

**MINISTRY OF HEALTHCARE OF UKRAINE
HSEEU "Ukrainian Medical Stomatological Academy"**

"Approved"

at the meeting of internal
medicine №1 department

Head of Department
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**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in gastroenterology clinic
<i>Study subject</i>	Management of the patients with abdominal pain
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

Poltava 2016.

1. Relevance of the topic: Correctly interpreting acute abdominal pain can be quite challenging. Few clinical situations require greater judgment, because the most catastrophic of events may be forecast by the subtlest of symptoms and signs. In every instance, the clinician must distinguish those conditions that require urgent intervention from those that do not and can best be managed nonoperatively. A meticulously executed, detailed history and physical examination are critically important for focusing the differential diagnosis, where necessary, and allowing the diagnostic evaluation to proceed expeditiously.

2. The main goal: To be able to choose and put into practice the approach to the patient with abdominal pain, to put diagnosis and to determine tactics of treatment and prophylaxis.

Specific goals:

- To select the information indicating the cause of abdominal pain;
- To create a scheme of diagnostic search;
- To identify the other signs of diseases that runs with abdominal pain (general examination, palpation, percussion, auscultation);
- To analyze and interpret the changes in the results of the laboratory and instrumental methods of investigation, depending on the course of the disease;
- To formulate and justify a preliminary diagnosis according to modern classifications;
- To conduct differential diagnostics of diseases with the abdominal pain;
- To develop a strategy of treatment depending on the disease and the existing complications;
- To provide medical care;
- To assess the patient's prognosis and to propose a plan of preventive actions;
- To apply deontological communication skills with patients.

3. Basic knowledge, abilities, skills (interdisciplinary integration)

Discipline	To know	To be able to
Anatomy	The structure of the gastrointestinal tract, blood supply, innervation	
Histology	The structure of the esophagus, stomach, intestines, liver, gallbladder, pancreas in health and disease	To interpret results of endoscopy, USI and biopsy
Regional anatomy	Interposition of the gastrointestinal organs	
Physiology	Indicators of gastrointestinal tract function, its value	To determine the function of gastrointestinal organs
Morbid anatomy	Changes in the structure of gastrointestinal tract organs in pathology	
Radiology	Radiological changes at pathology of gastrointestinal organs	Analyze the radiological picture of the chest cavity and abdominal cavity
Propaedeutic therapy	Diseases with abdominal pain as leading symptom	Perform an objective examination of the patient, analyze the clinical and laboratory results
Pharmacology	The mechanism of action,	Prescribe the drugs of these groups

	indications and contraindications for the IPP, H2-blockers, antacids, prokinetics, antibiotics, enzymes, pain killers, antispasmodics	
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4. Do the tasks for independent work during preparation for classes.

4.1. The list of key terms, parameters, characteristics:

Term	Definition
Chronic abdominal pain	is a pain that persists for more than 3 months either continuously or intermittently.
Functional gastrointestinal disorders	are disorders of gut–brain interaction. It is a group of disorders classified by GI symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing.
Visceral pain	comes from the abdominal viscera, which are innervated by autonomic nerve fibers and respond mainly to the sensations of distention and muscular contraction—not to cutting, tearing, or local irritation.
Somatic pain	comes from the parietal peritoneum, which is innervated by somatic nerves, which respond to irritation from infectious, chemical, or other inflammatory processes.
Referred pain	is pain perceived distant from its source and results from convergence of nerve fibers at the spinal cord.

4.2. Theoretical questions for the lesson:

1. Give the definitions of abdominal pain, name and define diseases which are characterized by abdominal pain.
2. Specify the risk factors for diseases of stomach, gallbladder, pancreas, intestines.
3. The pathophysiological mechanisms of abdominal pain in different pathologies.
4. Diagnostic criteria of ulcer disease, gastritis, cholecystitis, pancreatitis, functional disorders of biliary tract.
5. What are the endoscopic characteristics of gastric pathology?
6. Modern classifications of ulcer disease, gastritis, cholecystitis, pancreatitis, functional disorders of biliary tract.
7. Specify the principles and features of ulcer disease, gastritis, cholecystitis, pancreatitis, functional disorders of biliary tract pharmacotherapy according to modern recommendations.
8. What lifestyle modifications should be recommended for patients with abdominal pain according to the reason?

4.3. Practical tasks that are performed in class:

1. IPP include:

1) Famotidine

2) Itoprid

3) Pantoprazole

4) Clarithromycine

2. H2-blockers include:

1) Famotidine

2) Itoprid

3) Pantoprazole

4) Clarithromycine

3. Prokinetics include:

1) Famotidine

2) Itopride

3) Pantoprazole

4) Clarithromycine

4. Standart dosage of Omeprazole is:

1) 40 mg

2) 60 mg

3) 20 mg

4) 20-40 mg

5. Standart dosage of Pantoprazole is:

1) 20 mg

2) 60 mg

3) 40 mg

4) 20-40 mg

6. Standart dosage of Rabeprazole is:

1) 40 mg

2) 60 mg

3) 20 mg

4) 20-40 mg

7. Standart dosage of Esomeprazole is:

1) 20 mg

2) 60 mg

3) 40 mg

4) 20-40 mg

8. Standart dosage of Lansoprazole is:

1) 20 mg

2) 60 mg

3) 40 mg

4) 30 mg

9. What methods is informative to establish exocrine pancreatic deficiency?

1) US

2) Peroral cholecystography

3) EGDS

4) Fecal tests (koprogram)

5) ERCPG

10. 32 years old woman noticed periodic attacks of pain in the right subcostum, which can be relieved by no-shpa. Pain is not always related with meal, sometimes it appears at agitation, accompanied with pain in heart, palpitation. Objectively: emotional lability, palpation of abdomen detected painfulness in the area of gall bladder. What is the most reliable diagnosis?

1) Dyskinesia of biliary tract

2) Chronic cholecystitis

3) Chronic cholangitis

4) Chronic pancreatitis

5) Duodenitis

Topic Content

ABDOMINAL PAIN

A meticulously executed, detailed history and physical examination are critically important for focusing the differential diagnosis, where necessary, and allowing the diagnostic evaluation to proceed expeditiously. Making the diagnosis, it is important to pay attention on key points of patient's history:

- Age
- Time and mode of onset of the pain
- Pain characteristics
- Duration of symptoms
- Location of pain and sites of radiation
- Associated symptoms and their relationship to the pain
- Nausea, emesis, and anorexia
- Diarrhea, constipation, or other changes in bowel habits
- Menstrual history

The most common causes of abdominal pain on admission are acute appendicitis, nonspecific abdominal pain, pain of urologic origin, and intestinal obstruction. A diagnosis of "acute or surgical abdomen" is not acceptable because of its often misleading and erroneous connotations. Most patients who present with acute abdominal pain will have self-limited disease processes. However, it is important to remember that pain severity does not necessarily correlate with the severity of the underlying condition. The most obvious of "acute abdomens" may not require operative intervention, and the mildest of abdominal pains may herald an urgently correctable lesion. Any patient with abdominal pain of recent onset requires early and thorough evaluation and accurate diagnosis.

Maladies of the ABDOMEN		
Right		Left
Gallstones Stomach Ulcer Pancreatitis	Stomach Ulcer Heartburn/Indigestion Pancreatitis Gallstones Epigastric hernia	Stomach or Duodenal Ulcers Pancreatitis Biliary Colic
Kidney Stones Urinary Infect. Constipation Lumbar hernia	Pancreatitis Early Appendicitis Stomach Ulcer Inflammatory Bowel Small Bowel Umbilical Hernia	Kidney Stones Diverticulitis Constipation Inflammatory Bowel
Appendicitis Constipation Pelvic Pain Groin Pain Inguinal Hernia	Urinary Infection Appendicitis Diverticulitis Inflammatory Bowel Pelvic Pain	Diverticulitis Pelvic Pain Groin Pain Inguinal Hernia

PreventDisease.com

Mechanisms of abdominal pain. The pain of parietal peritoneal inflammation is steady and aching in character and is located directly over the inflamed area, its exact reference being possible because it is transmitted by somatic nerves supplying the parietal peritoneum. The intensity of the pain is dependent on the type and amount of material to which the peritoneal surfaces are exposed in a given time period. For example, the sudden release into the peritoneal cavity of a small quantity of sterile acid gastric juice causes much more pain than the same amount of grossly contaminated neutral feces. Enzymatically active pancreatic juice incites more pain and inflammation than does the same amount of sterile bile containing no potent enzymes. Blood is normally only a mild irritant and the response to urine can be bland, so exposure of blood and urine to the peritoneal cavity may go unnoticed unless it is sudden and massive. Bacterial contamination, such as may occur with pelvic inflammatory disease or perforated distal intestine, causes low-intensity pain until multiplication causes a significant amount of inflammatory mediators to be released. Patients with perforated upper gastrointestinal ulcers may present entirely differently depending on how quickly gastric juices enter the peritoneal cavity. Thus, the rate at which any inflammatory material irritates the peritoneum is important. The pain of peritoneal inflammation is invariably accentuated by pressure or changes in tension of the peritoneum, whether produced by palpation or by movement such as with coughing or sneezing.

The patient with peritonitis characteristically lies quietly in bed, preferring to avoid motion, in contrast to the patient with colic, who may be thrashing in discomfort. Another characteristic feature of peritoneal irritation is tonic reflex spasm of the abdominal musculature, localized to the involved body segment. Its intensity depends on the integrity of the nervous system, the location of the inflammatory process, and the rate at which it develops. Spasm over a perforated retrocecal appendix or perforation into the lesser peritoneal sac may be minimal or absent because of the protective effect of overlying viscera. Catastrophic abdominal emergencies may be associated with minimal or no detectable pain or muscle spasm in obtunded, seriously ill, debilitated, immunosuppressed, or psychotic patients. A slowly developing process also often greatly attenuates the degree of muscle spasm.

Intraluminal obstruction classically elicits intermittent or colicky abdominal pain that is not as well localized as the pain of parietal peritoneal irritation. However, the absence of cramping discomfort should not be misleading because distention of a hollow viscus may also produce steady pain with only rare paroxysms. Small-bowel obstruction often presents as poorly localized, intermittent periumbilical or supraumbilical pain. As the intestine progressively dilates

and loses muscular tone, the colicky nature of the pain may diminish. With superimposed strangulating obstruction, pain may spread to the lower lumbar region if there is traction on the root of the mesentery. The colicky pain of colonic obstruction is of lesser intensity, is commonly located in the infraumbilical area, and may often radiate to the lumbar region. Sudden distention of the biliary tree produces a steady rather than colicky type of pain; hence, the term biliary colic is misleading. Acute distention of the gallbladder usually causes pain in the right upper quadrant with radiation to the right posterior region of the thorax or to the tip of the right scapula, but it is also not uncommonly found near the midline. Distention of the common bile duct often causes epigastric pain that may radiate to the upper lumbar region. Considerable variation is common, however, so that differentiation between these may be impossible. The typical subscapular pain or lumbar radiation is frequently absent. Gradual dilatation of the biliary tree, as can occur with carcinoma of the head of the pancreas, may cause no pain or only a mild aching sensation in the epigastrium or right upper quadrant. The pain of distention of the pancreatic ducts is similar to that described for distention of the common bile duct but, in addition, is very frequently accentuated by recumbency and relieved by the upright position. Obstruction of the urinary bladder usually causes dull, low-intensity pain in the suprapubic region. Restlessness without specific complaint of pain may be the only sign of a distended bladder in an obtunded patient. In contrast, acute obstruction of the intravesicular portion of the ureter is characterized by severe suprapubic and flank pain that radiates to the penis, scrotum, or inner aspect of the upper thigh. Obstruction of the ureteropelvic junction manifests as pain near the costovertebral angle, whereas obstruction of the remainder of the ureter is associated with flank pain that often extends into the same side of the abdomen.

A frequent misconception is that pain due to intraabdominal vascular disturbances is sudden and catastrophic in nature. Certain disease processes, such as embolism or thrombosis of the superior mesenteric artery or impending rupture of an abdominal aortic aneurysm, can certainly be associated with diffuse, severe pain. Yet, just as frequently, the patient with occlusion of the superior mesenteric artery only has mild continuous or cramping diffuse pain for 2 or 3 days before vascular collapse or findings of peritoneal inflammation appear. The early, seemingly insignificant discomfort is caused by hyperperistalsis rather than peritoneal inflammation. Indeed, absence of tenderness and rigidity in the presence of continuous, diffuse pain (e.g., "pain out of proportion to physical findings") in a patient likely to have vascular disease is quite characteristic of occlusion of the superior mesenteric artery. Abdominal pain with radiation to the sacral region, flank, or genitalia should always signal the possible presence of a rupturing abdominal aortic aneurysm. This pain may persist over a period of several days before rupture and collapse occur.

Pain arising from the abdominal wall is usually constant and aching. Movement, prolonged standing, and pressure accentuate the discomfort and associated muscle spasm. In the case of hematoma of the rectus sheath, now most frequently encountered in association with anticoagulant therapy, a mass may be present in the lower quadrants of the abdomen. Simultaneous involvement of muscles in other parts of the body usually serves to differentiate myositis of the abdominal wall from other processes that might cause pain in the same region.

