) to chronic (duration > 6 months).

Etiology and pathophysiology of chronic pancreatitis

The TIGAR-O (Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis, Obstructive) classification system is based on risk factors for chronic pancreatitis (table 11).

Table 11 — TIGAR-O classification: risk factors associated with chronic pancreatitis

Classification	Risk factors
Toxic-metabolic	Alcohol
	Chronic renal failure
	Hypercalcemia (hyperparathyroidism)
	Hyperlipidemia (rare)
	Medications
	Tobacco
	Toxins
Idiopathic	Early and late onset
	Tropical pancreatitis (tropical calcific pancreatitis and fibrocalculous pancreatic diabetes)
Genetic	Autosomal dominant (cationic trypsinogen [codon 29 and 122 mutations])
	Autosomal recessive modifier genes (cystic fibrosis transmembrane conductance regulator and serine peptidase inhibitor, Kazal type 1 mutations, cationic trypsinogen [codon 16, 22, and 23 mutations], alpha 1-antitrypsin deficiency)
Autoimmune	Autoimmune chronic pancreatitis associated with inflammatory bowel disease, Sjögren syndrome, primary biliary cirrhosis
	Isolated autoimmune chronic pancreatitis
Recurrent and severe acute	Postirradiation

pancreatitis	Postnecrotic (severe acute pancreatitis)
	Recurrent acute pancreatitis
	Vascular ischemia
Obstructive	Pancreas divisum
	Sphincter of Oddi disorders
	Duct obstruction (pancreatic or ampullary tumors, post-traumatic pancreatic duct fibrosis)

Common drugs that may induce chronic pancreatitis include angiotensin-converting enzyme inhibitors, statins, didanosine, azathioprine, steroids, lamivudine, hydrochlorothiazide, valproic acid, oral contraceptives, and interferon.

Chronic alcohol use accounts for 70 percent of the cases of chronic pancreatitis in adults, and most patients have consumed more than 150 g of alcohol per day over 6 to 12 years. Disease characteristics include inflammation, glandular atrophy, ductal changes, and fibrosis. It is presumed that when a person at risk is exposed to toxins and oxidative stress, acute pancreatitis occurs. If the exposure continues, early- and late-phase inflammatory responses result in production of profibrotic cells, including the stellate cells. This can lead to collagen deposition, periacinar fibrosis, and chronic pancreatitis.

Autoimmune pancreatitis accounts for 5 to 6 percent of chronic pancreatitis and is characterized by autoimmune inflammation, lymphocytic infiltration, fibrosis, and pancreatic dysfunction.

Diagnostic approach of chronic pancreatitis

The diagnosis of chronic pancreatitis is made based on the clinical presentation and imaging studies.

Clinical manifestation

• chronic abdominal pain is commonly described as midepigastric postprandial pain that radiates to the back and that can sometimes be relieved by sitting upright or leaning forward;

• steatorrhea (fat and oil in the stool);

• symptoms of maldigestion (bloating, gas, cramps, and diarrhea);

• symptoms of nutritional deficiencies (e. g., fat-soluble vitamin deficiency and protein malnutrition with low albumin, prealbumin, or retinal binding protein);

• diabetes;

• weight loss.

Laboratory tests

• Leukocytosis — in patients with infection, abscess.

• Elevated serum amylase and lipase — nonspecific for chronic pancreatitis.

During episodes of acute pancreatitis, pancreatic enzyme levels are typically elevated more than three times the upper limits of normal; however, in most cases, serum amylase and lipase levels may be normal or only mildly elevated.

• Elevated total bilirubin, AP, and hepatic transaminase –suggests biliary pancreatitis and ductal obstruction by strictures or mass.

• Fasting serum glucose – elevation suggests pancreatic diabetes.

- *Pancreatic function tests:*
  - ➢ fecal fat estimation: > 7 g fat per day is abnormal (patient should be on a diet of 100 g fat per day during 72 hours);
  - ➢ fecal elastase: < 200 mcg/g (0.20 g/kg) of stool is abnormal;
  - ➢ secretin stimulation — best test for diagnosing pancreatic exocrine insufficiency — peak bicarbonate concentration < 80 mEq/l (80 mmol/l) in duodenal secretion;
  - ➢ serum trypsinogen: < 20 ng/ml (0.83 nmol/l) is abnormal.
- Visual stool examination.
- Lipid panel — significantly elevated triglycerides are a rare cause of chronic pancreatitis.
- Calcium — hyperparathyroidism is a rare cause of chronic pancreatitis.
- Immunoglobulin G4 serum antibody, antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate — abnormality may indicate autoimmune pancreatitis.

Imaging studies

Pathognomonic findings of chronic pancreatitis are calcifications within the pancreatic ducts, pseudocysts, ductal dilatation, thrombosis, pseudoaneurysms, necrosis, and parenchymal atrophy.

- Plain abdominal radiography — not routinely recommended, calcifications may be visible.
- Ultrasonography.
- CT — "classical" diagnostic chronic pancreatitis findings on CT include atrophy, dilated pancreatic duct (7 mm or more) and pancreatic calcification.
- Contrast-enhanced CT of the abdomen — is the initial imaging modality of choice; can visualize calcifications, pseudocysts, thrombosis, pseudoaneurysms, necrosis, and atrophy.
- Endoscopic retrograde cholangiopancreatography (ERCP) — has a high risk of complications (e. g., pancreatitis, hemorrhage, infection), is rarely recommended for diagnosis, mainly used in diagnosis of early chronic pancreatitis with normal computed tomography and pancreatic function tests.
- Magnetic resonance cholangiopancreatography (MRCP) — for evaluation of the pancreatic parenchyma and duct system, side branches.
- Endoscopic ultrasonography — useful in evaluation of early chronic pancreatitis, pancreatic mass, and cystic lesions; can be combined with fine-needle aspiration biopsy.
- Fluid also can be analyzed for tumor markers, such as carbohydrate antigen 19-9.

Histological features of chronic pancreatitis include parenchymal fibrosis, acinar atrophy, ductal distortion, and intraductal calcification.

Morbidity and mortality patients are typically caused by debilitating pain, progression to diabetes, and pancreatic cancer, with mortality being caused mainly by cardiovascular events and sepsis.

Rosemont criteria for chronic pancreatitis (2009)

Parenchymal features
- Major A: hyperechoic foci with stranding.
- Major B:lobularity with honeycombing.
- Minor:hyperechoic foci, lobularity, cysts, hyperechoic strands.

Ductal features
- Major A:calculi.
- Minor:main pancreatic duct dilation; irregular main pancreatic duct contour; hyperechoic main pancreatic duct margin; dilated side branches.

Endoscopic ultrasound diagnosis of chronic pancreatitis on the basis of Rosemont criteria

Consistent with chronic pancreatitis:
- 1 major A feature + ≥ 3 minor features or;
- 1 major A feature + major B feature or;
- 2 major A features.

Suggestive of chronic pancreatitis:
- 1 major A feature + < 3 minor features or;
- 1 major B + ≥ 3 minor features or;
- ≥ 5 minor features.

Indeterminate for chronic pancreatitis
- 3 or 4 minor features, no major features or;
- major B feature alone with < 3 minor features.

Normal
- ≤ 2 minor features, no major features.

Chronic pancreatitis is a syndrome of various disorders causing pancreatic inflammation lasting more than six months with irreversible pancreatic changes documented by one of the following:
- abdominal imaging (inflammatory masses; pancreatic parenchyma and ductal calcifications; pseudocysts);
- functional studies (pancreatic exocrine insufficiency with maldigestion of food; pancreatic endocrine insufficiency with diabetes mellitus with destruction of the islets);
- histologic changes (atrophy, fibrosis, and/or sclerosis).

Complications chronic pancreatitis:
- diabetes mellitus: an onset about five years after the initial diagnosis;
- pseudocysts: most of them are asymptomatic, but they can cause rupture, infection, intracystic bleeding, and obstruction of the surrounding structures;
- portal hypertension and gastric varices result from thrombosis of the splenic vein: this can cause pseudo-aneurysms to form, especially in the splenic artery;
- episodes of acute pancreatitis: can cause pancreatic abscesses, necrosis, sepsis, and multiorgan failure;
- pancreatic cancer: there is a 15-fold risk in patients with chronic pancrea-

titis who are alcoholics and a 40 percent lifetime risk for those with hereditary disease.

Differential diagnosis chronic pancreatitis

Chronic pancreatitis should be considered in the differential diagnosis of patients with acute or chronic abdominal pain of unknown etiology.

Elevations in serum amylase and lipase levels are nonspecific and can occur with mesenteric ischemia, biliary disease, complicated peptic ulcers, and renal insufficiency.

Differential diagnosis of chronic pancreatitis is necessary with acute cholecystitis, acute pancreatitis, pancreatic tumors, acute appendicitis, acute salpingitis, ovarian cysts, ectopic pregnancy, gastroparesis, intestinal obstruction, irritable bowel syndrome, Crohn's disease.

Management chronic pancreatitis

Management options for chronic pancreatitis include medical, endoscopic, and surgical treatments (table 12).

Table 12 — Chronic pancreatitis treatment options

Treatment type	Options
Medical	Analgesics (stepwise approach)
	Antidepressants (treatment of concurrent depression)
	Cessation of alcohol and tobacco use
	Denervation (celiac nerve blocks, transthoracic splanchnicectomy)
	Insulin (for pancreatic diabetes)
	Low-fat diet and small meals
	Pancreatic enzymes with PPIs or histamine H_2 blockers
	Steroid therapy (in autoimmune pancreatitis)
	Vitamin supplementation (A, D, E, K, and B_{12})
Endoscopic	Extracorporeal shock wave lithotripsy with or without endoscopy
	Pancreatic sphincterotomy and stent placement for pain relief
	Transampullary or transgastric drainage of pseudocyst
Surgical	Decompression
	Resection
Not recommended	Allopurinol
	Antioxidant therapy (vitamin C, vitamin E, selenium, methionine)
	Octreotide (sandostatin)
	Prokinetic agents (erythromycin)

Medical treatment

Chronic disabling pain is responsible for most of the morbidity of chronic pancreatitis; thus, treatment is directed toward pain relief and management of complications.

• *Lifestyle modification* (e. g., cessation of alcohol and tobacco use) and dietary changes (e.g., low-fat diet, eating small meals).

• *Analgesics coupled with antidepressants* to address the concurrent depression: NSAIDs and acetaminophen are the first-line agents for use in a step-

wise approach with long-acting and short-acting narcotics (narcotic addiction is a common consequence of treatment and should be closely monitored).

• *Pancreatic enzymes* (mezim, creon, pancitrat) (1–2 × 25 000 to 40 000 IU lipase per main meal, 1 × 10 000 IU lipase for snacks or light meals) are recommended for the treatment of steatorrhea and malabsorption.