Approach to the patient. Few abdominal conditions require such urgent operative intervention that an orderly approach need be abandoned, no matter how ill the patient. Only patients with exsanguinating intraabdominal hemorrhage (e.g., ruptured aneurysm) must be rushed to the operating room immediately, but in such instances, only a few minutes are required to assess the critical nature of the problem. Under these circumstances, all obstacles must be swept aside, adequate venous access for fluid replacement obtained, and the operation begun. Many of these patients have died in the radiology department or the emergency room while awaiting unnecessary examinations such as electrocardiograms or computed tomography (CT) scans. There are no contraindications to operation when massive intraabdominal hemorrhage is present. Fortunately, this situation is relatively rare. This statement does not necessarily apply to patients with intraluminal gastrointestinal hemorrhage, who can often be managed by other

means. Nothing will supplant an orderly, painstakingly detailed history, which is far more valuable than any laboratory or radiographic examination. This kind of history is laborious and time-consuming, making it not especially popular, even though a reasonably accurate diagnosis can be made on the basis of the history alone in the majority of cases. In cases of acute abdominal pain, a diagnosis is readily established in most instances, whereas success is not so frequent in patients with chronic pain.

IBS is one of the most common causes of abdominal pain and must always be kept in mind. The location of the pain can assist in narrowing the differential diagnosis; however, the chronological sequence of events in the patient's history is often more important than the pain's location. If the examiner is sufficiently open-minded and unhurried, asks the proper questions, and listens, the patient will usually provide the diagnosis. Careful attention should be paid to the extraabdominal regions.

Narcotics or analgesics should not be withheld until a definitive diagnosis or a definitive plan has been formulated; obfuscation of the diagnosis by adequate analgesia is unlikely.

An accurate menstrual history in a female patient is essential. It is important to remember that normal anatomic relationships can be significantly altered by the gravid uterus. Abdominal and pelvic pain may occur during pregnancy due to conditions that do not require surgery. Lastly, some otherwise noteworthy laboratory values (e.g., leukocytosis) may represent the normal physiologic changes of pregnancy.

In the examination, simple critical inspection of the patient, e.g., of facies, position in bed, and respiratory activity, provides valuable clues. The amount of information to be gleaned is directly proportional to the gentleness and thoroughness of the examiner. Once a patient with peritoneal inflammation has been examined brusquely, accurate assessment by the next examiner becomes almost impossible. Eliciting rebound tenderness by sudden release of a deeply palpating hand in a patient with suspected peritonitis is cruel and unnecessary. The same information can be obtained by gentle percussion of the abdomen (rebound tenderness on a miniature scale), a maneuver that can be far more precise and localizing. Asking the patient to cough will elicit true rebound tenderness without the need for placing a hand on the abdomen. Furthermore, the forceful demonstration of rebound tenderness will startle and induce protective spasm in a nervous or worried patient in whom true rebound tenderness is not present. A palpable gallbladder will be missed if palpation is so aggressive that voluntary muscle spasm becomes superimposed on involuntary muscular rigidity. As with history taking, sufficient time should be spent in the examination. Abdominal signs may be minimal but nevertheless, if accompanied by consistent symptoms, may be exceptionally meaningful. Abdominal signs may be virtually or totally absent in cases of pelvic peritonitis, so careful pelvic and rectal examinations are mandatory in every patient with abdominal pain. Tenderness on pelvic or rectal examination in the absence of other abdominal signs can be caused by operative indications such as perforated appendicitis, diverticulitis, twisted ovarian cyst, and many others. Much attention has been paid to the presence or absence of peristaltic sounds, their quality, and their frequency. Auscultation of the abdomen is one of the least revealing aspects of the physical examination of a patient with abdominal pain. Catastrophes such as a strangulating small intestinal obstruction or perforated appendicitis may occur in the presence of normal peristaltic sounds. Conversely, when the proximal part of the intestine above obstruction becomes markedly distended and edematous, peristaltic sounds may lose the characteristics of borborygmi and become weak or absent, even when peritonitis is not present. It is usually the severe chemical peritonitis of sudden onset that is associated with the truly silent abdomen.

Laboratory examinations may be valuable in assessing the patient with abdominal pain, yet, with few exceptions, they rarely establish a diagnosis. Leukocytosis should never be the single deciding factor as to whether or not operation is indicated. A white blood cell count $>20,000/\mu\text{L}$ may be observed with perforation of a viscus, but pancreatitis, acute cholecystitis, pelvic inflammatory disease, and intestinal infarction may also be associated with marked leukocytosis. A normal white blood cell count is not rare in cases of perforation of abdominal

viscera. The diagnosis of anemia may be more helpful than the white blood cell count, especially when combined with the history.

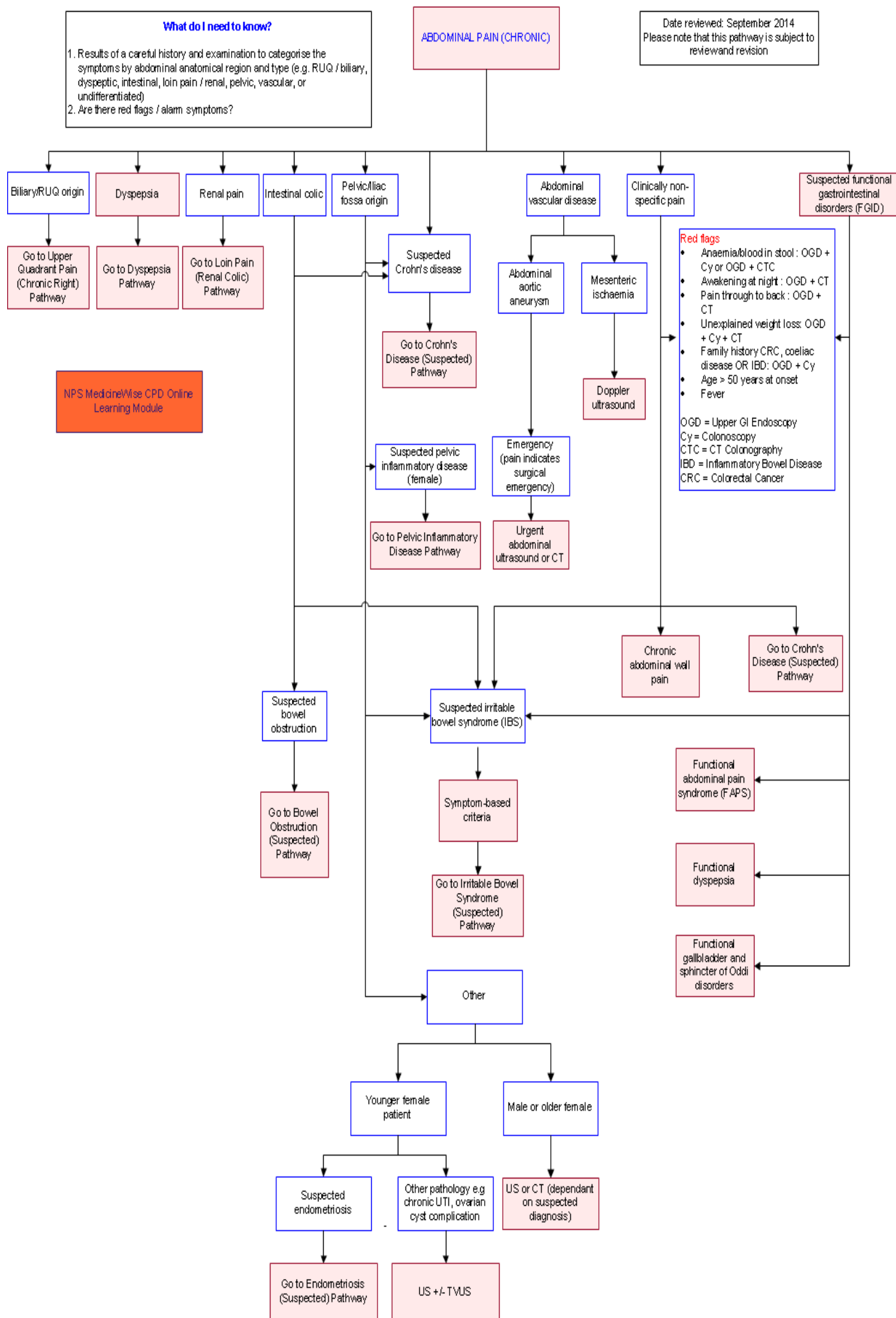
The urinalysis may reveal the state of hydration or rule out severe renal disease, diabetes, or urinary infection. Blood urea nitrogen, glucose, and serum bilirubin levels may be helpful. Serum amylase levels may be increased by many diseases other than pancreatitis, e.g., perforated ulcer, strangulating intestinal obstruction, and acute cholecystitis; thus, elevations of serum amylase do not rule out the need for an operation.

Plain and upright or lateral decubitus radiographs of the abdomen may be of value in cases of intestinal obstruction, perforated ulcer, and a variety of other conditions. They are usually unnecessary in patients with acute appendicitis or strangulated external hernias. In rare instances, barium or water-soluble contrast study of the upper part of the gastrointestinal tract may demonstrate partial intestinal obstruction that may elude diagnosis by other means. If there is any question of obstruction of the colon, oral administration of barium sulfate should be avoided. On the other hand, in cases of suspected colonic obstruction (without perforation), a contrast enema may be diagnostic.

In the absence of trauma, peritoneal lavage has been replaced as a diagnostic tool by CT scanning and laparoscopy. Ultrasonography has proved to be useful in detecting an enlarged gallbladder or pancreas, the presence of gallstones, an enlarged ovary, or a tubal pregnancy. Laparoscopy is especially helpful in diagnosing pelvic conditions, such as ovarian cysts, tubal pregnancies, salpingitis, and acute appendicitis.

Radioisotopic hepatobiliary iminodiacetic acid scans (HIDAs) may help differentiate acute cholecystitis or biliary colic from acute pancreatitis. A CT scan may demonstrate an enlarged pancreas, ruptured spleen, or thickened colonic or appendiceal wall and streaking of the mesocolon or mesoappendix characteristic of diverticulitis or appendicitis.

Sometimes, even under the best circumstances with all available aids and with the greatest of clinical skill, a definitive diagnosis cannot be established at the time of the initial examination. Nevertheless, even in the absence of a clear anatomic diagnosis, it may be abundantly clear to an experienced and thoughtful physician and surgeon that operation is indicated on clinical grounds alone. Should that decision be questionable, watchful waiting with repeated questioning and examination will often elucidate the true nature of the illness and indicate the proper course of action.



PEPTIC ULCER DISEASE

Definition. A **peptic ulcer** is a mucosal defect that penetrates the muscularis mucosae. Gastric and duodenal ulcers usually occur in an area of inflamed mucosa. This inflammation, termed gastritis, duodenitis, or bulbitis, can sometimes be recognized during endoscopy by signs of edema, reddening, and swelling of the mucosa, but microscopic evaluation of endoscopic biopsy specimens is required for a definitive diagnosis of mucosal inflammation.

Epidemiology. The worldwide prevalence of gastritis reflects the prevalence of *H. pylori*. Colonization with this bacterium is virtually always associated with chronic active gastritis, which persists as long as an individual remains colonized and only slowly disappears 6 to 24 months after the eradication of *H. pylori*. Although peptic ulcer disease is strongly related to *H. pylori* gastritis and duodenitis, the epidemiology of ulcer disease has shown secular variations even when *H. pylori* was ubiquitous.

Etiology. *Helicobacter pylori* (HP) infection, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, cytostatics, Zollinger-Ellison syndrome, systemic inflammatory diseases, stress, alcohol, genetic.

Pathogenesis. Most peptic ulcers are associated with colonization with *H. pylori*, which has urease activity. Urease activity creates a "cloud" of ammonia around the bacterium, thus neutralizing the lethal effects of gastric acid. Motility allows the bacterium to penetrate the mucus layer and promotes specific association of the bacteria with epithelial cells, further allowing evasion of gastric acidity.

On the basis of their activities, NSAIDs are divided into cyclooxygenase 1 (COX1) and COX2 inhibitors. The COX1 enzyme is involved in the production of prostaglandins, which play a role in normal cell regulation. The COX2 enzyme, which is also involved in the production of prostaglandins, is induced by inflammatory responses. Most NSAIDs have a nonselective COX inhibitory effect; selective COX2 inhibitors are associated with fewer gastroduodenal ulcers, but their use is limited by their adverse coronary effects. Because of the strong association between NSAIDs and ulcer disease and the risk for recurrence of ulcers with their continued use, patients with ulcers must be thoroughly assessed for the use of NSAIDs.

Gastroduodenal ulcers can result from underlying malignant disease. In the stomach, these tumors are related to gastric adenocarcinoma and, rarely, to mucosa-associated lymphoid tissue (MALT) lymphomas. Malignant ulcers in the duodenum may result from primary duodenal carcinomas or from penetrating pancreatic cancers.

Peptic ulcers can result from chronic gastric hyperacidity related to hypergastrinemia. The most important hypergastrinemic disorder is Zollinger-Ellison syndrome, a condition of marked hyperacidity leading to severe peptic ulcer disease caused by a gastrin-producing endocrine tumor.

But the most common element of ulcer pathogenesis is imbalance between factors of aggression (pepsin, [hydrochloric acid](#), hypertonus of n.vagus) and defense of mucous membrane and physiological regeneration. It leads to chronic inflammation and results in ulceration.

Classification:

According to location:

- gastric ulcers are subdivided into proximal ulcers, located in the body of the stomach, and distal ulcers, located in the antrum and angulus of the stomach; located along the curvature

– duodenal ulcers usually are located on the anterior or posterior wall of the duodenal bulb, or occasionally at both sites (“kissing” ulcers); lesions distal to the duodenal bulb are termed postbulbar ulcers; located in bulb – bulb ulcer.

According to size:

- small (less than 1cm in stomach; less than 0,3 in duodenum)
- average (1-2cm in stomach; 0,3-0,5cm in duodenum)
- big (2-4cm in stomach; 0,6-1,0cm in duodenum)
- huge (giant)

According to HP association:

- HP associated
- HP nonassociated

According to periods:

- [exacerbations](#)
- remission

According to grades:

- I – without complications, detected for the first time;
- II – without complication, with yearly [exacerbations](#);
- III – with complications,
- IV – recurrence after surgery.

According to complications:

- stenosis
- penetration
- perforation
- bleeding
- malignisation.

Example of diagnosis: Peptic ulcer disease, I grade, HP-positive, acute small (0,1x0,2cm) ulcer of duodenal bulb, period of exacerbation.

Clinical symptoms:

- dyspepsia (heartburn, blenching, nausea, vomiting giving relief, constipation)
- pain syndrome (always associated with meal, in epigastrium or pyloroduodenal area, intensive, may radiate to the back, thorax, other parts of abdomen, may be nocturnal (specific for duodenal ulcer), “painful hunger” relieved by food (specific for duodenal ulcer), may be postprandial and relieved by fasting (specific for duodenal ulcer))
- general weakness

NB! Remember about “red flags” symptoms!

Physical examination. Tongue is coated with white fur. Pain in epigastric or pyloroduodenal area at palpation.

The patient may present with pallor and may be hypovolemic. It is always useful to inquire about the characteristics of the stool, because ulcer-related bleeding may manifest not only obviously in the form of hematemesis but also insidiously as melena (black feces). In the case of massive ulcer bleeding with the rapid bowel passage of blood, patients may also present with red rectal blood loss. When a patient has acute perforation, severe epigastric and abdominal pain develops, and the patient appears distressed. Characteristically, intense contracture of the abdominal muscles is apparent on palpation, together with rebound tenderness and other signs of peritoneal irritation. With large amounts of intraabdominal air, percussion may reveal hypertympy over the liver.

Laboratory and instrumental methods:

- CBC
- biochemical blood test
- serum gastrin elevation
- gastrin provocative tests (intravenous secretin, meal)
- gastric analysis
- feces occult blood test
- upper endoscopy with biopsy (is the primary investigative tool in patients suspected of having acid peptic disease)
- ultrasound diagnostic of abdominal cavity
- gastroduodenoscopy barium contrast (inferior alternative)
- endoscopic ultrasound (selected cases only)
- ECG
- computed tomography (useful in selected cases)

HP testing:

- histologic examination of gastric mucosa
- bacteriologic examination of gastric mucosa
- fast urease test (in biopsy specimens)
- stool antigen test (more accurate)
- carbon-13 urea breath test (noninvasive and relatively simple test, but it is more expensive than stool or blood testing)
- serum antibodies (is not helpful to verify whether *H. pylori* has been eradicated with antibiotics because it may take many months or even years for *H. pylori* antibodies to fall to undetectable levels)
- polymerase chain reaction (PCR)

Differential diagnosis includes many disorders of the upper abdominal organs, including malignant diseases of the stomach, duodenum, pancreas, or bile ducts. The differential diagnosis of upper abdominal symptoms also includes liver and gallstone disease, pancreatitis, and motility disorders. In many patients with upper abdominal dyspeptic complaints, no underlying cause can be identified. In this “nonulcer” or functional dyspepsia group, complaints characteristic of gastroesophageal reflux, ulcer symptoms, or dysmotility symptoms may be prominent. A few of these patients (generally 5%) benefit from eradication of *H. pylori*.

Differential diagnosis of gastric and duodenal ulcer. Gastric ulcer: peak 50-60 y., pain often diffuse, variable - squeezing, heaviness, or sharp punctuating (may absent), poorly localized, may radiate to back, 1-3 h after food, aggravated by meals, severe gastric pain well radiating indicate penetration or perforation, seasonal occurrence (autumn, spring). Duodenal ulcer: male patients, peak 30-40 y., pain well localized epigastric, chronic, intermittent, relieved by alkalic food, often late onset 6-8 h after meal or independent (night), familiar occurrence, smokers, blood O type, complication - penetration onto pancreas.

Treatment. The goal of therapy for peptic ulcer disease is to relieve symptoms, heal craters, prevent recurrences, and prevent complications.

1) acid suppression

- Proton pump inhibitor (described in GERD)
- H₂-blockers (described in GERD)

2) anti HP therapy

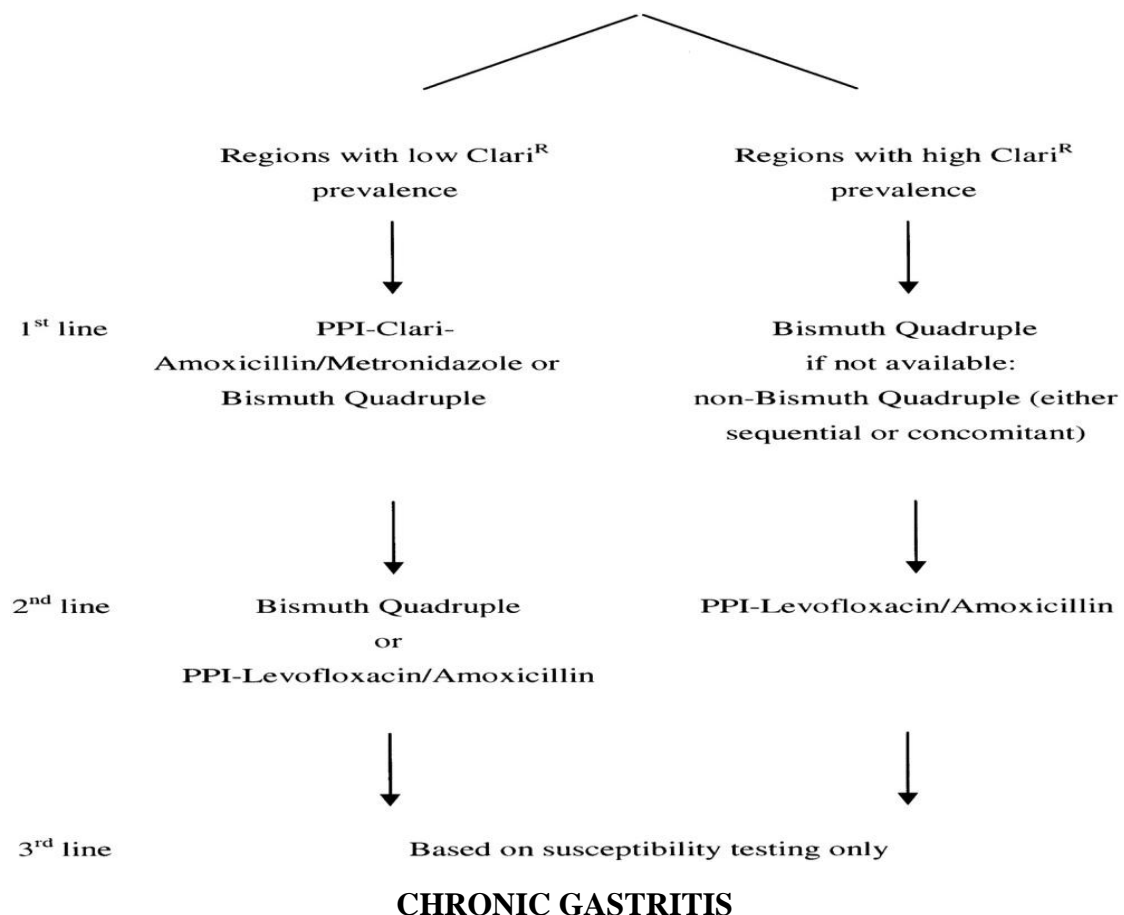
- First-line HP eradication therapy. Triple therapy (IPPs standard dose bid, clarithromycin 500mg bid, amoxicillin 1000mg bid/metronidazole 500 mg bid 10(7)-14 days)
- Sequential therapy (Standard-dose IPP bid 10 days, clarithromycin 500mg bid 5 days and after it amoxicillin 1000mg+metronidazole 500mg bid 5 days)
- Second-line. Quadruple therapy (IPP standard dose bid, [bismuth subcitrate](#) 120 mg qid, metronidazole 500mg tid, tetracycline 500 mg qid 10-14 days)
- “Rescue therapy” (IPPs standard dose bid, levofloxacin 500mg qd, amoxicillin 1000mg bid/rifampicine 300mg qd 10-14 days)

3) Sucralfate is the aluminum salt of a sulfated disaccharide. The drug forms a barrier or coating over the ulcer crater, stimulates prostaglandin synthesis, and binds to noxious agents such as bile salts. Although the exact mechanism of action is unclear, it appears sucralfates stimulate prostaglandins, which promote improved mucosal integrity and enhance epithelial regeneration. Because it requires multiple doses per day, patients are less likely to follow a sucralfate regimen even though it has been shown to be as effective as an H2 blocker in healing both duodenal and gastric ulcers. Sucralfate is not absorbed systemically, and its only remarkable side effect is constipation. Misoprostol is a prostaglandin E1 analog that increases mucosal resistance and inhibits acid secretion to a minor degree.

4) Misoprostol has been advocated for prophylaxis of NSAID-induced mucosal injury. The drug has significant side effects, primarily mild to moderate diarrhea, and is too costly to be used by most patients on long-term NSAIDs.

5) symptomatic treatment (mebeverine 200mg bid, itoprid 50 mg tid, UDCA 250 mg before sleep)

6) surgical treatment.



Definition.Chronic gastritis is an inflammatory, dystrophic chronic disease of the lining of the stomach, that is characterized by cell infiltration, abnormal regeneration and can lead to atrophy of [glandular epithelium](#), metaplasia and/or dysfunction of secretory, motoric or incretory activities of stomach.

Gastritis is mostly a histological term that needs biopsy to be confirmed.

- *Gastritis*: inflammation associated with epithelial cell damage and regeneration.
- *Gastropathy*: mucosal injury (in which there is cell damage and regeneration) without inflammation.
- *Atrophy*: loss of normal mucosal glands.
- *Metaplasia*: change in epithelial cell types.

Gastritis is categorized by endoscopic and histologic criteria, with granulocytes predominating in active gastritis and mononuclear cells in chronic gastritis.

Etiology.Helicobacter pylori affected in about half of populations in the world, is the major cause of gastritis. Other sources include chemical agents (nonsteroidal anti-inflammatory drugs, bile reflux into stomach, etc.) and autoimmunity. H. pylori are considered as a grade 1 carcinogen of gastric cancer. Dietary factors, alcohol, smoking and other diseases (diabetes mellitus, Crohn's disease, etc).

NB! According to some authors by irritants such as drugs (eg, nonsteroidal anti-inflammatory agents and alcohol), bile reflux, *gastropathy* is usually caused.

Pathogenesis.Chronic inflammation of gastric mucous membrane leads to regeneration breaks, that causes atrophy and possible mucous dysplasia of stomach.

Classification.According to endoscopic and histological divisions, combining topographical, morphological and etiological information to generate reproducible and clinically useful diagnoses Sidney classification was worked out (1996):

- Atrophic, autoimmune – Type A (diffuse, body and fundus of the stomach, associated with B₁₂-anemia)
- Nonatrophic – Type B (HP associated, antral)
- Multifocal (HP, diet factors, antrum+corpus)
- Chemical – Type C (chemical factors, alcohol, reflux-gastritis (bile), nonsteroidal anti-inflammatory drugs-associated)
- Radiation
- Lymphocytic (idiopathic, celiac disease-associated)
- Noninfectious granulomatosis (Crohn-disease, granulomatosis, sarcoidosis etc.)
- Eosinophilic (allergic)
- Other – bacterial, viral, fungal (specific gastritis).

Gastritis is also classified by the segment of involved stomach: antral-predominant gastritis, corpus-predominant gastritis, or pangastritis.

To evaluate the severity of atrophic changes new classification was proposed: Operative Link for Gastritis Assessment (OLGA, 2008). This system ranks the gastric cancer risk according to both the topography and the severity of gastric atrophy according to routine biopsy sampling.