The amount of pancreatic enzyme replacement necessary depends on the diet and on the amount of residual pancreatic function (which diminishes over time). The normal amount of lipase secreted is about 750,000–1,000,000 units (USP) per meal. (Note that earlier used IU, and 1 IU = 3 USP units). Since a minimum of 10 % of normal pancreatic enzyme output is needed to digest a meal, about 70,000–80,000 USP units of lipase are required for an average-sized adult (70 kg) with total pancreatic insufficiency. The amount can be reduced for smaller persons and those with residual pancreatic exocrine function — while monitoring symptoms and nutritional parameters.

The most widely used enzyme preparation is porcine pancreatin. The preparation contains a mixture of protease, lipase and amylase. Overall pancreatin preparation replacements must contain high lipase activity. Lipase of porcine pancreatin is destroyed by protease and acids, thus it is necessary to protect the pancreatin against the influence of gastric acids. Another factor that is of great importance is the particle size and the rate of which the porcine pancreatin is released into the duodenum. The best particle size is assumed to be a diameter of ≤ 2 mm, since these particles leaves the stomach at the same time as solid food. The enzymes should be released within 30 min.

Pancreatic enzyme supplements improve fat absorption, and hence reduces steatorrhea and this may have beneficial effects on drug absorption. In contrast high-dose enzyme replacement therapy with or without gastric acid suppression may cause additional challenges related to drug absorption and interactions if additional drug therapy is required. Thus, enzyme treatment can either enhance or complicate drug absorption in different aspects and this should be considered in the pharmacological management of clinical symptoms.

• *Acid suppression agents*, a histamine H_2 blocker, or a PPI reduces inactivation of the enzymes from gastric acid.

The decision to move to endoscopic or surgical interventions should be considered for treatment of correctable causes and when medical management no longer relieves pain, when quality of life is greatly decreased, or when patients are significantly malnourished.

Endoscopic treatment

Therapeutic indications for ERCP include treatment of symptomatic stones, strictures, and pseudocysts.

Ductal decompression by sphincterotomy or stent placement offers pain relief in most patients.

Endoscopic drainage is indicated for symptomatic or complicated pseudocysts.

In patients with significant stone burden, extracorporeal shock wave lithotripsy, with or without endoscopic drainage of the pancreatic duct, has been proposed as a safe technique.

Surgical treatment

Most patients undergo surgery when the initial medical and endoscopic treatments fail to relieve intractable abdominal pain. Surgery is also indicated for biliary or pancreatic stricture obstruction, duodenal stenosis, fistulas (peritoneal or pleural effusion), hemorrhage, intractable chronic abdominal pain, vascular complications and suspected pancreatic neoplasia.

Lateral pancreaticojejunostomy is the preferred surgical treatment in patients with pancreatic duct dilatation of 7 mm or more.

Pancreatoduodenectomy (Whipple procedure, pylorus-preserving, duodenum-preserving) is indicated in the treatment of chronic pancreatitis with pancreatic head enlargement and typically results in significant pain relief.

Pancreatic islet autotransplantation available in several major centers expert in the treatment of pancreatitis, is used in an attempt to both control severe pain and delay the development of diabetes mellitus.

KEY MESSAGES

• Diseases that can lead to exocrine pancreatic insufficiency are chronic pancreatitis, organ defect after necrotizing pancreatitis, pancreatic cancer, cystic fibrosis, functional pancreatic insufficiency.

• A diagnosis of chronic pancreatitis should be considered in patients presenting with chronic abdominal pain, malabsorption, diarrhea, steatorrhea (loose, bulky, offensive stools), weight loss, otherwise unexplained diabetes or acute pancreatitis.

• Contrast-enhanced CT is the recommended initial imaging study in patients with suspected chronic pancreatitis. Pathognomonic findings of chronic pancreatitis are calcifications within the pancreatic ducts, pseudocysts, ductal dilatation, thrombosis, pseudoaneurysms, necrosis, and parenchymal atrophy.

• Pancreatic enzyme supplementation is indicated for steatorrhea and malabsorption and may help relieve pain in patients with chronic pancreatitis.

• To patients with exocrine pancreatic insufficiency enteric-coated pancreatin should be given (minitablets of 2 mm diameter or micropellets of < 2 mm diameter), 1–2 × 25 000 to 40 000 IU per main meal, 1 × 10 000 IU for snacks or light meals.

• If steatorrhea does not improve, increase the dosage of pancreatin and consider additional acid blockade with PPIs.

6. DISEASES OF THE BOWEL

The length of the small intestine varies from 10 to 33 feet (3–10 metres). The average length is considered to be approximately 22 feet (6.5 metres). The

small bowel is divided into the duodenum, which is approximately 1 foot in length (25 cm) and extends from the pylorus to the duodenaljejunal flexure (this point is marked by the ligament of Treitz); the jejunum and the ileum. In the regulatory activity of the small intestine are involved hormones — secretin, cholecystokinin and the glucose-dependent insulinotropic peptide. There is a large flow of secretions cross the small bowel mucosa which is estimated to be between 1.5 and 2.5 litres of fluid within a 24-hour period. The absorptive capacity of the small bowel is enhanced by the surface area and the peristaltic movements. One of the major differences between the large and small intestine is the presence of bacterial activity in the large bowel. Anaerobes (particularly gram-positive *Firmicutes* and *Actinobacteria*, and gram-negative *Bacteroidetes*) are the predominant bacteria in the gastrointestinal tract of adult subjects.

6.1. Functional bowel disorders

Irritable bowel syndrome and functional constipation are the most common functional gastrointestinal disorders. They negatively affect quality of life and are associated with a significant economic burden related to direct and indirect annual health-care costs.

Irritable bowel syndrome is defined as abdominal discomfort or pain associated with altered bowel habits for at least three days per month in the previous three months, with the absence of organic disease. The prevalence of irritable bowel syndrome is 5 to 10 percent with peak prevalence from 20 to 39 years of age.

Classification of functional bowel disorders (according to Rome IV criteria — point **C**)

C. Functional bowel disorders

C1. Irritable bowel syndrome

C2. Functional constipation

C3. Functional diarrhea

C4. Functional abdominal bloating/distension

C5. Unspecified functional bowel disorders

C6. Opioid-induced constipation

C1. Irritable bowel syndrome

Diagnostic Criteria[a] for Irritable Bowel Syndrome

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation.

2. Associated with a change in frequency of stool.

3. Associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Irritable bowel syndrome is classified into 3 main subtypes according to the predominant disorder in bowel habits: irritable bowel syndrome with predominant constipation, irritable bowel syndrome with predominant diarrhea, and irritable bowel syndrome with mixed bowel habits. Patients who meet diagnostic

criteria for irritable bowel syndrome but whose bowel habits cannot be accurately categorized into 1 of the 3 groups should be categorized as having irritable bowel syndrome unclassified.

Diagnostic criteria for irritable bowel syndrome subtypes

Predominant bowel habits are based on stool form on days with at least one abnormal bowel movement.[a]

Irritable bowel syndrome with predominant constipation: more than one fourth (25 %) of bowel movements with Bristol stool form types 1 or 2 and less than one-fourth (25 %) of bowel movements with Bristol stool form types 6 or 7.

Irritable bowel syndrome with predominant diarrhea: more than one fourth (25 %) of bowel movements with Bristol stool form types 6 or 7 and less than one-fourth (25 %) of bowel movements with Bristol stool form types 1 or 2.

Irritable bowel syndrome with mixed bowel habits: more than one fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and more than one-fourth (25 %) of bowel movements with Bristol stool form types 6 or 7.

Irritable bowel syndrome unclassified: patients who meet diagnostic criteria for irritable bowel syndrome but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above.
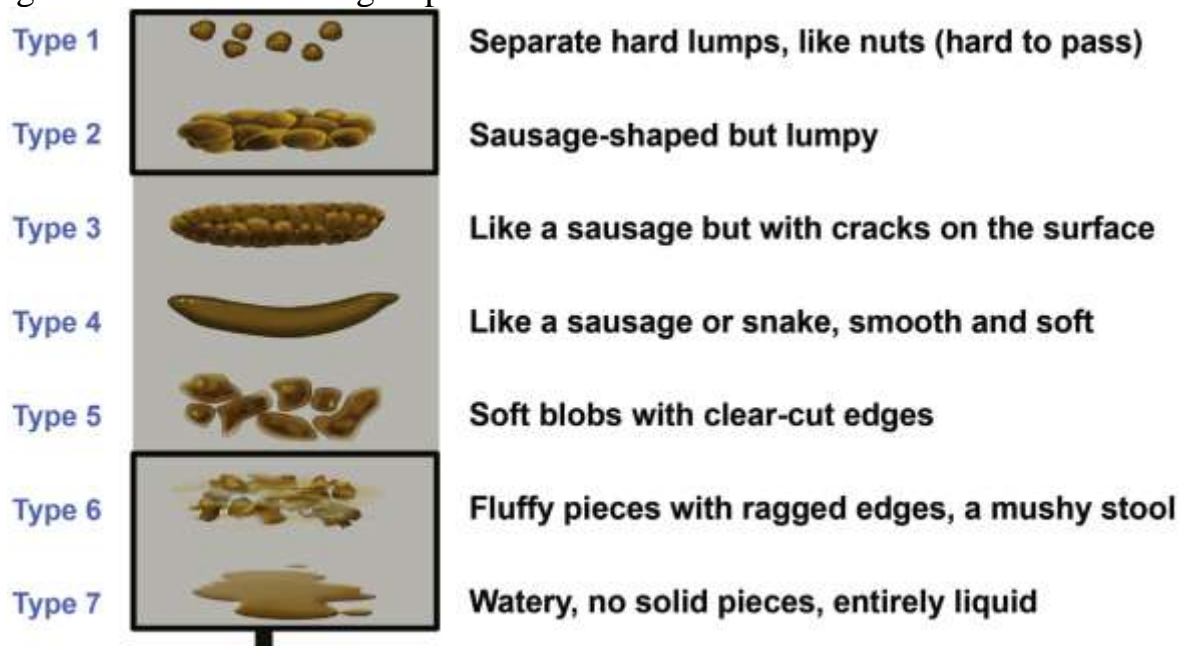
Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, entirely liquid

Figure 5 — Bristol stool form

C2. Diagnostic Criteria[a] for Functional Constipation

1. Must include 2 or more of the following:[b]

a. Straining during more than one-fourth (25 %) of defecations.

b. Lumpy or hard stools (Bristol stool form 1–2) more than one-fourth (25 %) of defecations.

c. Sensation of incomplete evacuation more than one-fourth (25 %) of defecations.

d. Sensation of anorectal obstruction/blockage more than one-fourth (25 %) of defecations.

e. Manual maneuvers to facilitate more than one fourth (25 %) of defecations (eg, digital evacuation, support of the pelvic floor.)

f. Fewer than 3 spontaneous bowel movements per week.

2. Loose stools are rarely present without the use of laxatives.

3. Insufficient criteria for irritable bowel syndrome.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

[b]For research studies, patients meeting criteria for opioid-induced constipation should not be given a diagnosis of Functional Constipation because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these 2 conditions might overlap.