		CORPUS			
		No atrophy (grade 0)	Mild atrophy (grade 1)	Moderate atrophy (grade 2)	Severe atrophy (grade 3)
ANTRUM	No atrophy (grade 0)	STAGE 0	STAGE I	STAGE II	STAGE II
	Mild atrophy (grade 1)	STAGE I	STAGE I	STAGE II	STAGE III
	Moderate atrophy (grade 2)	STAGE II	STAGE II	STAGE III	STAGE IV
	Severe atrophy (grade 3)	STAGE III	STAGE III	STAGE IV	STAGE IV

Complaints.Gastritis can be asymptomatic. But the most common symptoms are:

- dyspepsia (indigestion) – upper [abdominal postprandial fullness](#), [heartburn](#), nausea, [belching](#), early satiation, bloating
- pain syndrome – epigastric, especially after consumption of spicy, roasted food, usually dull, not intensive, after the meal, but it does not have regular and certain association with it
- general weakness
- symptoms of vitamins deficiency (type A gastritis)

Physical examination.Tongue is coated with white fur. Tenderness or pain in epigastrium at palpation.Signs of vitamins deficiency (pallor).

Clinical, laboratory and instrumental examination.Comprehensive assessment of clinical examination, serologic test (e.g., antibodies for infection or autoimmunity), endoscopy and histologic examination could be diagnostic tools for patients with gastritis.

Upper endoscopy with biopsy (2 from antrum, 2 from gastric body, 1 from incisura: site most likely to show atrophic gastritis and premalignant dysplasia). Typical histologic findings of gastritis are: chronic inflammatory infiltrates in lamina propria (lymphocytes, plasma cells and histiocytes), active inflammatory infiltrates in lamina propria and gastric glands (neutrophils and eosinophils) and loss of glandular units with replacement into fibrosis and smooth muscle proliferation, called as atrophy. Chromoendoscopy allows to visualize areas of intestine metaplasia.

- HP tests (described in peptic ulcer disease section)
- pH-monitoring
- antibodies to parietal cells (type A)
- antibodies to internal Castle factor (type A)
- gastropanel (IgG to HP, pepsinogen 1 and 2, gastrin – 17)
- CBC (inflammatory signs, anemia)

Differential diagnosis.Should be made with functional dyspepsia, peptic ulcer disease, GEDR, according to leading syndrome.

Treatment.

- Type A – treatment of anemia: cyanocobalamin 500mcg/ml (1-2ml) intramuscular 6 days, then it should be used once a week, after – once at 2 months (to treat anemia).
- Type B – HP eradication (described in peptic ulcer disease section).
- Type C – antacids, alginates, ursodeoxycholic acid (if bile reflux occurs) capsules 250 mg. PPIs, H2-blockers and prokinetics, ferments can be used if there is a need.

CHRONIC CHOLECYSTITIS

Definition.Chronic cholecystitis is an inflammation of the gallbladder with the presence of gallbladder-related symptoms because of motor dysfunction and changes in chemical and physical bile content (dyscholia). Cholesterolosis may be present, with deposits of cholesterol in the mucosa and muscle layers of the gallbladder.

Classification.

- calculous/acalculous;
- with dyskinesia of hyperkinetic/hypokinetic/mixed type;
- severity mild/moderate/severe;
- period of exacerbation/remission.

Epidemiology.In 5–10% of patients with cholecystitis, calculi obstructing the cystic duct are not found at surgery. In >50% of such cases, an underlying explanation for acalculous inflammation is not found. Affected patients are often young and female

Etiological factors and risk factors.The main etiological factor is an infection (staphylococcus, Proteus, Clostridia, Escherichia coli). The presence of bacteria in the bile occurs in >25% of patients with chronic cholecystitis. Additional factors include stress, functional disorders of gallbladder and bile ducts, endocrine diseases.

Risk factors are: fasting, total parenteral nutrition, septicemia, biliary infections, major trauma, burns, major nonbiliary surgery, childbirth, multiple blood transfusions, mechanical ventilation, opiates, immunosuppression—chemotherapy, HIV infection, transplantation, diabetes, ischemic heart disease, malignancy.

Pathogenesis.Inflammatory response can be evoked by three factors: mechanical inflammation produced by increased intraluminal pressure and distention with resulting ischemia of the gallbladder mucosa and wall, chemical inflammation caused by the release of lysolecithin (due to the action of phospholipase on lecithin in bile) and other local tissue factors, and bacterial inflammation, which may play a role in 50–85% of patients with cholecystitis. The organisms most frequently isolated by culture of gallbladder bile in these patients include Escherichia coli, Klebsiella spp., Streptococcus spp., and Clostridium spp. Infection can get the gallbladder from intestine, blood, by lymphatic system. Neuroendocrine lesions lead to motoric changes of gallbladder and releases in bile content changes and its stagnation.

Clinical features.As with biliary colic, the pain of cholecystitis localizes in abdominal right upper quadrant (RUQ) may radiate to the interscapular area, right scapula, or shoulder. The pain can be caused by roasted, fatty meal. Nausea and vomiting are relatively common and may produce symptoms and signs of vascular and extracellular volume depletion. Jaundice may occur when edematous inflammatory changes involve the bile ducts and surrounding lymph nodes. A low-grade fever is characteristically present, but shaking chills or rigors are not uncommon. Bitter taste in mouth, bloating and changes in feces can be present.

Diagnosis.The diagnosis of cholecystitis is usually made on the basis of a characteristic history and physical examination. The patient is anorectic and often nauseated. The RUQ of the abdomen is almost invariably tender to palpation. An enlarged, tense gallbladder is palpable in 25–50% of patients. Deep inspiration or cough during subcostal palpation of the RUQ usually produces increased pain and inspiratory arrest (Murphy's sign). Pain in point of Ker, positive symptoms of Ortner, Georhievsky-Myssi can be found. Localized rebound tenderness in the RUQ is common.

The triad of sudden onset of RUQ tenderness, fever, and leukocytosis is highly suggestive. Typically, leukocytosis in the range of 10,000–15,000 cells per microliter with a left shift on differential count is found. The serum bilirubin is mildly elevated (<85.5 $\mu\text{mol/L}$ [5 mg/dL]) in fewer than half of patients, whereas about one-fourth have modest elevations in serum aminotransferases (usually less than a fivefold elevation). Ultrasound will demonstrate

calculi in 90–95% of cases and is useful for detection of signs of gallbladder inflammation including thickening of the wall, pericholecystic fluid, and dilatation of the bile duct. The radionuclide (e.g., HIDA) biliary scan may be confirmatory if bile duct imaging is seen without visualization of the gallbladder.

Mirizzi's syndrome is a rare complication in which a gallstone becomes impacted in the cystic duct or neck of the gallbladder causing compression of the CBD, resulting in CBD obstruction and jaundice. Ultrasound shows gallstone(s) lying outside the hepatic duct. Endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), or magnetic resonance cholangiopancreatography (MRCP) will usually demonstrate the characteristic extrinsic compression of the CBD.

Although the clinical manifestations of acalculous cholecystitis are indistinguishable from those of calculous cholecystitis, the setting of acute gallbladder inflammation complicating severe underlying illness is characteristic of acalculous disease. Ultrasound or computed tomography (CT) examinations demonstrating a large, tense, static gallbladder without stones and with evidence of poor emptying over a prolonged period may be diagnostically useful in some cases.

Biliary dyskinesia may be diagnosed by food-cholecystokinin-stimulated US or a HIDA scan.

Complications.Empyema, gangrene, perforation, fistula, gallstone ileus, cholangitis, pancreatitis, etc.

Differential diagnosis.Hepatobiliary disorders, including cholecystitis and biliary colic, may mimic acute cardiopulmonary diseases. Although the pain arising from these gastrointestinal disorders usually localizes to the right upper quadrant of the abdomen, it is variable and may be felt in the epigastrium and radiate to the back and lower chest. This discomfort is sometimes referred to the scapula or may in rare cases be felt in the shoulder, suggesting diaphragmatic irritation. The pain is steady, usually lasts several hours, and subsides spontaneously, without symptoms between attacks.

Radioisotopic hepatobiliary iminodiacetic acid scans (HIDAs) may help differentiate cholecystitis or biliary colic from pancreatitis. ACT scan may demonstrate an enlarged pancreas, ruptured spleen, or thickened colonic or appendiceal wall, etc.

Treatment.In 80 to 90% of patients with abnormal stimulated motility, symptoms are relieved by cholecystectomy. Although surgical intervention remains the mainstay of therapy for acute cholecystitis or chronic cholecystitis with often periods of exacerbation and its complications, a period of in-hospital stabilization may be required before cholecystectomy. Meperidine or nonsteroidal anti-inflammatory drugs (NSAIDs) are usually employed for analgesia because they may produce less spasm of the sphincter of Oddi than drugs such as morphine. Antibiotic therapy is usually indicated in patients, even though bacterial superinfection of bile may not have occurred in the early stages of the inflammatory process. Antibiotic therapy is guided by the most common organisms likely to be present, which are *E. coli*, *Klebsiella* spp., and *Streptococcus* spp. Effective antibiotics include ureidopenicillins such as piperacillin or mezlocillin, ampicillin sulbactam, ciprofloxacin, moxifloxacin, and third-generation cephalosporins. Anaerobic coverage by a drug such as metronidazole should be added. Imipenem and meropenem represent potent parenteral antibiotics that cover the whole spectrum of bacteria causing ascending cholangitis. They should, however, be reserved for the most severe, life-threatening infections when other regimens have failed.

The optimal timing of surgical intervention in patients with cholecystitis depends on stabilization of the patient. Urgent (emergency) cholecystectomy or cholecystostomy is probably appropriate in most patients in whom a complication of cholecystitis such as empyema,

emphysematous cholecystitis, or perforation is suspected or confirmed. Patients with uncomplicated acute cholecystitis should undergo early elective laparoscopic cholecystectomy, ideally within 48–72 h after diagnosis.

CHOLELITHIASIS

Definition and classification. There are three different types of gallstones: cholesterol gallstones, mixed gallstones, and pigment stones, which can be further divided into black and brown stones. Cholesterol and mixed stones account for 80% of gallstone disease. Cholesterol stones contain more than 70% cholesterol, whereas mixed stones also contain significant amounts of pigments such as bilirubin. Black pigment stones, which are generally associated with hemolytic diseases, contain calcium salts, bilirubin, and proteins. Brown pigment stones are associated with intrahepatic cholangitis and infection; brown stones are seen after cholecystectomy, especially when they manifest as choledocholithiasis.

Epidemiology. Gallstones are quite prevalent in most Western countries. Gallstone formation increases after age 50. In the United States, the third National Health and Nutrition Examination Survey (NHANES III) has revealed an overall prevalence of gallstones of 7.9% in men and 16.6% in women. The prevalence was high in Mexican Americans (8.9% in men, 26.7% in women), intermediate for non-Hispanic whites (8.6% in men, 16.6% in women), and low for African Americans (5.3% in men, 13.9% in women).

Etiology and pathogenesis. Gallstones are formed because of abnormal bile composition. They are divided into two major types: cholesterol stones and pigment stones. Pigment stones are composed primarily of calcium bilirubinate; they contain <20% cholesterol and are classified into “black” and “brown” types, the latter forming secondary to chronic biliary infection. Cholesterol is essentially water insoluble and requires aqueous dispersion into either micelles or vesicles, both of which require the presence of a second lipid to solubilize the cholesterol. Cholesterol and phospholipids are secreted into bile as unilamellar bilayered vesicles, which are converted into mixed micelles consisting of bile acids, phospholipids, and cholesterol by the action of bile acids. If there is an excess of cholesterol in relation to phospholipids and bile acids, unstable, cholesterol-rich vesicles remain, which aggregate into large multilamellar vesicles from which cholesterol crystals precipitate.

There are several important mechanisms in the formation of lithogenic (stone-forming) bile. The most important is increased biliary secretion of cholesterol. This may occur in association with obesity, the metabolic syndrome, high-caloric and cholesterol-rich diets, or drugs (e.g., clofibrate) and may result from increased activity of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of hepatic cholesterol synthesis, and increased hepatic uptake of cholesterol from blood. In addition to environmental factors such as high-caloric and cholesterol-rich diets, genetic factors play an important role in gallstone disease. A single nucleotide polymorphism of the gene encoding the hepatic cholesterol transporter ABCG5/G8 has been found in 21% of patients with gallstones, but only in 9% of the general population. It is thought to cause a gain of function of the cholesterol transporter and to contribute to cholesterol hypersecretion.