C3. Diagnostic Criterion[a] for Functional Diarrhea

Loose or watery stools, without predominant abdominal pain or bothersome bloating, occurring in > 25 % of stools.[b]

[a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

[b]Patients meeting criteria for diarrhea-predominant irritable bowel syndrome should be excluded.

C4. Diagnostic Criteria[a] for Functional Abdominal Bloating/Distension

Must include both of the following:

1. Recurrent bloating and/or distention occurring, on average, at least 1 day per week; abdominal bloating and/or distention predominates over other symptoms.[b]

2. There are insufficient criteria for a diagnosis of irritable bowel syndrome, functional constipation, functional diarrhea, or postprandial distress syndrome.

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

[b]Mild pain related to bloating may be present as well as minor bowel movement abnormalities.

C5. Diagnostic Criterion[a] for Unspecified Functional Bowel Disorder

Bowel symptoms not attributable to an organic etiology that do not meet criteria for irritable bowel syndrome or functional constipation, diarrhea, or abdominal bloating/distention disorders.

[a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

C6. Diagnostic Criteria for Opioid-Induced Constipation

1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:

a. Straining during more than one-fourth (25 %) of defecations.

b. Lumpy or hard stools (Bristol stool form 1–2) more than one-fourth (25 %) of defecations.

c. Sensation of incomplete evacuation more than one-fourth (25 %) of defecations.

d. Sensation of anorectal obstruction/blockage more than one-fourth (25 %) of defecations.

e. Manual maneuvers to facilitate more than onefourth (25 %) of defecations (eg, digital evacuation, support of the pelvic floor).

f. Fewer than three spontaneous bowel movements per week.

2. Loose stools are rarely present without the use of laxatives.

Management

The goals of treatment are symptom relief and improved quality of life. Exercise, antibiotics, antispasmodics, peppermint oil, and probiotics appear to improve symptoms. Over-the-counter laxatives and antidiarrheals may improve stool frequency but not pain.

Treatment options *diarrhea-predominant IBS:*

- antibiotics;
- antidepressants;
- antidiarrheal medications;
- antispasmodics;
- complementary and alternative therapies;
- probiotics.

Treatment options *constipation-predominant IBS:*

- antibiotics;
- antidepressants;
- antispasmodics;
- complementary and alternative therapies;
- over-the-counter laxatives;
- probiotics.

Treatment options mixed presentation IBS with alternating diarrhea and constipation:

- antibiotics;
- antidepressants;
- antispasmodics;
- complementary and alternative therapies;
- probiotics.

Treatment with antidepressants and psychological therapies are also effective for improving symptoms.

Pelvic floor biofeedback therapy is effective for treating levator ani syndrome and defecatory disorders. Surgery may be useful in refractory cases.

KEY MESSAGES

- Abdominal pain is the most common symptom in irritable bowel syndrome and often is described as a cramping sensation. The absence of abdominal pain excludes irritable bowel syndrome.
- In irritable bowel syndrome other common symptoms include diarrhea, constipation, or alternating diarrhea and constipation.
- Patients with functional bowel disorders show a higher prevalence of psychological disorder, a higher rate of depression and anxiety.

6.2. Celiac disease

Celiac disease is a multisystem autoimmune disorder that can cause symptoms involving the gastrointestinal tract and other organ systems such as the skin and bones.

Celiac disease is an autoimmune disorder that occurs in genetically predisposed individuals in response to ingestion of gluten and is characterized by reversal changes of intestinal mucosa (from distortion of crypt architecture to total villous atrophy and infiltration of lamina propria by lymphocytes) and malabsorption of essentials micronutrients.

Pathogenesis of celiac disease

The disease is thought to develop by an interplay of genetic and autoimmune factors and the ingestion of gluten (ie, an environmental factor).

Celiac disease occurs in genetically predisposed individuals, ie, those who carry the HLA alleles DQ2 (DQA1*05, DQB1*02), DQ8 (DQA1*03, DQB1*0302), or both. Ingestion of gluten is necessary for the disease necessary for the disease to develop.

Gluten, the protein component of wheat, barley, and rye, contains proteins called prolamins, which vary among the different types of grain. In wheat, the prolamin is gliadin, which is alcohol-soluble. In barley the prolamin is hordein, and in rye it is secalin. The prolamin content in gluten makes it resistant to degradation by gastric, pancreatic, and intestinal brush border proteases. Gluten crosses the epithelial barrier and promotes an inflammatory reaction by both the innate and adaptive immune systems that can ultimately result in flattening of villi and crypt hyperplasia.

Certain viral infections during childhood, such as rotavirus and adenovirus infection, can increase the risk of celiac disease.

Clinical features of celiac disease

- *Diarrhea* is a common presenting symptom, although not all patients present with diarrhea.
- *Abdominal pain and weight loss.*
- *Pallor or decreased exercise tolerance* can develop due to anemia from iron malabsorption, and some patients have easy bruising due to vitamin K malabsorption.
- *Gynecologic and obstetric complications* include delayed menarche, amenorrhea, spontaneous abortion, intrauterine growth retardation, pretermdeli-

very, and low-birth-weight babies.

- *Osteoporosis and osteopenia* due to malabsorption of vitamin D.
- *Dermatitis herpetiformis* is one of the most common cutaneous manifestations of celiac disease.
- Association with *various other autoimmune diseases,* including Hashimoto thyroiditis, type 1 diabetes mellitus, primary biliary cirrhosis, primary sclerosing cholangitis, and Addison disease.
- Patients with celiac disease have a *higher risk of developing enteric malignancies*, particularly intestinal T-cell lymphoma, and they have smaller increased risk of colon, oropharyngeal, esophageal, pancreatic, and hepatobiliary cancer.

Diagnostic approach of celiac disease

- *Serologic tests.* Patients strongly suspected of having celiac disease should be screened for IgA antibodies to tissue transglutaminase while on a gluten-containing diet.
- *Biopsy:* one to two samples should be taken from the duodenal bulb and at least four samples from the rest of the duodenum, preferably from two different locations. Changes are from mild distortion of crypt architecture to total villous atrophy and infiltration of lamina propria by lymphocytes and their reversal after adherence to a gluten-free diet.
- *Genetic testing* for HLA-DQ2 and HLA-DQ8.

Management celiac disease

- The mainstay of treatment is **lifelong adherence to a gluten-free diet.** Most patients report improvement in abdominal pain within days of starting this diet and improvement of diarrhea within 4 weeks.

Foods that can be eaten on a gluten-free diet: beans, seeds, nuts (unprocessed), fresh eggs, fresh meat, fish, poultry, fruits, vegetables, dairy products, corn, millet, rice, sorghum, soy, oats, potatoes, vegetable oil, olive oil, rice cakes, homemade popcorn, tea, coffee, fresh juices.

- Concomitant conditions such as anemia and vitamin deficiency often require nutritional supplements.

KEY MESSAGES

- Celiac disease is associated not only with gastrointestinal symptoms, but with a variety of diseases, including dermatitis herpetiformis, malabsorption of several nutrients (potentially leading to osteoporosis, iron deficiency anemia, and other disorders), and intestinal malignancies.
- An initial screening test for celiac disease is serologic testing for immunoglobulin A antibodies to tissue transglutaminase; the confirmatory tests are invasive, involving upper endoscopy for duodenal biopsy in celiac disease and skin biopsy in dermatitis herpetiformis.
- The only effective treatment is lifelong adherence to a gluten-free diet, and nonadherence is a common cause of refractory disease.

• Mucosal changes are reversal after adherence to a gluten-free diet.

6.3. Inflammatory bowel disease

IBD — Crohn's disease and ulcerative colitis — is characterized by chronic inflammation of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors. Together, IBD is estimated to affect more than 0.4 % of Europeans and North Americans, a number that is expected to increase over time. It is well recognized that patients with IBD are at an increased risk of developing colorectal cancer, primarily the result of chronic intestinal inflammation. More recently, patients with IBD have also been shown to be at increased risk of developing extra-intestinal malignancies, thought to be a consequence of immunosuppressive therapies and an underlying inflammatory state.

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract characterized by inflammation at any point from the mouth to the rectum.

Diagnostic approach of Crohn's disease

Clinical manifestation Crohn's disease

In CD, any part of bowel from esophagus to anal canal may be involved.

Common symptoms of CD include abdominal pain, diarrhea, fatigue, fever, gastrointestinal bleeding, and weight loss. Symptoms depend upon the site of involvement.

Small intestinal involvement / ileocolonic involvement:

1. abdominal pain;

2. symptoms suggestive of recurrent partial intestinal obstruction may be present;

3. chronic diarrhea;

4. fever, anorexia, weight loss.

Large bowel involvement:

1. chronic diarrhea;

2. hematochezia;

3. perianal disease;

4. fever, weight loss;

5. abdominal pain.

Upper GI involvement:

1. dysphagia, odynophagia;

2. epigastric pain;

3. symptoms suggestive of gastric outlet obstruction.

Extraintestinal manifestations Crohn's disease:

• anemia;

• inflammatory arthropathies;

• ankylosing spondylitis;

• pyoderma gangrenosum;

• erythema nodosum;

• iritis, uveitis, episcleritis;

- nephrolithiasis;
- primary sclerosing cholangitis;
- venous thromboembolism.

Laboratory testing

Laboratory tests are useful for diagnosing CD, assessing disease activity, identifying complications, and monitoring response to therapy.

Testing patient with CD must include:

- total blood analysis: white blood cell, platelet, hemoglobin, hematocrit, erythrocyte sedimentation rate;
- biochemical blood analysis: blood urea nitrogen, creatinine, liver enzymes, C-reactive protein, iron, ferritin, total iron-binding capacity, vitamin B_{12}, folate, albumin, prealbumin, calcium, vitamin D;
- stool culture and testing for *Clostridium difficile* toxin;
- fecal lactoferrin and calprotectin — markers for bowel inflammation;
- presence of antibodies to *Escherichia coli* outer membrane porin and *Saccharomyces cerevisiae.*

Instrumental testing

- EGD is recommended in patients with upper gastrointestinal symptoms, asymptomatic patients with iron deficiency anemia, and patients with active CD who have a normal colonoscopy.
- Colonoscopy with ileoscopy and biopsy is valuable in the diagnosis of CD at the junction of the ileum and colon.

Characteristic endoscopic findings include skip lesions, cobblestoning, ulcerations, and strictures.

Histology may show neutrophilic inflammation, noncaseating granulomas, Paneth cell metaplasia, and intestinal villi blunting.

- Capsule endoscopy — better yield for nonstricturing small bowel CD than small bowel follow-through and colonoscopy with ileoscopy; should be avoided in patients with small bowel strictures because capsule retention may occur.
- Computed tomography enterography — permits visualization of the bowel wall and lumen; exposes patient to ionizing radiation.
- CT — reveals intraintestinal inflammation and extraintestinal manifestations; exposes patient to ionizing radiation.
- Magnetic resonance enterography — permits visualization of the bowel and lumen; expensive; no ionizing radiation.
- Magnetic resonance imaging — reveals intraintestinal inflammation and extraintestinal manifestations without radiation.
- Scintigraphy — uses radiolabeled leukocytes to diagnose bowel inflammation and to estimate disease extent and activity; role in clinical practice is limited.
- Small bowel follow-through — radiographic examination of small bowel after ingestion of contrast medium (barium).

• Ultrasonography — detects increase in vascular flow, abscess, sinus tracts, and lymphadenopathy.

Management Crohn's disease

Therapeutic recommendations are determined by disease location, activity, and severity, and by disease-associated complications.

The goals of therapy are control of symptoms, induction of clinical remission, and maintenance of remission with minimal adverse effects.

Two principal strategies are currently used for CD management:

• a traditional "step-up" approach begins with corticosteroids or mesalamine products and advances to immunomodulators or anti-TNF agents (table 13).

• A "top-down" approach begins with anti-TNF agents.

Table 13 — Immunomodulator therapy for Crohn's disease

Drug	Dosage	Common adverse effects
6-mercaptopurine	50 mg by mouth per day (maximum: 1.5 mg/kg/day)	Myelosuppression, hepatic toxicity, immunosuppression, hepatic encephalopathy, pancreatitis, rash, hyperpigmentation, lymphoma, fever.
Azathioprine	50 mg by mouth per day (maximum: 2.5 mg/kg/day)	Gastritis, nausea, vomiting, lymphoma, fever. May cause pancreatitis, leukopenia, anemia, thrombocytopenia.
Drug	Dosage	Common adverse effects
Budesonide	9 mg by mouth every morning for up to eight weeks (induction)	Diarrhea, nausea, arthralgias, headache, respiratory tract infection, sinusitis.
Methotrexate	25 mg subcutaneously or intramuscularly per week	Alopecia, photosensitivity, rash, diarrhea, anorexia, nausea, vomiting, stomatitis, leukopenia, pneumonitis. May also cause hyperuricemia, gastrointestinal hemorrhage, myelosuppression, hepatotoxicity, lung fibrosis, renal failure
Prednisone	20 to 40 mg by mouth per day	Hypertension, fluid retention, hypernatremia, osteoporosis, depression, increased risk of infection.
Anti–tumor necrosis factor agents		
Adalimumab	160 mg subcutaneously once at week 0, then 80 mg once at week 2, then 40 mg every two weeks	Injection site reactions (e. g., erythema, itching, hemorrhage, pain, swelling), infection, tuberculosis, malignancies (e. g., lymphoma), autoantibodies/lupus-like syndrome.
Certolizumab	400 mg subcutaneously once at weeks 0, 2, and 4, then 400 mg every four weeks	Injection site reactions, upper respiratory tract infection, headache, hypertension, rash, infections.
Infliximab	5 mg/kg intravenously once at weeks 0, 2, and 6, then every eight weeks	Infusion-related reactions (e. g., dyspnea, flushing, headache, rash, chest pain, hypotension, pruritus, urticaria, anaphylaxis),

		delayed reaction (e. g., serum sickness, myalgia, arthralgia), infections, pneumonia, cellulitis, abscess, skin ulceration, sepsis, bacterial infection, autoantibodies/lupus-like syndrome, lymphoma

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation of the colon. Ulcerative colitis always involves the rectum (i. e., proctitis), and it may extend proximally in a contiguous pattern to involve the sigmoid colon (i. e., proctosigmoiditis), the descending colon (i. e., left-sided colitis), or the entire colon (i. e., pancolitis).

The hallmark symptoms of ulcerative colitis are:
- intermittent bloody diarrhea;
- rectal urgency;
- tenesmus.

Extraintestinal manifestation of UC:
  - osteoporosis;
  - oral ulcerations;
  - arthritis;
  - primary sclerosing cholangitis;
  - uveitis;
  - pyoderma gangrenosum;
  - deep venous thrombosis;
  - pulmonary embolism.

Diagnostic approach of ulcerative colitis
- *Relevant history:*
  - stool frequency, consistency, blood and mucous;
  - nocturnal diarrhea;
  - weight loss;
  - family history;
  - extraintestinal manifestations (joints, rashes, eyes);
  - travel abroad.
- *Examinations:*
  - pulse;
  - temperature;
  - abdominal tenderness;
  - abdominal distension.
- *Investigations:*
  - full blood count, erythrocyte sedimentation rate;
  - liver function tests;
  - C reactive protein;
  - urea;

➢ electrolytes (hypokalemia may demonstrate persistent diarrhea);

➢ stool culture;

➢ testing for *Clostridium difficile* toxin;

➢ stool examinations for ova and parasites;

➢ sigmoidoscopy, colonoscopy: characteristic changes include loss of the typical vascular pattern, friability, exudates, ulcerations, and granularity in a continuous, circumferential pattern (table 14).

➢ biopsy.

Table 14 — Disease extent in ulcerative colitis

Extent	Disease	Description
E1	Ulcerative proctitis	Involvement limited to rectum
E2	Left sided UC (distal colitis)	Involvement distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Disease severity in ulcerative colitis

• *Mild*

➢ Fewer than four stools daily, with or without blood.

➢ No systemic disturbance.

➢ Normal erythrocyte sedimentation rate and C reactive protein values.

• *Moderate*

➢ Four to six stools a day with minimal systemic disturbance.

• *Severe*

➢ More than six stools a day containing blood and evidence of systemic disturbance (fever, tachycardia, anaemia, or hypoalbuminaemia).

The differential diagnosis of ulcerative colitis includes any condition that produces chronic, intermittent diarrhea, such as Crohn's disease, ischemic colitis, infectious colitis, irritable bowel syndrome, and pseudomembranous colitis (table 15–17).

Table 15 — The main differential diagnosis of ulcerative colitis and Crohn's disease

Ulcerative colitis	Crohn's disease
Acute self limiting colitis	Intestinal tuberculosis
Amoebic colitis	Acute self limiting colitis
Crohn's disease	Amoebic colitis
HIV enteropathy	Ulcerative colitis
	Behcet's disease
	NSAID enteropathy
	HIV enteropathy

Table 16 – Differential diagnosis of ulcerative colitis

Disease	Clinical characteristics
Crohn's colitis	Perianal lesions common; frank bleeding less common than in ulcerative colitis

Infectious colitis	Sudden onset; pathogens present in stool; pain may be a predominant feature
Irritable bowel syndrome	Meets Rome III criteria for irritable bowel syndrome
Ischemic colitis	Affects older age groups; vascular disease often present; sudden onset, often painful
Pseudomembranous colitis	Recent antibiotic use; *Clostridium difficile* toxin detectable in stool

Table 17 — Comparison of ulcerative colitis and Crohn's disease

Feature	Ulcerative colitis	Crohn's disease
Abdominal pain	Variable	Common
Depth of inflammation	Mucosal	Transmural
Diarrhea	Severe	Less severe
Distribution	Diffuse, contiguous spread; always involves rectum; spares proximal gastrointestinal tract	Segmental, noncontiguous spread ("skip lesions"); less common rectal involvement; occurs in entire gastrointestinal tract
Fistula and sinus tracts	Rare	Common

Complications inflammatoty bowel disease

1. Hemorrhage: profuse bleeding from ulcers in UC. Bleeding is less common in CD. Massive bleeding in CD is more often seen from ileal ulceration than colitis.

2. Strictures, bowel perforation and intra-abdominal abscesses in CD.

3. Fistulas and perianal disease in CD.

4. Colorectal cancer: significantly increased risk of colon cancer in UC after 8 years of diagnosis; the risk is lower in CD as compared to UC.

Management ulcerative colitis

1. 5-aminosalicylic acid (side effects: agranulocytosis, diarrhea, headache, nausea, rash, renal impairment).

1.1. Sulfasalazine 2 to 6 g (daily dosage).

1.2. Mesalazine 2.4 to 4.8 g (daily dosage).

Mesalazine (5-aminosalicylic acid) is rapidly absorbed from the jejunum so the drug can be delivered to the colonic mucosa in several ways.

Topical preparations can be applied per rectum. In oral preparations the active ingredient can be coated with a pH sensitive resin or semipermeable membrane for slow release, or 5-aminosalicylic acid can be linked to another molecule by an azo bond that is enzymatically cleaved in the colon (balsalazide, olsalazine, and sulfasalazine).

2. Prednisone 40 to 60 mg (side effects: adrenal insufficiency, hyperglycemia, osteoporosis). Corticosteroids may be applied topically (suppositories, liquid or foam enemas), orally (as prednisolone or prednisone), or intravenously (as hydrocortisone).

3. Azathioprine daily dosage 1.5 to 2.5 mg per kg (side effects: flu-like symptoms — myalgia, headache, and diarrhea; hepatotoxicity; leukopenia).

4. 6-mercaptopurine daily dosage 0.75 to 1.5 mg per kg (side effects: head-

ache, diarrhea, hepatotoxicity, leukopenia, myalgias).

5. Infliximab daily dosage 5 mg per kg (side effects: arthralgias, fever, infection, malaise, myalgias).

Colectomy for the treatment of ulcerative colitis is warranted in patients who develop dysplasia or cancer.

Toxic megacolon, which is a presentation of fulminant ulcerative colitis, is characterized by dilation of the transverse colon to more than 5.5 cm on supine abdominal radiography and requires emergent surgical evaluation.

KEY MESSAGES

• In Crohn's disease any part of bowel from esophagus to anal canal may be involved.

• Transmural inflammation with fistula and sinus tract are common for Crohn's disease.

• Extraintestinal manifestations often occur in IBD.

• Presence of antibodies to *Escherichia coli* outer membrane porin and *Saccharomyces cerevisiae* is suggestive of Crohn's disease, whereas perinuclear antineutrophil cytoplasmic antibody is more suggestive of ulcerative colitis.

• Fecal lactoferrin and calprotectin are surrogate markers for bowel inflammation and may help distinguish between inflammatory conditions and irritable bowel syndrome.

• The goals of therapy IBD are control of symptoms, induction of clinical remission, and maintenance of remission with minimal adverse effects.

6.4. Pseudomembranous colitis

Pseudomembranous colitis is an inflammatory condition of the colon characterized by elevated yellow-white plaques that coalesce to form pseudomembranes on the mucosa. Patients with the condition commonly present with abdominal pain, diarrhea, fever, and leukocytosis. Because pseudomembranous colitis is often associated with *C. difficile* infection, stool testing and empiric antibiotic treatment should be initiated when suspected.

C. difficile is an obligate anaerobic organism and toxin-producing gram-positive rod with the ability to form spores. Antibiotics, such as clindamycin, penicillins, fluoroquinolones, and cephalosporins, are typically associated with *C. difficile* infection, but disease can occur with almost any anti-bacterial agent, including vancomycin and metronidazole, which are commonly used for treatment.