An additional disturbance of bile acid metabolism that is likely to contribute to supersaturation of bile with cholesterol is enhanced conversion of cholic acid to deoxycholic acid, with replacement of the cholic acid pool by an expanded deoxycholic acid pool. It may result from enhanced dehydroxylation of cholic acid and increased absorption of newly formed deoxycholic acid. An increased deoxycholate secretion is associated with hypersecretion of cholesterol into bile. While supersaturation of bile with cholesterol is an important prerequisite for gallstone formation, it is generally not sufficient by itself to produce cholesterol precipitation

in vivo. Most individuals with supersaturated bile do not develop stones because the time required for cholesterol crystals to nucleate and grow is longer than the time bile remains in the gallbladder. An important mechanism is nucleation of cholesterol monohydrate crystals, which is greatly accelerated in human lithogenic bile. Accelerated nucleation of cholesterol monohydrate in bile may be due to either an excess of pronucleating factors or a deficiency of antinucleating factors. Mucin and certain nonmucin glycoproteins, principally immunoglobulins, appear to be pronucleating factors, while apolipoproteins A-I and A-II and other glycoproteins appear to be antinucleating factors. Pigment particles may possibly play a role as nucleating factors. In a genome-wide analysis of serum bilirubin levels, the uridine diphosphate-glucuronyltransferase 1A1 (UGT1A1).

Gilbert's syndrome gene variant was associated with the presence of gallstone disease. Because most gallstones associated with the UGT1A1 variant were cholesterol stones, this finding points to the role of pigment particles in the pathogenesis of gallbladder stones. Cholesterol monohydrate crystal nucleation and crystal growth probably occur within the mucin gel layer. Vesicle fusion leads to liquid crystals, which, in turn, nucleate into solid cholesterol monohydrate crystals. Continued growth of the crystals occurs by direct nucleation of cholesterol molecules from supersaturated unilamellar or multilamellar biliary vesicles.

A third important mechanism in cholesterol gallstone formation is gallbladder hypomotility. If the gallbladder emptied all supersaturated or crystal-containing bile completely, stones would not be able to grow. The incidence of gallstones is increased in conditions associated with infrequent or impaired gallbladder emptying such as fasting, parenteral nutrition, or pregnancy and in patients using drugs that inhibit gallbladder motility. Biliary sludge is a thick, mucous material that, upon microscopic examination, reveals lecithin-cholesterol liquid crystals, cholesterol monohydrate crystals, calcium bilirubinate, and mucin gels. Biliary sludge typically forms a crescent-like layer in the most dependent portion of the gallbladder and is recognized by characteristic echoes on ultrasonography. The presence of biliary sludge implies two abnormalities: the normal balance between gallbladder mucin secretion and elimination has become deranged, and nucleation of biliary solutes has occurred. That biliary sludge may be a precursor form of gallstone disease is evident from several observations. It should be emphasized that biliary sludge can develop with disorders that cause gallbladder hypomotility; i.e., surgery, burns, total parenteral nutrition, pregnancy, and oral contraceptives—all of which are associated with gallstone formation. However, the presence of biliary sludge implies supersaturation of bile with either cholesterol or calcium bilirubinate. Two other conditions are associated with cholesterol-stone or biliary-sludge formation: pregnancy and rapid weight reduction through a very-low-calorie diet. There appear to be two key changes during pregnancy that contribute to a "cholelithogenic state": a marked increase in cholesterol saturation of bile during the third trimester and sluggish gallbladder contraction in response to a standard meal, resulting in impaired gallbladder emptying.

To summarize, cholesterol gallstone disease occurs because of several defects, which include bile supersaturation with cholesterol, nucleation of cholesterol monohydrate with subsequent crystal retention and stone growth, and abnormal gallbladder motor function with delayed emptying and stasis.

Black pigment stones are composed of either pure calcium bilirubinate or polymer-like complexes with calcium and mucin glycoproteins. They are more common in patients who have chronic hemolytic states (with increased conjugated bilirubin in bile), liver cirrhosis, Gilbert's syndrome, or cystic fibrosis. Gallbladder stones in patients with ileal diseases, ileal resection, or ileal bypass generally are also black pigment stones. Enterohepatic recycling of bilirubin in ileal disease states contributes to their pathogenesis.

Brown pigment stones are composed of calcium salts of unconjugated bilirubin with varying amounts of cholesterol and protein. They are caused by the presence of increased amounts of unconjugated, insoluble bilirubin in bile that precipitates to form stones. Deconjugation of an excess of soluble bilirubin mono- and diglucuronides may be mediated by endogenous β -glucuronidase but may also occur by spontaneous hydrolysis. Sometimes, the enzyme is also produced when bile is chronically infected by bacteria, and such stones are brown. Pigment stone formation is frequent in Asia and is often associated with infections in the gallbladder and biliary tree.

Clinical features. Gallstones usually produce symptoms by causing inflammation or obstruction following their migration into the cystic duct or common bile duct (CBD). The most specific and characteristic symptom of gallstone disease is biliary colic that is a constant and often long-lasting pain. Obstruction of the cystic duct or CBD by a stone produces increased intraluminal pressure and distention of the viscus that cannot be relieved by repetitive biliary contractions. The resultant visceral pain is characteristically a severe, steady ache or fullness in the epigastrium or right upper quadrant (RUQ) of the abdomen with frequent radiation to the interscapular area, right scapula, or shoulder. Biliary colic begins quite suddenly and may persist with severe intensity for 30 min to 5 h, subsiding gradually or rapidly. An episode of biliary pain persisting beyond 5 h should raise the suspicion of acute cholecystitis. Nausea and vomiting frequently accompany episodes of biliary pain. An elevated level of serum bilirubin and/or alkaline phosphatase suggests a common duct stone. Fever or chills (rigors) with biliary pain usually imply a complication, i.e., cholecystitis, pancreatitis, or cholangitis. Complaints of short-lasting, vague epigastric fullness, dyspepsia, eructation, or flatulence, especially following a fatty meal, should not be confused with biliary pain. Such symptoms are frequently elicited from patients with or without gallstone disease but are not specific for biliary calculi. Biliary colic may be precipitated by eating a fatty meal, by consumption of a large meal following a period of prolonged fasting, or by eating a normal meal; it is frequently nocturnal, occurring within a few hours of retiring. The characteristic presentation also involves biliary jaundice.

Diagnosis. Ultrasonography of the gallbladder is very accurate in the identification of cholelithiasis and has replaced oral cholecystography. Stones as small as 1.5 mm in diameter may be confidently identified provided that firm criteria are used (e.g., acoustic "shadowing" of opacities that are within the gallbladder lumen and that change with the patient's position, by gravity). Biliary sludge is material of low echogenic activity that typically forms a layer in the most dependent position of the gallbladder. This layer shifts with postural changes but fails to produce acoustic shadowing; these two characteristics distinguish sludges from gallstones. Ultrasound can also be used to assess the emptying function of the gallbladder.

The plain abdominal film may detect gallstones containing sufficient calcium. Plain radiography may also be of use in the diagnosis of emphysematous cholecystitis, porcelain gallbladder, limey bile, and gallstone ileus.

Oral cholecystography (OCG) has historically been a useful procedure for the diagnosis of gallstones but has been replaced by ultrasound and is regarded as obsolete. It may be used to assess the patency of the cystic duct and gallbladder emptying function. Further, OCG can also delineate the size and number of gallstones and determine whether they are calcified. Radiopharmaceuticals such as ^{99m}Tc -labeled N-substituted iminodiacetic acids (HIDA, DIDA, DISIDA, etc.) are rapidly extracted from the blood and are excreted into the biliary tree in high concentration even in the presence of mild to moderate serum bilirubin elevations. Failure to image the gallbladder in the presence of biliary ductal visualization may indicate cystic duct obstruction, acute or chronic cholecystitis, or surgical absence of the organ. Such scans have some application in the diagnosis of acute cholecystitis.

Complications. Acute cholecystitis, which is the most common serious complication of gallstone disease, can lead to perforation of the gallbladder, peritonitis, fistula into the intestine or duodenum with gallstone ileus or obstruction, and abscesses in the liver or abdominal cavity. Acute cholecystitis is caused by obstruction of the cystic duct, and the ensuing increased intraluminal pressure can lead to vascular compromise of the gallbladder. Salmonella and other less common microorganisms such as *Vibrio cholerae*, *Leptospira*, and *Listeria* can cause primary cholecystitis.

Treatment. In asymptomatic gallstone patients, the risk of developing symptoms or complications requiring surgery is quite small. Thus, a recommendation for cholecystectomy in a patient with gallstones should probably be based on assessment of three factors: the presence of symptoms that are frequent enough or severe enough to interfere with the patient's general routine; the presence of a prior complication of gallstone disease, i.e., history of acute cholecystitis, pancreatitis, gallstone fistula, etc.; or the presence of an underlying condition predisposing the patient to increased risk of gallstone complications (e.g., calcified or porcelain gallbladder and/or a previous attack of acute cholecystitis regardless of current symptomatic status). Patients with very large gallstones (>3 cm in diameter) and patients harboring gallstones in a congenitally anomalous gallbladder might also be considered for prophylactic cholecystectomy. Laparoscopic cholecystectomy is a minimal access approach for the removal of the gallbladder together with its stones. Its advantages include a markedly shortened hospital stay, minimal disability, and decreased cost, and it is the procedure of choice for most patients referred for elective cholecystectomy. Laparoscopic cholecystectomy has become the "gold standard" for treating symptomatic cholelithiasis.

Stone dissolution carefully can be performed in selected patients with a functioning gallbladder and with radiolucent stones <10 mm in diameter. For good results within a reasonable time period, this therapy should be limited to radiolucent stones smaller than 5 mm in diameter. The dose of ursodeoxycholic acid (UDCA) should be 10–15 mg/kg per day. Stones larger than 10 mm in size rarely dissolve. Pigment stones are not responsive to UDCA therapy. However, in addition to the vexing problem of recurrent stones (30–50% over 3–5 years of follow-up), there is also the factor of taking an expensive drug for up to 2 years. The advantages and success of laparoscopic cholecystectomy have largely reduced the role of gallstone dissolution to patients who wish to avoid or are not candidates for elective cholecystectomy. However, patients with cholesterol gallstone disease who develop recurrent choledocholithiasis after cholecystectomy should be on long-term treatment with UDCA.

FUNCTIONAL BILIARY DISORDERS

The concept that disordered function of the gallbladder (GB) and sphincter of Oddi (SO) can cause pain is based mainly on the fact that many patients have biliary-type pain in the absence of recognized organic causes, and that some apparently are cured by removal of the GB or ablation of the sphincter.

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 infrascapular region
3. Waking from sleep

Definition.In conformity with the Rome consensus IV that defines functional gastrointestinal disorders as symptom complexes not explained by a clearly identified mechanism or by a structural alteration, we use the term functional gallbladder disorder (FGBD) to describe patients with biliary pain and an intact GB without stones or sludge.

Classification.

- Functional Gallbladder Disorder
- Functional Biliary Sphincter Disorder
- Functional Pancreatic Sphincter Dysfunction

Epidemiology.Biliary pain is a common clinical problem, and cholecystectomy is a frequent operation. The number and proportion done for FGBD seems to be increasing in the United States, where case series now list it as the indication for cholecystectomy in 10%-20% of adults and in 10%-50% of children. FGBD is rarely diagnosed outside the United States.

Functional Gallbladder Disorder

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

Pathogenesis.FGBD is often diagnosed by a low gallbladder ejection fraction (GBEF) at cholecystokinin-stimulated cholescintigraphy (CCK-CS). Although the relationship between GBEF and clinical outcome remains unclear, gallbladder dysmotility may still play a role in the pathogenesis of symptoms, by promoting gallbladder inflammation, which is commonly found. Microlithiasis is associated with a delayed ejection fraction on scintigraphy. Investigators have found multiple defects in gallbladder contractility, including spontaneous activity and abnormal responses to both CCK and neural stimulation. A vicious cycle of stasis and inflammation exists in the GB. Some patients may have intrinsic defects in contractility, and subtle defects in bile composition may also play a role. Studies have shown elevated sphincter of Oddi (SO) pressures in patients with GB dyskinesia, but without correlation between GBEF and SO pressure. GB dysfunction may represent a more generalized dysmotility, as in irritable bowel syndrome and chronic constipation, and perhaps gastroparesis. Experimental evidence has implicated several molecules that can link inflammation to motility, the most important of which may be prostaglandin E₂ (PGE₂).

Diagnosis.GB stones should be excluded by ultrasound scanning (repeated if necessary), and complemented with EUS. Other tests may be needed to rule out peptic ulcer disease, subtle chronic pancreatitis, fatty liver disease, or musculoskeletal syndromes. Esophageal manometry, gastric emptying tests, and transit studies may be required if symptoms suggest alternative dysfunctional syndromes. Further management depends on the level of clinical suspicion. The diagnosis of FGBD may be made by exclusion if the pains are typical and severe. A key issue is whether current methods for assessing GB muscular function are useful.

CCK-CS is a popular diagnostic test, but its value is controversial. The test involves the intravenous administration of technetium 99m (Tc 99m)labeled hepatobiliary iminodiacetic acid analogs. These compounds are readily excreted into the biliary tract, and are concentrated in the GB. The net activity-time curve for the GB is derived from serial observations, and GB emptying

is expressed as the GBEF, which is the percentage change of net GB counts. An interdisciplinary panel proposed a standardized test and emphasized that proper patient selection is a critical step when considering whether to perform CCK-CS, because delayed emptying is seen in many other conditions, including asymptomatic individuals and patients with other functional gastrointestinal disorders. The injection of CCK can cause biliary-like pain, but using this observation to determine patient-care decisions was discouraged by the panel, because CCK also increases bowel motility, which can cause symptoms. In some countries, CCK preparations have not been approved for human use.

GB emptying can be assessed with ultrasound scanning after CCK or fatty meal stimulation, but these methods have not become popular. Attempts are being made to study emptying patterns during magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT) scanning with results that appear to mimic those of cholescintigraphy.

Treatment.Symptoms suggestive of FGBD often resolve spontaneously, so that early intervention is unwarranted. Patients may respond to reassurance and medical treatments such as antispasmodics, neuromodulators, or ursodeoxycholic acid, although their value has not been evaluated formally.

Cholecystectomy is considered when these methods fail, and symptoms are severe. The reported results of surgery vary widely. Many claim benefit in >80% of patients, but most studies are of poor quality with several potential biases; none have limited intervention to patients with negative EUS exams. However, cholecystectomy is claimed to benefit most patients with “typical biliary” symptoms, raising the question as to what additional utility is afforded by CCK-CS. One study reported symptomatic relief after cholecystectomy in 94% of patients with a low GBEF, but also in 85% of those with a normal GBEF. That many patients with suspected FGBD are not helped by cholecystectomy is shown by the significant number who present afterward with “postcholecystectomy pain,” and are considered for another contentious diagnosis, sphincter of Oddi dysfunction (SOD).

Functional Biliary Sphincter Disorder

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

Pathogenesis.Classical teaching is that aberrant sphincter physiology leads to biliary pain by increased resistance to bile outflow and subsequent rise in intrabiliary pressure. This concept is intuitively appealing, leading to widespread acceptance, especially by biliary endoscopists. However, both theoretical and experimental evidence indicate a more complex pathophysiology. There is evidence that sphincter dynamics are altered after cholecystectomy. Animal studies have shown a cholecystosphincteric reflex with distention of the GB that results in sphincter relaxation. Interruption of this reflex could affect sphincter behavior by an altered response to CCK, or because the loss of innervation unmasks the direct contractile effects of CCK on smooth muscle.

Abnormalities in both basal pressure and responsiveness to CCK have also been described in humans. The simple concept of SOD leading to obstruction and biliary pain is now being challenged. One explanation for this syndrome stems from the concept of nociceptive

sensitization. Significant tissue inflammation, such as cholecystitis, will activate nociceptive neurons acutely and, if it persists, will also result in sensitization and the gain in the entire pain pathway is increased. In most patients with GB disease, cholecystectomy removes the ongoing stimulus and the system reverts back to its normal state. However, in a subset of patients, the “gain” stays at a high level. In such patients, even minor increases in biliary pressure (within the physiological range) can trigger nociceptive activity and the sensation of pain (allodynia).

A relevant related phenomenon is cross-sensitization. Many viscera share sensory innervation. For example, nearly half of the sensory neurons in the pancreas also innervate the duodenum. Therefore, it is difficult to distinguish pain resulting in one organ from that in another. Persistent sensitization in one organ can lead to sensitization of the nociceptive pathway from an adjacent organ. Thus, an entire region can be sensitized with innocuous stimuli (such as duodenal contraction after a meal) leading to pain that was indistinguishable from that associated with the initial insult.

Motor phenomena, such as sphincter hypertension, might still be relevant, but more as a marker for the syndrome rather than the cause.

Diagnosis. The first task in patients with post-cholecystectomy pain is to exclude organic causes. Possibilities include retained stones or partial GB; postoperative complications (such as a bile leak or duct stricture); other intra-abdominal disorders, such as pancreatitis, fatty liver disease, peptic ulceration, functional dyspepsia and irritable bowel syndrome; musculoskeletal disorders; and other rare conditions.

Nonbiliary findings are more likely when the symptoms are atypical and longstanding, similar to those suffered preoperatively and without a period of relief postoperatively, and when the GB did not contain stones. The initial diagnostic approach should consist of a careful history and physical examination, followed by standard liver and pancreas blood tests, upper endoscopy, and abdominal imaging. Although ultrasound or computed tomography scanning may be used initially, MRCP or EUS provide more complete information.

The report of a “dilated bile duct” on any of these studies is difficult to interpret. It is widely believed that the bile duct enlarges after cholecystectomy. However, some studies have shown no change, others only a slight increase in size; there is a gradual increase with age. Regular narcotic use can cause biliary dilation, although usually associated with normal liver enzymes. EUS is the best way to rule out duct stones and pathology of the papilla.

A major problem with assessing diagnostic tools in this context is the lack of a gold standard. One could argue that the only proof that the sphincter is (or was) the cause of the pain is if patients are satisfied by the results of sphincter ablation, albeit recognizing the often prolonged placebo effect of endoscopic retrograde cholangiopancreatography (ERCP) intervention. Many tests are assessed by comparison with the results of manometry, whose validity is also uncertain. Liver enzymes, which peak with attacks of pain, might be a good sign of obstruction by spasm (or passage of stones). Another problem is that most patients have intermittent pains, so that measurements taken when pain-free are open to question. The drainage dynamics of the bile duct have been tested after stimulation with a fatty meal or injection of CCK and measuring any dilatation of the duct with abdominal or endoscopic ultrasound.

Hepatobiliary scintigraphy involves intravenous injection of a radionuclide and deriving time-activity curves for its excretion throughout the hepatobiliary system. This technique has been used to assess the rate of bile flow into the duodenum and to look for any evidence of obstruction. Interpretation of the literature is difficult due to the use of different test protocols, diagnostic criteria, and categories of patients, and whether the results are compared with manometry (usually) or the outcome of sphincterotomy. Various parameters are used: time to peak activity, slope values, and hepatic clearance at predefined time intervals, disappearance

time from the bile duct, duodenal appearance time, and the hepatic hilumoduodenum transit time. The reported specificity of hepatobiliary scintigraphy was at least 90% when manometry was used as the reference standard, but the level of sensitivity is more variable.

Endoscopic retrograde cholangiopancreatography and sphincter of Oddi manometry. ERCP should be reserved for patients who need sphincter manometry or endoscopic therapy, such as those with strong objective evidence for biliary obstruction.

ERCP allows measurement of both the biliary and pancreatic sphincters, but the method is imperfect. Recording periods are short and subject to movement artifact.

The assessable variables at SO manometry include the basal sphincter pressure and the phasic wave amplitude, duration, frequency, and propagation pattern. However, only basal pressure has so far been shown to have clinical significance. The standard upper limit of normal for baseline biliary sphincter pressure is 35-40 mm Hg. Normal pancreatic sphincter pressures are accepted as similar to those of the bile duct, although reference data are more limited. For patients in whom the indication for SO manometry is biliary pain and not idiopathic pancreatitis, some authorities avoid pancreatic cannulation entirely to reduce the frequency of pancreatitis.

Sphincter manometry has been recommended in patients with suspected biliary type II SOD because 3 randomized trials showed that biliary manometry predicted the response to biliary sphincterotomy. However, in clinical practice, biliary sphincterotomy is often performed empirically in those patients. Manometry is no longer recommended in patients without objective findings.

Treatment. Many patients are disabled with pain and desperate for assistance.

Because of the risks and uncertainties involved in invasive approaches, it is important to explore conservative management initially. Nifedipine, phosphodiesterase type-5 inhibitors, trimebutine, hyoscine butylbromide, octreotide, and nitric oxide have been shown to reduce basal sphincter pressures in SOD and asymptomatic volunteers during acute manometry. H₂ antagonists, gabexate mesilate, ulinastatin, and gastrokinetic agents also showed inhibitory effects on sphincter motility. Amitriptyline, as a neuromodulator, also has been used along with simple analgesics. A trial of duloxetine had encouraging results. Transcutaneous electrical nerve stimulation and acupuncture also have been shown to reduce SO pressures, but their long-term efficacy has not been evaluated.

Endoscopic therapy: sphincterotomy. Consensus opinion remains that patients with definite evidence for SO obstruction should be treated with endoscopic sphincterotomy without manometry.

Freeman and colleagues showed that normal pancreatic manometry, delayed gastric emptying, daily opioid use, and age younger than 40 years predicted poor outcomes. It has been reported that patients are more likely to respond if their pain was not continuous, if it was accompanied by nausea and vomiting, and if there had been a pain-free interval of at least 1 year after cholecystectomy.

ERCP in patients with SOD (with or without manometry) is associated with a high risk of pancreatitis. The rate is 10%-15%, even in expert hands using pancreatic stent placement and/or rectal nonsteroidal anti-inflammatory drugs.

Sphincterotomy adds the risk of bleeding and retroduodenal perforation, which both occur in about 1% of cases, and also a significant risk for late restenosis, especially after pancreatic sphincterotomy.

Surgical sphincteroplasty can be performed primarily or after failed endoscopic therapy.

Functional Pancreatic Sphincter Dysfunction

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

Pathogenesis. The idea that dysfunction of the pancreatic sphincter can cause pancreatic pain and pancreatitis is popular. It seems a logical extension to the consensus that sphincter hypertension can cause biliary pain. Obstruction at the sphincter causes pancreatitis in animal experiments, and in several clinical situations, including tumors of the papilla, duct stones, and by mucus plugs in intrapancreatic mucinous neoplasm. In addition, opiates increase sphincter pressure and have been implicated in attacks of pancreatitis. Finally, patients with unexplained attacks of pancreatitis are often found to have elevated pancreatic sphincter pressures.

It remains possible that the finding of sphincter abnormality in these patients is an epiphenomenon, the result of previous attacks, or due to an unexplained cause. The fact that many patients eventually develop features of chronic pancreatitis suggests that the underlying pathogenesis of the disease is not altered.

Diagnosis. Measuring the size of the pancreatic duct by MRCP or EUS before and after an intravenous injection of secretin has been used to demonstrate sphincter dysfunction. One report suggests that the results do not correlate with sphincter manometry, but may predict the outcome of sphincterotomy in patients with otherwise unexplained pancreatitis.

Treatment. Patients with recurrent acute pancreatitis that remains unexplained after detailed investigation should be reassured that the attacks may stop spontaneously and if they recur, they usually follow the same course and are rarely life threatening. They should be counseled to avoid factors that may precipitate attacks (eg, alcohol, opiates). While certain medications (such as antispasmodics and calcium channel blockers) are known to relax the sphincter, there have been no trials of their use.

In earlier days, cholecystectomy was often recommended after 2 unexplained attacks of pancreatitis, assuming that small stones or microlithiasis were responsible. That approach seems less acceptable now that these are easier to exclude with modern imaging. Others have approached the problem of microlithiasis with biliary sphincterotomy, or treatment with ursodeoxycholic acid.

Pancreatic sphincterotomy would be the logical treatment if the sphincter dysfunction is indeed causative. Historically, complete division of the both sphincters was done by an open transduodenal approach. Case series of patients who have undergone this procedure have claimed resolution of episodic pancreatitis in the majority of patients. The pancreatic sphincterotomies performed endoscopically are much smaller, and repeat manometry studies in patients with recurrent problems often show them to be incomplete.

Manometry has not been repeated in patients without recurrent symptoms, so it is not clear whether treatment has failed because of inadequacy of the sphincterotomy, or an incorrect diagnosis. Stenosis of the pancreatic orifice is not uncommon after pancreatic sphincterotomy, and repeat ERCP treatment rarely resolves the problem.

Endoscopic biliary sphincterotomy is known to reduce pancreatic sphincter pressures in many cases. At the present time, practitioners and patients should approach invasive treatments in this context with considerable caution, recognizing the short and long-term risks, and the marginal evidence for benefit.

CHRONIC PANCREATITIS

Definition. Chronic pancreatitis is a complex process that implies the presence of irreversible and permanent fibrosis, often with chronic mononuclear cell inflammation, damage to nerves,

and loss of ducts, acini, and islets. Thus, the condition is defined by the presence of histologic abnormalities, including chronic inflammation, fibrosis, and progressive destruction of both exocrine and eventually endocrine tissue (atrophy).

Classification.

- according to etiology: primary, secondary, idiopathic.
 - Toxic-metabolic (Alcoholic, Tobacco smoking, Hypercalcemia, Hyperlipidemia, Chronic renal failure, Medications—phenacetin abuse, Toxins—organotin compounds (e.g., dibutyltin dichloride, DBTC));
 - Idiopathic (Early onset, Late onset, Tropical);
 - Genetic (Cationic trypsinogen (PRSS1), Cystic fibrosis transmembrane conductance regulator gene (CFTR), Calcium-sensing receptor (CASR), Chymotrypsin C gene (CTRC), Pancreatic secretory trypsin inhibitor gene (SPINK1));
 - Autoimmune (Type 1 autoimmune chronic pancreatitis, IgG4 systemic, Type 2 autoimmune chronic pancreatitis);
 - Recurrent and severe acute pancreatitis (Postnecrotic (severe acute pancreatitis), Recurrent acute pancreatitis, Vascular diseases/ischemia, Radiation induced);
 - Obstructive (Pancreas divisum, Duct obstruction (e.g., tumor), Preampullary duodenal wall cysts, Posttraumatic pancreatic duct scars).
- according to integral index of severity M-ANNHEIM: A, B, C, D.
- according to severity: mild, moderate, severe.
- according to deficiency of gland: with/without exocrine/endocrine deficiency.
- according to phase: exacerbation, remission.
- according to clinical picture: painful, pseudotumor, painless forms.
- according to Cambridge classification: it divides chronic pancreatitis to five severity groups according to morphologic changes of the main pancreatic duct and its side branches. It was defined in 1983 in the Cambridge symposium.