The less common non-*C.difficile* causes of pseudomembranous colitis should be excluded: Behcet's disease, collagenous colitis, inflammatory bowel disease, ischemic colitis, other infections organisms - bacteria, parasites, viruses, and a handful of drugs and toxins.

Diagnostic approach of pseudomembranous colitis

• Medical history with information on recent hospitalizations or procedures, antibiotic use (clindamycin, penicillins, fluoroquinolones, cephalosporins, etc.), infections, exposure to sick contacts, recent travel, and medications taken.

• Abdominal pain, diarrhea, fever, and leukocytosis.

• Testing for *C. difficile* demonstration of the toxin or detection of toxigenic organisms:

➢ the cell culture cytotoxicity assay is the gold standard, but it is labor- and time-intensive;

➢ polymerase chain reaction for the toxin gene or genes (more widely available tests);

➢ enzyme immunoassay for toxins A and B;

➢ stool evaluation for glutamate dehydrogenase (is an enzyme produced by both toxigenic and nontoxigenic strains of *C. difficile)*, which can yield results readily within hours.

• Colonoscopy or flexible sigmoidoscopy demonstrate pseudomembranes - elevated yellow-white nodules or plaques on the mucosal surfaces of the colon.

• Plain radiography of the abdomen may show evidence of colonic ileus, small bowel ileus, ascites, nodular thickening, or "thumbprinting", a finding of wide transverse bands associated with haustral thickening. Severe disease may be demonstrated by marked colonic dilatation, perforation, or pneumoperitoneum.

• CT findings include colonic wall thickening and nodularity, bowel wall stranding and edema, ascites, the "accordion" sign (ingested oral contrast becomes trapped between thickened haustral folds), and the "double-halo" sign (submucosal edema indicated by two or three concentric rings in the large bowel seen on transverse imaging).

Proposed *criteria for severe disease* include:
• WBC count greater than 15,000/mm^3;
• elevated creatinine (greater than 1.5 times baseline);
• advanced age;
• and/or hypoalbuminemia (serum albumin less than 3.0 g/dl).

Management *C. difficile* infection

If testing for *C. difficile* is positive, treatment is generally based on the severity and the complications of the illness:

• **Mild or moderate *C. difficile* infection** should be treated with oral metronidazole 500 mg three times per day for 10 to 14 days.

• **Severe infection** should be treated with oral vancomycin 125 mg four times per day for 10 to 14 days.

• **Severe *C. difficile* infection complicated by hypotension, shock, ileus, or megacolon** should be treated with a combination of high-dose oral vancomycin (and possibly rectal vancomycin as well) at 500 mg four times per day plus intravenous metronidazole.

KEY MESSAGES

• Pseudomembranous colitis is a nonspecific pattern of injury resulting from decreased oxygenation, endothelial damage, and impaired blood flow to the mucosa that can be triggered by a number of disease states.

• Chemicals, medications, ischemia, microscopic colitis, other infectious

organisms, and inflammatory conditions can all predispose to pseudomembrane formation and should be included in the differential diagnosis.

• As most patients with pseudomembranous colitis have *C. difficile* infection, it should be excluded first. Empiric treatment for *C. difficile* should be started if the patient is seriously ill.

• Testing for *C. difficile* is with polymerase chain reaction, enzyme immunoassay for toxins A and B, and glutamate dehydrogenase measurement.

• Toxic megacolon as a complication of pseudomembranous colitis is characterized by dilation of the transverse colon to more than 5.5 cm on supine abdominal radiography and requires emergent surgical evaluation.

• Management *C. difficile* infection includes metronidazole and *oral* vancomycin.

6.5. Microscopic colitis

Microscopic colitis, initially described in 1980, is characterized by the presence of grossly normal-appearing mucosa with abnormal biopsy findings of lymphocytic inflammatory infiltrate within the lamina propria. Microscopic colitis includes two subtypes — *collagenous & lymphocytic colitis*. Collagenous colitis is differentiated from lymphocytic colitis histologically by the presence or absence of thick subepithelial deposits of collagen.

Collagenous colitis was first described in 1976 in a middle-aged woman with abdominal cramping and chronic watery diarrhea. Symptoms may be explained by dysfunctions in electrolyte movement across the epithelium of the colon and tight junctions between colonic cells, and increased levels of nitric oxide and prostaglandins, which appear to cause increased secretion.

Diagnostic approach of microscopic colitis

Microscopic colitis are characterized by sudden onset of symptoms (which can mimic infectious causes) and a clinical course that is chronic and benign, with frequent relapses.

• Symptoms:
  ➢ frequent, watery, non-bloody diarrhea - the most typical feature;
  ➢ abdominal cramping;
  ➢ nausea, vomiting;
  ➢ flatulence;
  ➢ fecal incontinence;
  ➢ mucus-containing stools;
  ➢ fatigue;
  ➢ weight loss.

• Association with other autoimmune conditions, including thyroid disorders, rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease, and celiac disease.

• On endoscopic examination the colon usually appears normal or has only

minimal changes, including mild erythema or pallor.

• Histology of microscopic colitis is typically characterized by preserved crypt architecture, a mixed inflammatory infiltrate extending into the lamina propria, and deposition of collagen in a band-like or irregular distribution below the epithelium.

Management microscopic colitis

Many cases of microscopic colitis resolve spontaneously, both clinically and histologically.

• The first step in the management of microscopic colitis usually entails discontinuation of offending agents, such as NSAIDs and diarrhea-promoting agents, likely caffeine, alcohol, and dairy products.

• Anti-diarrheal medications like loperamide and diphenoxylate/atropine can be effective in symptomatic management and are often first-line agents for milder cases of microscopic colitis.

• Corticosteroids: budesonide is effective in the induction and maintenance of symptom and histologic resolution, as well as improving quality of life in collagenous colitis. Budesonide is preferred over other corticosteroids because its rapid hepatic metabolism minimizes systemic effects.

• Bismuth salicylate.

• Mesalasine.

• Other agents: *Boswellia serrata* extract, prednisolone, and probiotics.

KEY MESSAGES

• Microscopic (collagenous and lymphocytic) colitis are characterized by sudden onset of frequent, watery, non-bloody diarrhea in patients with a normal endoscopic structure of colon but with abnormal biopsy data.

• Morphological findings in microscopic colitis includes of lymphocytic inflammatory infiltrate within the lamina propria and/or subepithelial deposits of collagen.

• Microscopic colitis has a chronic and benign course and can resolve spontaneously — clinically and histologically.

6.6. Ischemic colitis

Ischemic colitis encompasses a wide and heterogeneous spectrum of disease that includes mild and reversible colopathy, acute colitis (including pseudomembranous colitis), chronic colitis, chronic disease with stricture, gangrenous bowel, and fulminant pan-colitis.

It is the most common form of gastrointestinal ischemic disease (50–60 %), and is also a common cause of lower gastrointestinalbleeding, along with diverticulosis and angiodysplasias.

Non-gangrenous colitis is the most common form of ischemic colitis (80–85 %), approximately 50 % of cases are transient and reversible. Chronic ischemic colitis appears to occur in 30–40 % of cases.

The pathophysiology of ischemic colitis varies based on the underlying etiology.

Ischemic colitis is typically seen in individuals older than 60 years of age, but can present in younger individuals with suggestive history.

The risk factors of ischemic colitis includes:

• advanced age;

• atherosclerosis;

• vascular occlusion (trauma, vascular surgery, thrombosis, or embolism);

• small-vessel disease (diabetes mellitus, rheumatoid arthritis, amyloidosis, radiation, systemic vasculitides);

• shock/low-flow states;

• medications (estrogens/progesterones, ergotamine, sodium polystyrene, catecholamines/vasopressors, alosetron, digitalis, gold-containing compounds, NSAIDs, neuroleptic agents);

• illicit use of cocaine and amphetamines;

• sickle cell disease;

• hypercoagulable disorders;

• long-distance running;

• chronic renal failure/end-stage renal disease requiring hemodialysis;

• colonic obstruction (intrinsic and extrinsic);

• endoscopic or other invasive GI procedures.

Diagnostic approach of ischemic colitis

• Symptoms at initial presentation:

➢ acute onset of mild to moderate, cramping, lower abdominal pain, followed by tenesmus and sudden urges to defecate, with the passage of bright red to maroon blood or bloody diarrhea within 24 hours.

• Total blood loss is usually minimal and does not typically require blood transfusion.

• Severe abdominal tenderness and peritoneal signs are not usually observed but could be an indicator of transmural colonic necrosis, colonic perforation, or fulminant/gangrenous ischemic colitis.

• Additional signs: fever and leukocytosis.

• *Endoscopic examination* is highly variable but appears to have clustered findings based on disease type:

➢ transient ischemic colitis — edematous and friable mucosa, erythema, erosions, ulcerations, petechial hemorrhage, hemorrhagic nodules, and sharply demarcated areas of involvement;

➢ severe/gangrenous ischemic colitis — dark, blue-black nodules and dusky mucosa, as well as pseudopolyps and pseudomembranes;

➢ chronic ischemic colitis — luminal strictures with transmural fibrosis,

granular mucosa, and haustral changes.
- *Histologic exam* reveal:
  - ➤ mucosal infiltration by leukocytes and inflammatory milieus;
  - ➤ erosions and ulcerations secondary to mucosal necrosis;
  - ➤ hemorrhage and hyalinization within the lamina propria;
  - ➤ crypt destruction;
  - ➤ crypt abscesses;
  - ➤ mucosal atrophy and fibrotic tissue, with pseudomembranes and pseudopolyps seen in more severe ischemia.
- *Radiographic studies* of the abdomen can show non-specific findings like "thumbprinting", distended, air-filled loops of bowel, colonic wall thickening, and loss of haustral markings.
- *Barium enema* can show early findings of colonic ischemia, which include "thumbprinting" and pseudopolyps/pseudotumors. Barium enema should also be avoided when gangrenous bowel or perforation is suspected.
- *Mesenteric angiography* should be considered when concomitant acute mesenteric ischemia is suspected.
- *CT* findings: colonic wall thickening greater than 1 cm, pneumatosis coli, and segmental colonic involvement.
- *Ultrasound/sonography*, color Doppler sonography — for identifying the extent of colonic involvement, bowel wall thickening, and the presence of extra-colonic fluid in colonic ischemic disease.

Management ischemic colitis

Management of ischemic colitis varies based on the severity of disease.
- If there is no evidence of gangrene, perforation, or peritonitis, medical management and supportive care is usually advised:
  - ➤ bowel rest;
  - ➤ decompression via nasogastric or rectal tube;
  - ➤ intravenous fluid resuscitation;
  - ➤ discontinuation of any precipitating drugs or therapies;
  - ➤ antibiotics targeted against gut bacteria to prevent translocation.
- In gangrenous and/or fulminant ischemic colitis, emergent surgery is typically the first line of treatment.