Score	Cambridge Class	Severity	ERCP findings	Ultrasound or CT findings
Score 1	0	none	no abnormal signs	no abnormal signs
Score 2	0	equivocal	<3 abnormal branches	one abnormal sign: main pancreatic duct 2 - 4mm in diameter enlarged gland 1 to 2 times the normal
Score 3	I	mild	3 or more abnormal branches	≥ 2 abnormal signs: cavities <10mm duct irregularity focal acute necrosis pancreenchymal heterogeneity increased echogenicity of duct wall contour irregularity of head or body
Score 4	II	moderate	>3 abnormal side branches and	as score 3

			abnormal main duct	
Score 5	III	severe	all above and 1 or more of: large cavity >10mm intraductal filling defects duct obstruction (stricture) duct dilatation or irregularity	all above and 1 or more of: large cavity >10mm intraductal filling defects duct obstruction (stricture) duct dilatation or irregularity calculi and/or pancreatic calcification contiguous organ invasion

- A modified, clearer version of Cambridge classification:

Severity	ERCP findings	Ultrasound or CT findings
none	no abnormal LSB	normal gland size and shape, homogeneous parenchyma
equivocal	MPD normal	one of the following: <3 abnormal LSB MPD 2-4mm gland enlarged over 2 times the normal size heterogeneous parenchyma
mild	MPD normal	two or more of the following: >3 abnormal LSB MPD 2-4mm slight gland enlargement heterogeneous parenchyma
moderate	MPD changes LSB changes	small cysts <10mm MPD irregularity focal acute pancreatitis (<1/3 of the gland) increased enhancement or echogenicity of MPD walls gland contour irregularity
severe	Any of the above changes plus one or more of the following: cavity >10mm in diameter intraductal filling defects calculi MPD obstruction or stricture severe MPD irregularity contiguous organ invasion	

Epidemiology. The prevalence of symptomatic chronic pancreatitis in Western countries is about 25 to 30 per 100,000 population, with an estimated incidence of 3 to 9 cases per 100,000. Interestingly, the prevalence of histologic evidence of chronic pancreatitis in autopsy studies approaches 5%, indicating that many people apparently develop chronic pancreatic damage as a consequence of normal aging, other diseases, or exposure to toxins, such as consumption of alcohol, but do not develop any symptoms or signs of chronic pancreatitis during life.

Etiological factors and risk factors.In Western countries, alcohol and tobacco abuse are the dominant causes of chronic pancreatitis. Alcohol causes about 70 to 80% of all cases of chronic pancreatitis in the United States and other major industrial countries. Substantial and prolonged ingestion of alcohol is usually required, on the order of 5 to 8 drinks daily over more than 5 years. Most people who consume this much alcohol do not develop chronic pancreatitis, pointing to important cofactors such as genetic background and cigarette smoking. There is evidence that tobacco alone can cause chronic pancreatitis, and the combination of alcohol and tobacco may be synergistic.

Other factors are hereditary (this pancreatitis is an autosomal dominant disease characterized by early onset of acute and chronic pancreatitis, the development of exocrine and endocrine pancreatic insufficiency, and a high risk of pancreatic adenocarcinoma) and autoimmune lesions.

Risk factors also include nutritive factors (e.g., excess fat consumption with meal, etc.) and less common metabolic processes (hypercalcemia, chronic renal failure, etc.)

Normal physiology.The pancreas secretes amylolytic, lipolytic, and proteolytic enzymes into the duct lumen. Amylolytic enzymes, such as amylase, hydrolyze starch to oligosaccharides and to the disaccharide maltose. The lipolytic enzymes include lipase, phospholipase A₂, and cholesterol esterase. Bile salts inhibit lipase in isolation, but colipase, another constituent of pancreatic secretion, binds to lipase and prevents this inhibition. Bile salts activate phospholipase A and cholesterol esterase. Proteolytic enzymes include endopeptidases (trypsin, chymotrypsin), which act on internal peptide bonds of proteins and polypeptides; exopeptidases (carboxypeptidases, aminopeptidases), which act on the free carboxyl- and amino-terminal ends of peptides, respectively; and elastase. The proteolytic enzymes are secreted as inactive zymogen precursors. Autodigestion of the pancreas is prevented by the packaging of pancreatic proteases in precursor (proenzyme) form, intracellular calcium homeostasis (low intracellular calcium in the cytosol of the acinar cell promotes the destruction of spontaneously activated trypsin), acid-base balance, and the synthesis of protective protease inhibitors (pancreatic secretory trypsin inhibitor [PSTI] or SPINK1), which can bind and inactivate about 20% of intracellular trypsin activity. Chymotrypsin C can also lyse and inactivate trypsin. These protease inhibitors are found in the acinar cell, the pancreatic secretions, and the α 1- and α 2-globulin fractions of plasma. Loss of any of these four protective mechanisms leads to premature enzyme activation, autodigestion, and acute pancreatitis.

Pathogenesis.Multiple episodes of acute inflammation, whether clinical or subclinical, eventually change the inflammatory milieu of the pancreas, with a shift to chronic inflammation, the activation of pancreatic stellate cells, and the production of fibrosis. This process is self-sustaining and produces the characteristic histologic damage noted previously. Genetic mutations predispose to chronic pancreatitis, but the genetic predisposition is superimposed on exposure to various toxins, which precipitate acute pancreatitis, with cellular necrosis or apoptosis, that progresses in some individuals, particularly those with multiple episodes, to a chronic and fibrotic process. One important contributor to the pain in chronic pancreatitis is damage to pancreatic nociceptive nerves and the complex neuroimmune interaction driven by the chronic inflammatory state. Chronic pain produces visceral, spinal cord, and central hyperalgesia, and the pain may become self-perpetuating even if therapy on the pancreas is successful. In addition to this neural mechanism, increased pressure within the gland, associated ischemia, obstruction of the pancreatic duct, and a pseudocyst can cause pain.

Mutations in the trypsinogen (PRSS1) gene in these families appear to cause a gain in function in which the mutant trypsinogen, once activated to trypsin, is difficult to inactivate. This trypsin, if present in an amount that overwhelms normal protective mechanisms, can activate

other pancreatic enzymes and lead to pancreatic damage and eventually to chronic pancreatitis. One of the protective mechanisms is a trypsin inhibitor called SPINK1. Loss of function mutations in SPINK1 may predispose to chronic pancreatitis, but unlike PRSS1 mutations, are not sufficient to cause chronic pancreatitis. Major mutations in CFTR lead to cystic fibrosis, which is associated with chronic pancreatitis and pancreatic atrophy. Milder mutations in CFTR, which predispose to chronic pancreatitis without causing the sinopulmonary features of cystic fibrosis, are encountered in patients with idiopathic chronic pancreatitis.

Autoimmune pancreatitis is a disease that most often presents as a masslike lesion with obstructive jaundice, mimicking cancer, but it also may present as chronic pancreatitis and rarely as acute pancreatitis. Characteristic features of the disease include a diffuse swelling of the pancreas, elevations in serum immunoglobulin G4 (IgG4), and involvement of other organs, especially biliary strictures, salivary gland inflammation, retroperitoneal fibrosis, and renal lesions. Histologically, these organs are infiltrated by chronic inflammatory cells, especially plasma cells bearing IgG4 on their surface. Tropical pancreatitis is seen primarily in southern India. Characteristic features include childhood onset, exocrine insufficiency, diffuse pancreatic calcifications, and inevitable diabetes. There may be a genetic component (SPINK1), but cofactors such as malnutrition and dietary toxins have been suggested. In southern India, this disease is becoming uncommon and is being replaced by alcohol as the most common cause of idiopathic chronic pancreatitis.

Although most chronic pancreatitis evolves from multiple episodes of acute pancreatitis, a single severe acute attack that causes substantial pancreatic necrosis can destroy enough gland to produce exocrine and endocrine insufficiency. In addition, diseases that cause repeated attacks of pancreatitis can lead to chronic pancreatitis.

Clinical features. Patients with chronic pancreatitis seek medical attention predominantly because of two symptoms: abdominal pain or maldigestion and weight loss. The abdominal pain may be quite variable in location, severity, and frequency. The pain can be constant or intermittent with frequent pain-free intervals, and it is generally felt in the epigastrium with radiation to the back. If pain is episodic, the patient may be labeled as having acute pancreatitis or an acute flare of chronic pancreatitis. When pain is severe, nausea and vomiting may occur. Pain may worsen, improve, or remain stable over time. Eating may exacerbate the pain, leading to a fear of eating with consequent weight loss. The spectrum of abdominal pain ranges from mild to quite severe, with narcotic dependence as a frequent consequence.

Maldigestion is manifested as chronic diarrhea, steatorrhea, weight loss, and fatigue. Patients with chronic abdominal pain may or may not progress to maldigestion, and ~20% of patients will present with symptoms of maldigestion without a history of abdominal pain. Despite steatorrhea, clinically apparent deficiencies of fat-soluble vitamins are surprisingly uncommon.

Up to 5% of patients do not have pain and instead present with exocrine (steatorrhea, weight loss) or endocrine (diabetes) pancreatic insufficiency. The disease tends to be progressive over time, even if the original cause (e.g., alcohol) is removed.

Diagnosis. The diagnosis may be suspected based on the clinical features but should be confirmed by tests that identify structural damage to the pancreas or derangements in pancreatic function.

Physical findings in these patients are usually unimpressive, so that there is a disparity between the severity of abdominal pain and the physical signs that usually consist of some mild tenderness. The diagnosis of early or mild chronic pancreatitis can be challenging because there is no biomarker for the disease. In contrast to acute pancreatitis, the serum amylase and lipase levels are usually not strikingly elevated in chronic pancreatitis. Elevation of serum bilirubin and

alkaline phosphatase may indicate cholestasis secondary to common bile duct stricture caused by chronic inflammation. Many patients have impaired glucose tolerance with elevated fasting blood glucose levels. The fecal elastase-1 and small-bowel biopsy are useful in the evaluation of patients with suspected pancreatic steatorrhea. The fecal elastase level will be abnormal and small-bowel histology will be normal in such patients. A decrease of fecal elastase level to <100 μg per gram of stool strongly suggests severe pancreatic exocrine insufficiency.

Chronic pancreatitis is a slowly progressive disease in which visible damage to the gland (e.g., on a CT scan) and functional failure (e.g., steatorrhea or diabetes) may not be apparent for years. All diagnostic tests are most accurate when the disease is far advanced, and all are far less accurate in the early stages of disease.

Tests of Pancreatic Structure. Plain abdominal radiographs may demonstrate diffuse or focal pancreatic calcification in patients with advanced chronic pancreatitis. Although specific for chronic pancreatitis, these findings are quite insensitive. Abdominal ultrasound is of limited utility because overlying gas often limits the ability to visualize the pancreas. An abnormal pancreatic duct, pancreatic calcifications, gland atrophy, or changes in echotexture are seen in about 60% of patients. CT is the most widely used diagnostic test for chronic pancreatitis, and high-quality images can be obtained of the pancreas and pancreatic duct. Characteristic findings include a dilated pancreatic duct, ductal or parenchymal calcifications, and atrophy. These structural changes take years to develop, so CT is not as accurate in early or less advanced disease. Like CT, MRI allows detailed images of the pancreas, and the addition of MRCP allows even better assessment of pancreatic duct morphology. At some centers, secretin is administered at the time of MRCP to allow better visualization of the pancreatic duct. ERCP provides the most detailed images of the pancreatic duct. Changes in the duct, including dilation, irregularity, ductal stones, and strictures, can be appreciated. These findings are not completely specific for chronic pancreatitis and can be seen in other situations, including with pancreatic cancer and in very elderly individuals. ERCP carries risk but has the advantage of providing both diagnostic and therapeutic impact. EUS allows very detailed images of pancreatic parenchyma and duct. A normal EUS essentially excludes chronic pancreatitis, whereas a very abnormal EUS is highly consistent with chronic pancreatitis.

Tests of Pancreatic Function. Serum trypsinogen (also called trypsin) is abnormally low in patients with far advanced chronic pancreatitis but is often normal in patients with less advanced disease. Levels lower than 20 ng/mL are seen in patients with chronic pancreatitis that is sufficient to cause functional failure (e.g., steatorrhea). Serum levels of amylase or lipase are not useful for chronic pancreatitis. Serum glucose levels will be elevated in those with endocrine insufficiency. Quantification of fat in stool during a 72-hour collection while on a high-fat diet can be used to document steatorrhea but is rarely performed. Qualitative analysis of fat with Sudan staining of a stool specimen has poor sensitivity and specificity. Fecal levels of pancreatic elastase are diminished to less than 100 $\mu\text{g/g}$ in patients with advanced chronic pancreatitis and steatorrhea. The test can be performed while patients are taking pancreatic enzyme therapy. For a pancreatic function test, a tube is passed into the duodenum, where pancreatic secretions are collected over the course of 1 hour in 15-minute aliquots and analyzed for bicarbonate concentration after a supraphysiologic dose of secretin is administered. A normal study is defined by at least one of the samples having a bicarbonate concentration of more than 80 mEq/L. The test becomes abnormal earlier in the disease process than any other test, so it is well suited to diagnose chronic pancreatitis earlier in its clinical course; however, it is not widely available. An alternative, using endoscopy instead of a tube, is possible but somewhat less sensitive.