Severe colonic ischemia carries a high mortality rate and this is likely a combination of both the extent of disease itself and the innate risks of emergent and repeated surgery.

KEY MESSAGES
- Ischemic colitis is caused by a mismatch between local blood flow, from acute or chronic compromise of the colonic vasculature, and metabolic demand of colonocytes.
- In most cases, no definitive cause is identified.
- Typical features are acute onset of mild to moderate, cramping, lower ab-

dominal pain, followed by tenesmus and sudden urges to defecate, with the passage of bright red to maroon blood or bloody diarrhea within 24 hours.

• There are 3 disease types: transient ischemic colitis, severe/gangrenous ischemic colitis, and chronic ischemic colitis.

• Patients with isolated right-sided colonic ischemia appear to have more pronounced abdominal discomfort and decreased or absent hematochezia, a worse prognosis, with higher rates of surgical intervention and mortality.

6.7. Gut microbiota

The human body is not only a complex group of organs and systems, but also contains more than 500 different species of microorganisms. During phylogenesis, symbiosis of macroorganism and microflora was steadily improving, resulting in transformation of microbiota into a kind of vital regulatory body, consisting of a large number of microbial cells, the number of which is 1–3 times higher than the number of own human cells.

Human biological entity is a stable symbiosis of two equal autonomous systems: macroorganism (host) and symbiotic microorganisms that are evolutionarily adapted to life in relatively open human organs on the basis of mutually beneficial relations. This "organ" has a wide range of functions that are vital for whole body. Microorganisms that are routinely found in healthy people considered to the normal microbiota, which is defined as a set of populations of microbes in individual organs and systems in certain qualitative and quantitative ratios that support the host organism's biochemical, metabolic and immunological balance necessary for health maintenance.

Human microbiota includes hundreds of different species with a total number of the cells over 10^{11}–10^{13}. Moreover, microorganism species composition depends on the organ inhabited.

The largest number of microorganisms is in the habitats of the digestive tract. Each part of the digestive system is characterized by different composition of microbial flora (table 18).

Table 18 — The content and composition of microflora in different parts of the human digestive tract in health

Habitats of the digestive tract	The number of microorganism cells per 1 g of content		Dominant microflora
	Lumen microflora	Surface microflora	
Mouth	10^8–10^9	10^{11}–10^{12}	*Streptococcus* (60–90 %), *Lactobacillus, Bifidobacterium, Propionibacterium, Bacteroides, Actinomyces*
Stomach	10^2–10^3	10^5–10^6	Acid resistant *Lactobacillus, Streptococcus, Staphylococcus*
Proximal small intestine	10^3–10^5	10^{10}–10^{11}	*Streptococcus, Lactobacillus, Enterococcus, Bifidobacterium, Escherichia*

Distal small intestine	10^8–10^{10}	10^{10}–10^{12}	*Lactobacillus, Escherichia, Enterococcus, Bacteroides, Bifidobacterium*
Colon	10^{11}–10^{12}	10^{10}–10^{12}	*Bifidobacterium, Lactobacillus, Propionibacterium, Bacteroides — 90–95 %, Escherichia, Enterococcus — 5–10 %*

However, the most simple method to count the bacteria number is the investigation of fecal samples and this does not fully reflect the microbiota content throughout the digestive system. So, the true composition of microflora and its functions may be misleading.

Additionally, the data from different studies vary because of a great inter-individual difference in microflora. The most studied part of digestive tract regarding microflora is colon which characterized by the largest variety of micro-organisms. The dominant species of obligate microflora are asporogenous gram-positive and gram-negative saccharolytic anaerobes: *Bifidobacterium*, *Lactobacillus*, *Propionibacterium*, *Bacteroides. Bifidobacteria* and *Bacteroides* comprise 85–98 % of intestinal microflora.

Recent evidence suggests that gut microbiota is involved in the control of body weight, energy homeostasis and inflammation.

Prebiotics and probiotics are of interest because they have been shown to alter the composition of gut microbiota and to affect food intake, appetite, body weight and composition as well as metabolic functions through gastrointestinal pathways and modulation of the gut bacterial community.

KEY MESSAGES

• Intestinal epithelium is the largest surface of cross-talks with gut microbes. Innate immune system of the intestine is one of the most important factors involved in the interaction between microflora and the host. This symbiosis can on the one hand lead to the destruction of pathogenic microorganisms, while at the same time promoting tolerance to commensal, thus creating ecological niches for useful and consistently associated with the gut microorganisms.

• The result of the interaction of epithelial cells with symbiotic physiological microflora is formation of pre-epithelial film that consists of a layer of molecules of mucus secretory IgA, immune cells, microcolonies of obligate bacteria, enzymes and metabolites of microorganisms and the host. This barrier closes the way to specific receptors on the epithelium for the living cells of harmful microflora and its toxins.

• Gut microbiota is involved in the control of biochemical, metabolic and immunological balance.

7. EMERGENCIES IN GASTROENTEROLOGY

7.1. Gastrointestinal bleeding

Depending on the rate of blood loss, GI bleeding can manifest in several forms and can be classified as overt, occult or obscure.

Overt GI bleeding, otherwise known as acute GI bleeding, is visible and can present in the form of hematemesis, "coffee-ground" emesis, melena, or hematochezia.

Occult or chronic GI bleeding as a result of microscopic hemorrhage can present as Hemoccult-positive stools with or without iron deficiency anemia. The American Gastroenterological Association defines occult GI bleeding as the initial presentation of a positive fecal occult blood test result and/or iron-deficiency anemia when there is no evidence of visible blood loss to the patient or clinician.

Obscure GI bleeding refers to recurrent bleeding in which a source is not identified after upper endoscopy and colonoscopy. Obscure bleeding may be either overt or occult.

Upper GI bleeding includes hemorrhage originating from the esophagus to the ligament of Treitz, at the duodenojejunal flexure. Many upper GI bleeding cases (e. g. erosive gastritis and esophagitis, angiodysplasia, gastric antral vascular ectasia or watermelon stomach, Cameron erosions, portal hypertensive gastropathy and small ulcers) cause iron-deficiency anemia but do not usually present as emergencies.

Lower GI bleeding is defined as bleeding that originates from a site distal to the ligament of Treitz.

In recent years upper GI bleeding has been redefined as bleeding above the ampulla of Vater within reach of an upper endoscopy; lower GI bleeding has been further subdivided into mid GI bleeding coming from the small bowel between the ampulla of Vater to the terminal ileum, and lower GI bleeding coming from the colon.

Causes of acute upper GI bleeding
- Peptic ulcer disease
- gastritis/duodenitis
- esophageal varices
- Mallory-Weiss tear
- Esophagitis
- gastric cancer
- Dieulafoy's lesion
- gastric arteriovenous malformations
- portal gastropathy

Causes of acute lower GI bleeding

Small bowel
- Angiodysplasia
- jejunoileal diverticula
- Meckel's diverticulum
- neoplasms/lymphomas (benign and malignant)

- enteritis/Crohn's disease
- aortoduodenal fistula in patient with synthetic vascular graft

Large bowel
- diverticular disease
- arteriovenous malformations
- colitis (includes ischemia, infectious anal fissures, IBD, and radiation)
- colonic neoplasms/post-polypectomy bleeding
- anorectal causes (includes hemorrhoids and rectal varices)
- colonic tuberculosis

Clinical presentation gastrointestinal bleeding

Upper GI bleeding usually presents with hematemesis (vomiting of fresh blood), "coffee-ground" emesis (vomiting of dark altered blood), and/or melena (black tarry stools). Hematochezia (passing of red blood from rectum) usually indicates bleeding from the lower GI tract, but can occasionally be the presentation for a briskly bleeding upper GI source. The presence of frank bloody emesis suggests more active and severe bleeding in comparison to coffee-ground emesis. Variceal hemorrhage is life threatening and should be a major consideration in diagnosis as it accounts for up to 30 % of all cases of acute upper GI bleeding and up to 90 % in patients with liver cirrhosis.

Lower GI bleeding classically presents with hematochezia, however bleeding from the right colon or the small intestine can present with melena. Bleeding from the left side of the colon tends to present bright red in color, whereas bleeding from the right side of the colon often appears dark or maroon-colored and may be mixed with stool.

Other presentations which can accompany both upper and lower GI bleeding include hemodynamic instability, abdominal pain and symptoms of anemia such as lethargy, fatigue, syncope and angina.

Patients with acute bleeding usually have normocytic red blood cells. Microcytic red blood cells or iron deficiency anemia suggests chronic bleeding. In contrast to patients with acute upper GI bleeding, patients with acute lower GI bleeding and normal renal perfusion usually have a normal blood urea nitrogen-to-creatinine or urea-to-creatinine ratio.

In general, anatomic and vascular causes of bleeding present with painless, large-volume blood loss, whereas inflammatory causes of bleeding are associated with diarrhoea and abdominal pain.

Diagnostic approach of gastrointestinal bleeding

Options for the investigation of acute GI bleeding include upper endoscopy and/or colonoscopy, nuclear scintigraphy, CT angiogram and catheter angiography. The investigation of choice would be guided by the suspected location of bleeding (upper *vs* lower GI) based on clinical presentation.

The standard of care for the initial diagnostic evaluation of suspected acute GI bleeding is urgent upper endoscopy and/or colonoscopy (table 19).

Table 19 — Differential diagnosis of specific GI sources of bleeding

Cause	History and clinical findings
Upper GI tract	
Peptic ulcer disease	Use of aspirin, NSAIDs, or tobacco
Esophageal varices	Alcohol abuse; jaundice; signs of portal hypertension, including: ascites, palmar erythema, spider angiomata, hepatomegaly, splenomegaly, and rectal varices
Mallory-Weiss tear	Bleeding preceded by vomiting, retching, or seizures
Gastric cancer	Left supraclavicular adenopathy; palpable mass; abdominal pain; weight loss; cachexia
Lower GI tract	
Diverticular disease	Age > 60 years; painless bleeding; possible recent constipation
Arteriovenous malformations	Age > 60 years; painless bleeding; chronic renal failure
Colonic neoplasms	Age > 50 years; abdominal pain; weight loss; muscle wasting; protein calorie malnutrition; right-sided colon cancer may be associated with palpable right-sided abdominal mass; hepatomegaly; liver nodules; history of adenomatous polyps or longstanding ulcerative colitis; prior exposure to ionized radiation; family history of familial polyposis coli or cancer family syndrome
Inflammatory bowel disease	Ulcerative colitis: starts in younger patients (20 to 40 years of age); usually involves the rectum; associated with diarrhea mixed with blood and mucus
	Crohn's disease: starts in younger patients (20 to 40 years of age); perianal, peritoneal, and/or abdominal wall fistulas may be associated

Cause	History and clinical findings
Radiation colitis	History of radiation treatment to abdomen and/or pelvis
Hemorrhoids	Perianal mass may be painful (external hemorrhoid) or painless (internal hemorrhoid); commonly starts in younger patients; associated with constipation, pregnancy, or post-partum period
Anal fissures	More common in patients with history of constipation; associated with severe sharp pain occurring with straining on defecation; pain resolves within an hour after defecation; commonly starts at 20 to 40 years of age
Colon tuberculosis	History of pulmonary tuberculosis or past exposure to tuberculosis
Aortoduodenal fistula	History of abdominal aortic aneurysm surgically repaired with synthetic vascular graft placement

As investigations are being planned, infusions of PPI or octreotide should be initiated for suspected bleeding peptic ulcer and varices respectively.

Management non-variceal bleeding

Patients should be admitted to ICU and urgent gastroenterology consult should be requested. Endotracheal intubation to protect the airway may be necessary in cases of severe hematemesis with mental status change and high risk of aspiration.

Offer PPI IV to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy. Do not offer acid-suppression drugs (PPI or H2-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding.

The use of IV erythromycin (approximately 3 mg/kg) prior to endoscopy is helpful to empty the stomach of large amount of blood for better endoscopic visualization although it is not routinely recommended for all upper GI bleeding cases.

For the endoscopic treatment of non-variceal upper gastrointestinal bleeding, use one of the following:

• a mechanical method (for example, clips) with or without adrenaline;

• thermal coagulation with adrenaline;

• fibrin or thrombin with adrenaline.

Do not use adrenaline as monotherapy for the endoscopic treatment of non-variceal upper gastrointestinal bleeding.

Offer interventional radiology to unstable patients who rebleed after endoscopic treatment. Refer urgently for surgery if interventional radiology is not promptly available.

Surgery should also be notified in cases of massive bleeding. Blood transfusion to hemoglobin above 7–8 gm/dL for patients without severe co-morbidities and above 10 gm/dL for patients with severe co-morbidities, correction of coagulopathy (if INR > 1.5) and thrombocytopenia (if platelet < 50 000/ml).

Treatment with fibrinolysis inhibitors (tranexamic acid) is interesting in theory, as is the administration of drugs that reduce overall gastric secretion of acid and pepsin (eg, somatostatin). There is insufficient scientific evidence to determine the effect of treatment with somatostatin or tranexamic acid during the acute phase of bleeding peptic ulcer.

Eradication of H. pylori in *H. pylori* positive patients reduces the risk of recurrent bleeding in the ensuing 12 months. Eradication prevents recurrent bleeding more effectively than long-term acid suppression alone.

Preventive treatment with PPI may reduce the risk of bleeding peptic ulcer in people who are taking antiplatelet drugs (in ischemic heart disease) or painkilling medication (in osteoarthritis or rheumatoid arthritis).

Management variceal bleeding

Empirical use of octreotide or similar agents (terlipressin) should be considered in cases highly suspicious of variceal bleeding.

Offer prophylactic antibiotic therapy at presentation to patients with suspected or confirmed variceal bleeding.

Endoscopic therapies are currently the primary treatment for bleeding varices. Balloon tamponade using the Sengstaken-Blakemore tube may be life saving in patients with torrential oesophageal haemorrhage.

In patients with confirmed oesophageal varices is band ligation superior to injection sclerotherapy in terms of re-bleeding and death. Consider transjugular intrahepatic portosystemic shunts (TIPS) if bleeding from oesophageal varices is not controlled by band ligation.

KEY MESSAGES

• The use of IV erythromycin (approximately 3 mg/kg) prior to endoscopy is helpful for better endoscopic visualization in bleeding patients.

• Eradication of *H. pylori* reduces the risk of recurrent bleeding.

• In patients who have suffered a bleeding peptic ulcer but who need continuing treatment with low-dose aspirin or NSAIDs, the risk of re-bleeding can be reduced by preventive treatment, ie, administration of a PPI.

7.2. Acute liver failure

Acute liver failure is a syndrome of varying aetiology resulting in rapid loss of hepatic metabolic and immuological functions, manifesting as altered mentation and coagulopathy and in many cases progressive multi-organ failure, in a previously normal individual. The condition is associated with high mortality and is a frequent indication for liver transplantation.

The most common cause of ALF is acetaminophen (paracetamol) toxicity, followed by viral hepatitis.

The term *acute liver failure* has replaced older terms such as *fulminant hepatic failure*, *hyperacute liver failure*, and *subacute liver failure,* which were used for prognostic purposes. Patients with *hyperacute* liver failure (defined as development of encephalopathy within 7 days of onset of illness) generally have

a good prognosis with medical management, whereas those with *subacute* liver failure (defined as development of encephalopathy within 5 to 26 weeks of onset of illness) have a poor prognosis without liver transplant.

Fulminant hepatic failure: potentially reversible disorder that is the result of severe liver injury with onset of encephalopathy within eight weeks of symptoms and in the absence of pre-existing liver disease.

Acute liver failure: evidence of coagulopathy (INR > 1.5) and any degree of mental alteration (encephalopathy) occurring within 26 weeks of onset of illness in a patient without preexisting liver disease.

Note: Diagnosis of hepatic encephalopathy is clinical.

West Haven grading of encephalopathy is followed:

Grade I: Changes in behaviour with minimal change in level of consciousness.

Grade II: Disorientation, drowsiness, asterixis, inappropriate behaviour.

Grade III: Marked confusion, incoherent speech, sleeping but rousable.

Grade IV: Comatose, unresponsive, decorticate or decerebrate posturing.

Patients presenting with acute hepatitis should be monitored for altered sensorium or asterixis. Liver span (normal 12–15 cm) should be examined daily. Spleen tip may be palpable in 20 % patients with acute hepatitis due to reticuloendothelial cell hyperplasia. Evidence of chronic liver disease in the form of spider naevi, gynecomastia, palmar erythema, splenomegaly or ascites goes against the diagnosis of ALF.

The major complications in ALF usually associated with death include cerebral edema, seizures, infections, bleeding due to coagulopathy and renal failure. These events infrequently get further aggravated by electrolyte and acid base imbalance and hypoglycaemia.

General measures in acute liver failure:

1. Patients with altered mentation should be admitted to ICU.

2. Avoid stimulation, avoid sedation.

3. Nurse with head end elevation to 30°.

4. Consider intubation if grade III/IV encephalopathy.

5. Fluid and electrolyte maintenance. Any fluid may be used.

6. Enteral nutrition preferred till grade 1–2 encephalopathy. Protein intake 1 g/kg.

7. Injection PPI (proton pump inhibitor) IV once daily to prevent stress induced erosive gastritis / ulcers.

Specific measures in acute liver failure:

1. Injection vitamin K 10 mg IV single dose.

2. Injection mannitol bolus 0.5–1g/kg if signs of cerebral edema: systolic hypertension, bradycardia, irregular respiration or unequal pupils or posturing. Use mannitol only if plasma Osmolality is < 320 mosmol/l.

3. Antibiotics. Surveillance blood culture followed by prophylactic antimicrobials.

Suggested protocol: piperacillin + tazobactam, teicoplanin, metronidazole and fluconazole. Modify as per prevalence of local flora / sensitivity pattern.

4. Injection N-acetyl cysteine 150 mg/kg over 1 hour, 12.5 mg/kg/hour over next 4 hours and then 6.25 mg/kg/hour over 67 hours. Start early in course of illness i. e., for patients with grade 1 or 2 hepatic encephalopathy.

5. Treatment directed at aetiology:

a. Acetaminophen: N-acetyl cysteine (antidote).

b. *Herpes virus*: acyclovir (if skin lesions in 50 % only).

c. Amanita phalloides: penicillin G 1 million units/kg/day.

d. HELLP/AFLP: terminate pregnancy.

e. Hepatitis B virus: tenofovir; concerns of lactic acidosis with entecavir.

Avoid in acute liver failure:

1. Fresh frozen plasma (FFP) as it interferes with assessment for liver transplantation. Use only if invasive procedure planned.

2. Platelet transfusion with platelets > 10,000/ml unless invasive procedure planned.

3. Protein restriction to < 1g/kg.

4. Branched chain amino acids.

5. Lactulose.

6. Injection L-ornithine L-aspartate.

7. Prophylactic anticonvulsants.

8. Hypothermia.

Principles the management hepatic encephalopathy

1. Aggressive supportive therapy:

    intensive care unit, organ support system, nutrition.

2. Identification and removal of precipitating factors:

    control of GI bleed, sepsis, hyponatremia, renal failure, constipation, psycho-active drugs.

3. Reduction of nitrogenous load from the gut:

    lactulose, antibiotics, enema.

4. Manipulation of neurotransmitters:

    flumazenil, branched chain amino acids.

5. Ammonia lowering therapy:

    L-ornithinel-aspartate (LOLA), L-ornithine phenyl acetate (LOPA), sodium benzoate, hypothermia.

6. Novel therapies:

    Molecular adsorbtion recirculating system (MARS), probiotics (lactulose) with increased capacity to consume ammonia.

Attempted non-orthotopic liver transplantation therapies for ALF:

ALF toxin removal:

● plasma exchange;

● hemodialysis;

- hemofiltration;
- Charcoal hemoperfusion;
- hemodiabsorption.

Toxin removal with hepatic cell assistance:
- extracorporeal perfusion with animal or human liver;
- artificial liver support systems using hepatocytes:
  - Hepat Assist;
  - ELAD system;
  - Gerlach system;
  - BAL system;
- hepatocyte transplantation;
- Molecular adsorption recirculating system (MARS).

KEY MESSAGES

- Acetaminophen (paracetamol) is the most common cause of acute liver failure.
- The major complications in acute liver failure usually associated with death include cerebral edema, seizures, infections, bleeding due to coagulopathy and renal failure.
- For management hepatic encephalopathy avoid sedative drugs, indicate the flumazenil, branched chain amino acids, lactulose, antibiotics.

REFERENCES

1. A guide to managing acute liver failure / T. Singh, N. Gupta, N. Alkhouri [et al] // Cleve Clin J Med. — 2016. — Vol. 83. — P. 453–462.

2. A position statement on NAFLD/NASH based on the EASL 2009 special conference / V. Ratziu, S. Bellentani, H. Cortez-Pinto, [et al] // J Hepatol. — 2010. — Vol. 53. — P. 372–845.

3. *Ahmed, M.* Eosinophilic esophagitis in adults: an update / M. Ahmed // World J Gastrointest Pharmacol Ther. — 2016. — Vol. 7. — P. 207–13.

4. *Badillo, R.* Diagnosis and treatment of gastroesophageal reflux disease / R. Badillo, D. Francis // World J Gastrointest Pharmacol Ther. — 2014. — Vol. 5. — P. 105–112.

5. *Björnsson, E. S.* Hepatotoxicity by Drugs: The Most Common Implicated Agents / E. S. Björnsson // Int J Mol Sci. — 2016. — Vol. 17. — P. 224.