As the disease advances over years, structural and functional damage accumulate to the point that essentially all diagnostic tests are positive. In most patients, the diagnosis is established by routine tests such as CT or MRI; EUS and ERCP are rarely needed for diagnostic purposes in patients with longstanding chronic pancreatitis. The diagnostic challenge lies with patients who present with a severe pain syndrome suggestive of chronic pancreatitis but who have a normal CT or MRI. In these patients, EUS is the best choice unless the physician has access to a secretin-based pancreatic function test. ERCP should not be used for purely diagnostic purposes because patients with a normal-appearing pancreas are particularly prone to complications, especially post-ERCP pancreatitis.

STRUCTURAL TESTS	FUNCTIONAL TESTS
Biopsy	Hormonal (secretin) test
Endoscopic ultrasound	Fecal elastase
Endoscopic retrograde cholangiopancreatography	Serum trypsin
Magnetic resonance imaging with magnetic resonance cholangiopancreatography	Fecal fat
Computed tomography	Blood glucose
Ultrasonography	
Plain x-ray	

Complications. Exocrine or endocrine insufficiency, pancreatic pseudocyst, malignancy, chronic abdominal pain, jaundice, diabetes mellitus/impaired glucose tolerance, gastroparesis, malabsorption/maldigestion, biliary stricture and/or biliary cirrhosis, portal hypertension, bacterial (abcess, parapancreatitis), systemic (renal failure, liver failure, DIC).

Treatment. Medical therapy starts with vigorous attempts to assist patients in stopping alcohol and tobacco.

- Abdominal pain: Most patients will require analgesics and adjunctive agents. If there is mild to moderate pain, acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDS) may bring relief. Ibuprofen, Naproxen are examples of NSAIDS. If these medications do not control the pain opioids such as Hydrocodone, Codeine, Methadone, Fentanyl, Oxycodone, Hydromorphone or Morphine can be prescribed. If they don't bring relieve, Tramadol, 50 mg, one to three times daily can be used. It may be helpful to use selective serotonin reuptake inhibitors (citalopram, fluoxetine, sertraline, paroxetine, and others), gabapentin (starting at 100 mg at night), or pregabalin (starting at 50 mg three times daily). Finally, pancreatic enzyme therapy may have some beneficial effect on pain. Autoimmune pancreatitis responds promptly to steroid therapy (usually 40mg of prednisone daily for 4 weeks, with a taper of 5 mg/week over the next 7 weeks), but relapse may occur, particularly in the biliary tree.

-Exocrine insufficiency: the treatment of steatorrhea with pancreatic enzymes is straightforward even though complete correction of steatorrhea is unusual. Enzyme therapy usually brings diarrhea under control and restores absorption of fat to an acceptable level and affects weight gain. Thus, pancreatic enzyme replacement has been the cornerstone of therapy. Recent data suggest that dosages up to 80,000–100,000 units of lipase taken during the meal may be necessary to normalize nutritional parameters in malnourished chronic pancreatitis patients, and some may require acid suppression with proton pump inhibitors. Enzyme therapy, which significantly reduces fecal fat levels and may reduce weight loss, is divided into enteric-coated capsules and non-enteric-coated tablets. Non-enteric-coated preparations, as noted previously, are not clinically available but theoretically are the agents of choice if the goal is to treat pain. However, the enteric-coated preparations are used more frequently for exocrine insufficiency because they are more potent and require fewer pills. Enzymes are identified by the lipase

content of the pill or capsule, although they all contain proteases and amylase as well. The goal of enzyme therapy, which is to administer at least 10% of normal pancreatic output with each meal, translates to approximately 30,000 IU of lipase with each meal. Most current products are measured in U.S. Pharmacopeia (USP) units, which are one third the amount of an international unit (IU) (e.g., up to 90,000 USP units of lipase with each meal). Because most patients are still producing some enzymes (including gastric lipase), it is usually not necessary to use the full dosage of 90,000 USP units with each meal. Enzymes should be split during the meal (e.g., equally split before, during, and immediately after the meal). Success of enzyme therapy is generally defined as weight gain and reduction or absence of visible oil in the stool. Failure of enzyme therapy is most often due to inadequate dose. Increasing the dose up to the full 90,000 USP units with meals and encouraging compliance are appropriate as a first step. Some enteric-coated preparations may not release sufficient enzymes in the small bowel unless they are used with an agent to reduce gastric acid. Some patients may not respond owing to the presence of a second disease that also causes malabsorption, such as small intestinal bacterial overgrowth. Recommended dose of lipase per one meal is 25000-40000 IU.

- Endocrine insufficiency: like exocrine insufficiency, diabetes mellitus is a very late complication of chronic pancreatitis, occurring years or decades after disease onset. Unlike type 1 diabetes mellitus, there is destruction of the entire islet, which reduces secretion of both insulin and glucagon.

- Surgical therapy: patients with a dilated pancreatic duct (generally >5 mm) are candidates for endoscopic and surgical therapy, which involves decompression of the dilated duct. Endoscopic ultrasound-guided celiac plexus block or neurolysis can help to relieve the pain. Thoracoscopic splanchnicectomy, endoscopic therapy (stent, stone removal, lithotripsy), such surgical therapy as pancreaticojejunostomy (modified Puestow operation), partial pancreatic resection (Whipple operation, duodenum-preserving pancreatic head resection, others), total pancreatectomy with islet cell autotransplantation can be performed in treatment according to present indications in patient.

Materials for self-control:

Situation tasks:

1. Patient P., 35 years old, complains of pressing epigastric pain in 1 hour after eating, heartburn, sour belch. He is considered to be ill during last 2 years. A pain in pyloroduodenal area presents upon the abdominal palpation. Upper endoscopy found an antral gastritis. What is the preliminary diagnosis? What additional tests are necessary?
2. Patient has symptoms of digestive disorder, such as fatty diarrhea in 4 hours after meal, abdominal pain, especially in upper left part. Diarrhea can be changed by constipation for 3-5 days. Moderate pain found in the choledochpancreatic area. The level of amylase in blood is normal. Survey sciagraphy: calcinates, located highly to newel. What is the probable diagnosis? What groups of preparations for treatment can be prescribed?

Tests:

1. A 27 y. o. man complains of pain in epigastrium which is reduced by meal. EGDS visualizes antral erosive gastritis, in biopsy material of antral mucous *Helicobacter Pylori* was detected. What is the most probable diagnose?

- A. Gastritis of type A
- B. Gastritis of type B

- C. Reflux - gastritis
- D. Menetrier's disease
- E. Rigid antral gastritis

2. 69 y. o. man complains of appetite loss, sensation of heaviness and bloating in epigastrium after meal, belching with air and smell of spoiled food, nausea. Achilia was established according to analysis of stomach secretion. Thinning of mucosa with vivid blood vessels was visualized on FGDS. What is the most probable diagnosis?

- A. Rigid gastritis
- B. Stomach cancer
- C. Atrophic gastritis
- D. Chronic colitis
- E. Non-ulcerative dysphagia

3. A 33 y. o. male patient was got to hospital. The patient is pale, after an attempt to stand up he complains of strong dizziness. There was coffee-like vomiting approximately an hour ago. BP- 90/60 mm Hg., pulse- 120 b/min. From anamnesis: the patient has been suffering from ulcer of stomach, which didn't disturb him for 4 years. An ulcer was visualized at upper endoscopy. Your diagnosis:

- A. Ulcer of stomach, complicated with bleeding
- B. Ulcer of duodenum, complicated with bleeding
- C. Erosive gastritis
- D. Acute pleurisy
- E. Acute myocardial infarction, abdominal form

4. A man, 21 years old, complains of periodic epigastric pain. According to performed examination, chronic gastritis with hyperacidity was found out. Prescribed treatment has positive results. What medicine is expedient to use for primary ulcer prophylaxis?

- A. Famotidine
- B. Cerucal
- C. Vicalin
- D. Maalox
- E. Gastrofarm

5. The 48 years old patient complains of periodic pain in epigastrium, without irradiation, heartburn, which amplify after meals, migraine and sleeplessness. After reception of 20 mg of rabeprazole during first two days these symptoms disappeared. For what disease this clinical picture is typical?

- A. Type A chronic gastritis
- B. Duodenal ulcer
- C. Functional dyspepsia
- D. Chronic pancreatitis
- E. Chronic hepatitis

6. 50 years old patient complains of pain attacks in the right subcostum, vomiting with bile, nausea. During last 5 years pain in epigastral area was persistent, which was associated with

nausea, violations of defecation, dryness in mouth. Objectively: pulse is 92/min., body overweight, tongue is coated with white fur, icteric scleras. Abdomen is soft, painful in the projection of gall bladder, local muscular tension in the right subcostum, positive Ker's symptom. In blood test: L - $9,6 \times 10^9/l$, blood sedimentation - 14 mm/h. What is the most credible previous diagnosis?

- A. Cholecystolithiasis
- B. Chronic gastritis, type A
- C. Dyskinesia of biliary tract
- D. Chronic acalculous cholecystitis
- E. Chronic hepatitis

7. 55 years old patient complains of pain attacks in the right subcostum, vomiting with bile, nausea. During last year pain in epigastral area, which was associated with nausea, violations of defecation, dryness in mouth were noticed. Objectively: pulse is 95/min., body overweight, tongue is coated with white fur, icteric scleras. Abdomen is soft, painful in the projection of gall bladder, local muscular tension in the right subcostum, positive Ker's symptom. In blood test: L - $9,6 \times 10^9/l$, blood sedimentation - 16 mm/h. What is the most informative method of examination to confirm the diagnosis?

- A. Ultrasonic research of gallbladder
- B. Scintigraphy of liver
- C. Bacteriological research of bile
- D. Cholecystography
- E. Retrograde cholangiopancreatography

8. 32 years old woman noticed periodic attacks of pain in the right subcostum, which can be relieved by no-shpa. Pain is not always related with meal, sometimes it appears at agitation, accompanied with pain in heart, palpitation. Objectively: emotional lability, palpation of abdomen detected painfulness in the area of gall bladder. What is the most reliable diagnosis?

- A. Dyskinesia of biliary tract
- B. Chronic cholecystitis
- C. Chronic cholangitis
- D. Chronic pancreatitis
- E. Duodenitis

9. A 68 years old patient has been suffering from chronic pancreatitis for 35 years. During the last 5 years he has been observing because of pain syndrome, abdominal bloating, frequent defecations up to 3-4 times a day (feces are greyish, glossy, with admixtures of undigested food), progressing weight loss. The symptoms are caused by:

- A. Exocrine pancreatic insufficiency
- B. Endocrine pancreatic insufficiency
- C. Syndrome of lactase deficiency
- D. Irritable bowels syndrome
- E. Chronic enterocolitis

10. A 40-year-old woman has been suffering from chronic pancreatitis for the last 8 years. Lately she has been noticing an increase in daily feces with foul smell, abdominal

distention, gurgling. The patient complains of diarrhea, weakness, fatigability, loss of appetite, loss of weight. What syndrome can be suspected in this case?

- A. Irritable colon
- B. Malabsorption
- C. Maldigestion
- D. Exudative enteropathy
- E. Endocrine gland failure

Correct answers for the situation tasks:

1. Chronic gastritis. Determination of H. pylori.
2. Chronic pancreatitis. Enzymes, H₂-blockers, antispasmodics, analgetics.

The answers for the tests:

- 1-B, 2-C, 3-A, 4-A, 5-C, 6-A, 7-A, 8-A, 9-A, 10-B.

Recommended literature:

1. Goldman's Cecil medicine / [edited by] Lee Goldman, Andrew I. Schafer. – 24th ed. USA 2012, Elsevier p. 2569
2. Harrison's Principles of Internal Medicine / D. Kasper, A. Fauci, S. Hauser, D. Longo. -19 ed. – N.Y.: McGraw-Hill Professional, 2015. - Vol. 1, Vol.2.-3000 p.
3. Maastricht V/Florence Consensus Report on Managing Helicobacter pylori Infection
<http://www.jwatch.org/na42519/2016/10/20/maastricht-v-florence-consensus-report-managing>
- 4.3. Rome IV criteria: functional gastrointestinal disorders.
<http://theromefoundation.org/wp-content/uploads/gallbladder-and-sphincter-of-oddi-disorders.pdf>
5. <http://www.imagingpathways.health.wa.gov.au/index.php/imaging-pathways/gastrointestinal/gastrointestinal/chronic-abdominal-pain#teaching-points>

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