6. Bowel Disorders / E. Brian, [et al] // Gastroenterology. — 2016. — Vol. 150. — P. 1393–1407.

7. Celiac disease: Managing a multisystem disorder / G. S. Kochhar, T. Singh, A. Gill, [et al] // Cleve Clin J Med. — 2016. — Vol. 83. — P. 217–27.

8. *Chen, Y.* Cholesterol gallstone disease: focusing on the role of gallbladder / Y. Chen, J. Kong, S. Wu // Lab Invest. — 2015. — Vol. 95. — P. 124–31.

9. *Chen, Z. J.* Management of upper gastrointestinal bleeding emergencies: evidence-based medicine and practical considerations / Z. J. Chen, M. L. Freeman // World J Emerg Med. — 2011. — Vol. 2. — P. 5–12.

10. Chronic pancreatitis: A diagnostic dilemma / S. N. Duggan [et al] // World J Gastroenterol. — 2016. — Vol. 22. — P. 2304–13.

11. *Chung, C. S.* A systematic approach for the diagnosis and treatment of idiopathic peptic ulcers / C. S. Chung, T. H. Chiang, Y. C. Lee // Korean J Intern Med. — 2015. — Vol. 30. — P. 559–570.

12. Cirrhosis in children and adolescents: an overview // World J Hepatol. — 2015. — Vol. 7. – P. 392–405.

13. Diagnosis and management of autoimmune hepatitis / M. P. Manns [et al] // Hepatology — 2010. — Vol. 51. — P. 2193–2198.

14. Diagnosis of gastrointestinal bleeding: A practical guide for clinicians / B. S. Kim [et al] // World J Gastrointest Pathophysiol. — 2014. — Vol. 5. — P. 467–478.

15. Dyspepsia / M. Feldman [et al] Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 7th ed. Philadelphia, Pa.: Saunders. — 2002.

16. EASL clinical practice guidelines for HFE hemochromatosis / J Hepatol. — 2010. — Vol. 53. — P. 3–22.

17. EASL Clinical Practice Guidelines: Wilson's disease / J Hepatol. — 2012. — Vol. 56. — P. 671–85.

18. Esophageal Disorders / A. Qasim, [et al] // Gastroenterology. — 2016. — Vol. 150. — P. 1368–79.

19. Gallbladder and Sphincter of Oddi Disorders / P. Cotton, [et al] // Gastroenterology. — 2016. — Vol. 150. — P. 1420–29.

20. Gallbladder dysfunction: how much longer will it be controversial? / N. Goussous, [et al] // Digestion. — 2014. — Vol. 90. — P. 147–54.

21. Gastritis staging in clinical practice: the OLGA staging system / M. Rugge [et al] // Gut. — 2007. — Vol. 56. — P. 631–636.

22. Gastroduodenal Disorders / V. Stanghellini [et al] // Gastroenterology. — 2016. — Vol. 150. — P. 1380–92.

23. *Ghoshal, U. C.* Esophageal function tests in clinical practice: a review / U. C. Ghoshal, R. Singh, A. Misra // Trop Gastroenterol. — 2010. — Vol. 31. — P. 145–154.

24. *Hammer, H. F.* Pancreatic exocrine insufficiency: diagnostic evaluation and replacement therapy with pancreatic enzymes / H. F. Hammer // Dig Dis. — 2010. — Vol. 28. — P. 339–43.

25. Hepatic encephalopathy: From pathophysiology to therapeutic management / M. Bismuth [et al] // Eur J Gastroenterol Hepatol. — 2011. — Vol. 23. — P. 8–22.

26. Hereditary Hemochromatosis // Am Fam Physician. — 2013. — Vol. 87. — P. 183–90.

27. Immunology and vaccines and nanovaccines for *Helicobacter pylori* infection / M. Milani M [et al] // Expert Rev Vaccines. — 2015. — Vol. 14. — P. 833–840.

28. Irritable bowel syndrome and chronic constipation: Fact and fiction / M. Bellini [et al] // World J Gastroenterol. — 2015. — Vol. 21. — P. 11362–70.

29. *Kobyliak, N.* Pathophysiological role of host microbiota in the development of obesity / N. Kobyliak, O. Virchenko, T. Falalyeyeva // Nutr J. — 2016. — Vol. 15. — P. 43.

30. Kyoto global consensus report on Helicobacter pylori gastritis / K. Sugano [et al] // Gut. — 2015. — Vol. 64. — P. 1353–67.

31. *Langan, R. C.* Ulcerative Colitis: Diagnosis and Treatment / R. C. Langan // Am Fam Physician. — Vol. 76. — P. 1323–30.

32. *Ma, X.* Chinese herbal medicine-induced liver injury / X. Ma, J. H. Peng, Y. Y. Hu // J. Clin. Transl. Hepatol. — 2014. — Vol. 2. — P. 170–75.

33. Management of *Helicobacter pylori* infection — the Maastricht IV / Florence Consensus Report / P. Malfertheiner [et al] // Gut. — 2012. — Vol. 61. — P. 646–664.

34. Management of Helicobacter pylori infection — the Maastricht V / Florence Consensus Report P. Malfertheiner [et al] // Gut. — 2016. — P. 1–25.

35. *Martinucci, I.* Barrett's esophagus in 2016: From pathophysiology to treatment / I. Martinucci [et al] // World J Gastrointest Pharmacol Ther. — 2016. — Vol. 7. — P. 190–206.

36. *McNamara, D. A.* Nonulcer dyspepsia. Current concepts and management / D. A. McNamara, M. Buckley, C. A. O'Morain // Gastroenterol Clin North Am. — 2000. — Vol. 29. — P. 807–818.

37. *O'Shea, R. S.* Alcoholic liver disease / R. S. O'Shea, S. Dasarathy, A. J. McCullough // J Hepatol. — 2010. — Vol. 51. — P. 307–28.

38. *Patel, A.* Clinical application of probiotics in the treatment of *Helicobacter pylori* infection — a brief review / A. Patel, N. Shah, J. B. Prajapati // J Microbiol Immunol Infect. — 2014. — Vol. 47. — P. 429–437.

39. *Pedersen, J. S.* Management of cirrhotic ascites / J. S. Pedersen, F. Bendtsen, S. Møller // Ther Adv Chronic Dis. — 2015. — Vol. 6. — P. 124–37.

40. Pharmacological challenges in chronic pancreatitis / A. E. Olesen [et al] // World J Gastroenterol. — 2013. — Vol. 19. — P. 7302–7.

41. Primary biliary cirrhosis: Pathophysiology, clinical presentation and therapy. World J Hepatol. — 2015. — Vol. 7. — P. 926–41.

42. Rodriguez-Castro, K. I. Wilson's disease: A review of what we have learned / K. I. Rodriguez-Castro // World J Hepatol. — 2015. — Vol. 29. — P. 2859–70.

43. Rome III: The Functional Gastrointestinal Disorders / D. A. Drossman [et al] // 3rd ed. McLean, Va.: Degnon Associates. — 2006.

44. *Safavi, M.* Medicinal plants in the treatment of *Helicobacter pylori* infections / M. Safavi, M. Shams-Ardakani, A. Foroumadi // Pharm Biol. — 2015. — Vol. 53. — P. 939–960.

45. *Safavi, M.* Treatment of *Helicobacter pylori* infection: current and future insights / M. Safavi, R. Sabourian, A. Foroumadi // World J Clin Cases. — 2016. — Vol. 4. — P. 5–19.

46. *Schuppan, D.* Liver cirrhosis / D. Schuppan, N. H. Afdhal // Lancet. — 2008. — Vol. 371. — P. 838–51.

47. *Selgrad, M.* Guidelines for treatment of *Helicobacter pylori* in the East and West / M. Selgrad, J. Bornschein, P. Malfertheiner // Expert Rev Anti Infect Ther. — 2011. — Vol. 9. — P. 581–588.

48. *Shalimar, L.* Management in acute liver failure / L. Shalimar, S. K. Acharya // J Clin Exp Hepatol. — 2015. — Vol. 5 (Suppl 1). — P. 104–115.

49. *Silva, A. C.* Effect of gum chewing on air swallowing, saliva swallowing and belching / A. C. Silva, L. R. Aprile, R. O. Dantas // Arq Gastroenterol. — 2015. — Vol. 52. —P. 190–194.

50. *Sipponen, P.* Chronic gastritis / P. Sipponen, H. Maaroos // Scandinavian Journal of Gastroenterology. — 2015. — Vol. 50. — P. 657–667.

51. *Sipponen, P.* Chronic gastritis / P. Sipponen, H. I. Maaroos // Scandinavian Journal of Gastroenterology. — 2015. — Vol. 50. — P. 657–667.

52. *Tack, J.* Functional gastroduodenal disorders / J. Tack [et al] // Gastroenterology. — 2006. — Vol. 130. — P. 1466–1479.

53. *Talley, N. G.* Functional dyspepsia: new insights into pathogenesis and therapy / N. G. Talley // Korean J Intern Med — 2016. — Vol. 31. — P. 444–456.

54. *Tang, D. M.* Pseudomembranous colitis: not always Clostridium difficile. Tang DM, Urrunaga NH, von Rosenvinge EC. // Cleve Clin J Med. — 2016. — Vol. 83. — P. 361–6.

55. The stomach in health and disease / R. H. Hunt, [et al] // Gut. — 2015. — Vol. 64. — P. 1650–68.

56. *Torres, D. M.* Diagnosis and therapy of nonalcoholic steatohepatitis / D. M. Torres, S. A. Harrison // Gastroenterology. — 2008. — Vol. 134. — P. 1682–98.

57. *Trivedi, P. J.* Review article: overlap syndromes and autoimmune liver disease / P. J. Trivedi, G.M. Hirschfield // Aliment Pharmacol Ther. — 2012. — Vol. 36. — P. 517–33.

58. *Wallace, J. L.* Mechanisms, prevention and clinical implications of nonsteroidal anti-inflammatory drug-enteropathy / J. L.Wallace // World J Gastroenterol. — 2013. — Vol. 19. — P. 1861–1876.

59. *Wilkins, T.* Diagnosis and Management of Crohn's Disease / T. Wilkins // Am Fam Physician. — 2011. — Vol. 84. — P. 1365–75.

60. *Wilkins, T.* Diagnosis and Management of IBS in Adults / T. Wilkins // Am Fam Physician. — 2012. — Vol. 86. — P. 419–26.

61. *Williamson, K. D.* Primary sclerosing cholangitis: a clinical update / K. D. Williamson, R. W. Chapman // Br Med Bull. — 2015. — Vol. 114. — P. 53–64.

62. *Wittenburg, H.* Complications of liver cirrhosis / H. Wittenburg, U. Tennert, T. Berg // Internist. — 2011. — Vol. 52. —P. 1061–70.

63. *Yang, J. C.* Treatment of *Helicobacter pylori* infection: current status and future concepts / J. C. Yang, C. W. Lu, C. J. Lin // World J Gastroenterol. — 2014. — Vol. 20. — P. 5283–5293.