Cholelithiasis, chronic cholecystitis, biliary dyskinesia

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Plan of lecture

- Cholelithiasis: etiology, pathogenesis, diagnosis, treatment;
- Chronic cholecystitis: etiology, pathogenesis, diagnosis, treatment;
- Biliary dyskinesia: etiology, pathogenesis, diagnosis, treatment;

Cholelithiasis

- Cholelithiasis involves the presence of gallstones, which are concretions that form in the biliary tract, usually in the gallbladder (Douglas M Heuman, Anastasios A Mihas, Anastasios A Mihas, Jeff Allen Cholelithiasis. Medscape. https://emedicine.medscape.com/article/175667-overview

Etiology and pathogenesis of cholelithiasis

- Cholelithiasis by etiology and pathogenesis; diagnosis; additional investigation is presented on visual programming language “Dragon” [Parondzhanov VD. How to improve the work of the mind. Algorithms without programming - it's easy! M.: Delo, 2001: 360] (fig. 1,2,3).

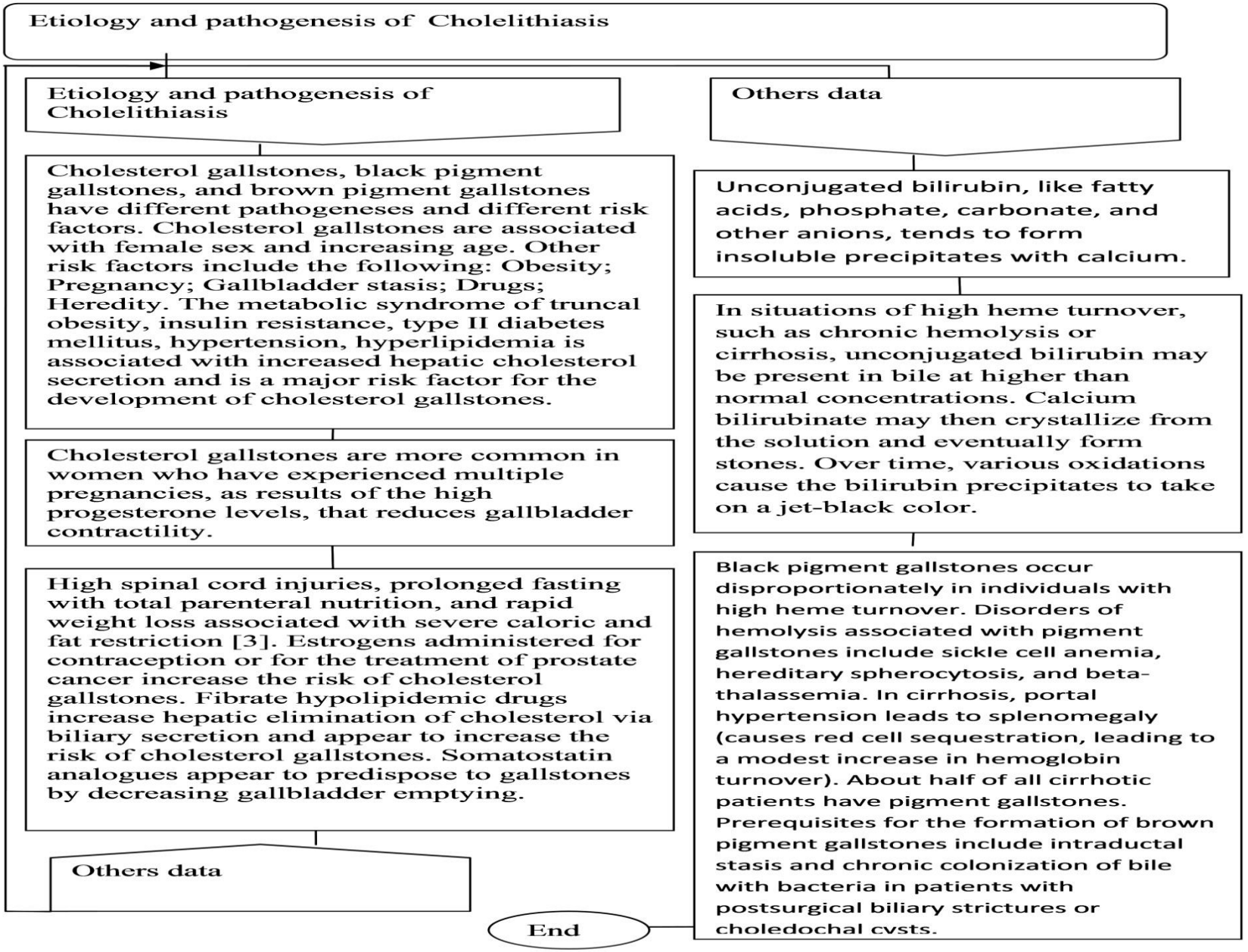
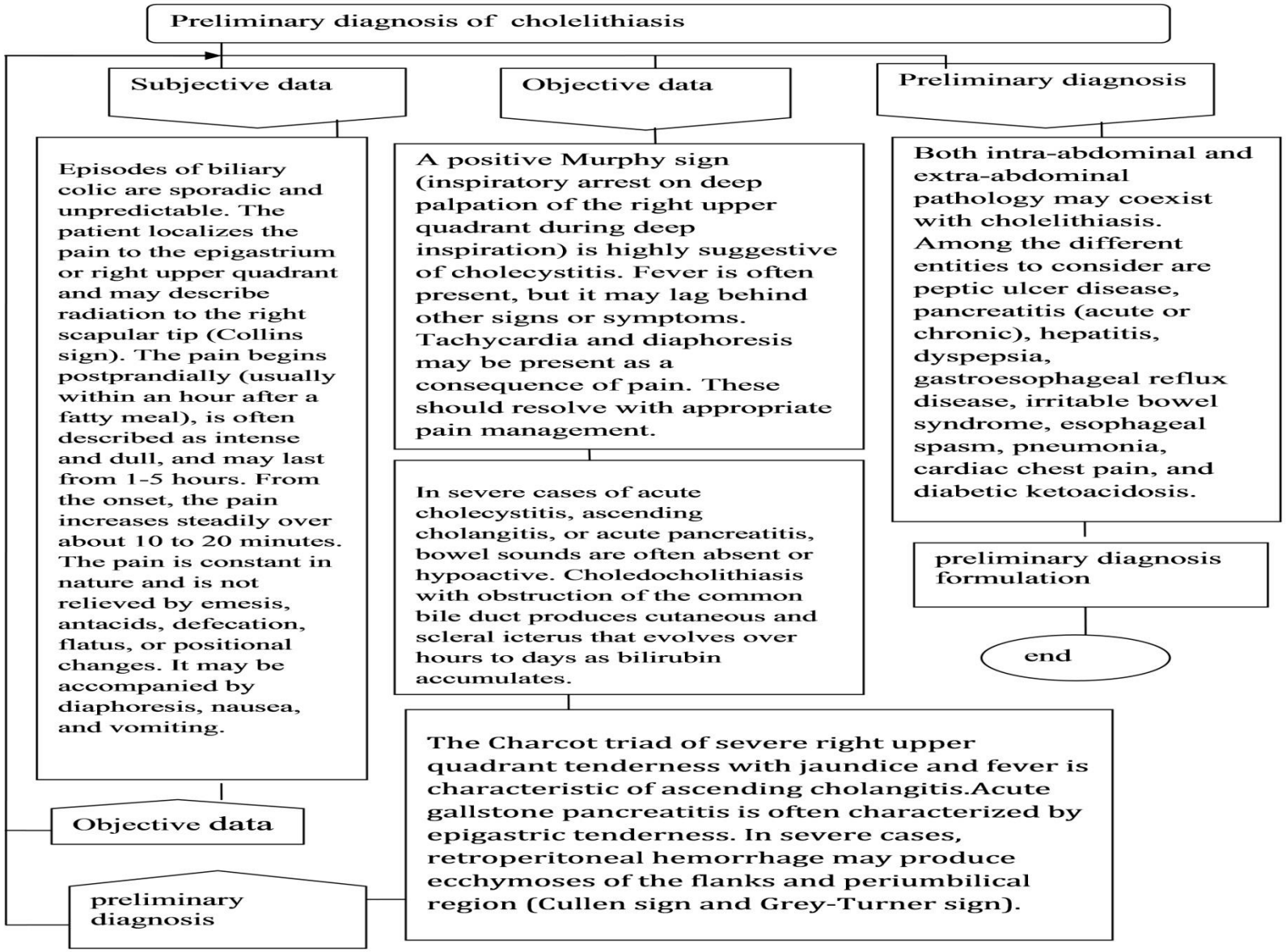
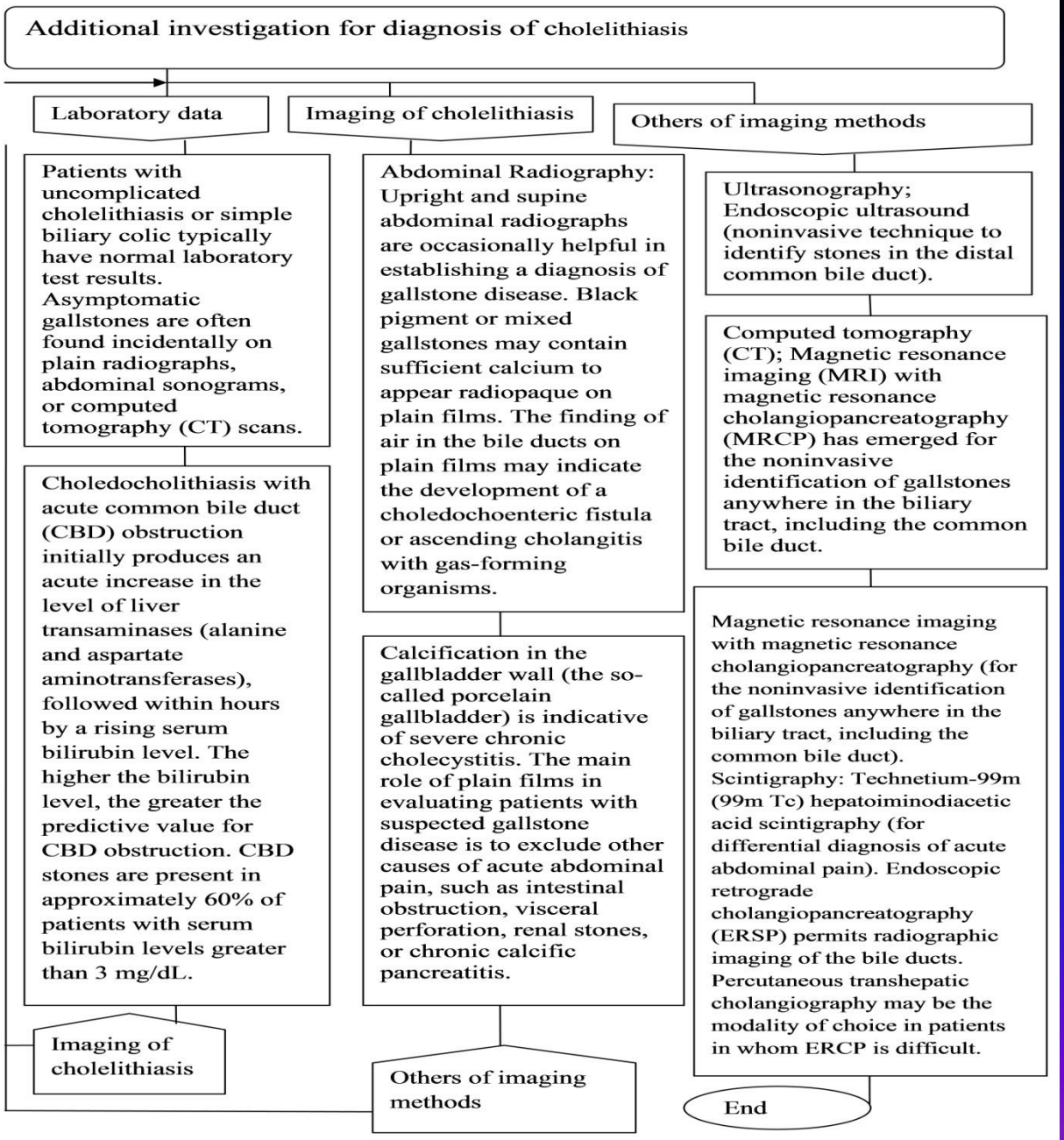


Fig. 1. Etiology and pathogenesis of cholelithiasis

Preliminary diagnosis of cholelithiasis is presented on visual programming language "Dragon" [2] (fig. 2).




Additional investigation for diagnosis of cholelithiasis
Laboratory data
Imaging of cholelithiasis
Others of imaging methods
Patients with uncomplicated cholelithiasis or simple biliary colic typically have normal laboratory test results. Asymptomatic gallstones are often found incidentally on plain radiographs, abdominal sonograms, or computed tomography (CT) scans.
Choledocholithiasis with acute common bile duct (CBD) obstruction initially produces an acute increase in the level of liver transaminases (alanine and aspartate aminotransferases), followed within hours by a rising serum bilirubin level. The higher the bilirubin level, the greater the predictive value for CBD obstruction. CBD stones are present in approximately 60% of patients with serum bilirubin levels greater than 3 mg/dL.
Imaging of cholelithiasis
Abdominal Radiography: Upright and supine abdominal radiographs are occasionally helpful in establishing a diagnosis of gallstone disease. Black pigment or mixed gallstones may contain sufficient calcium to appear radiopaque on plain films. The finding of air in the bile ducts on plain films may indicate the development of a choledochoenteric fistula or ascending cholangitis with gas-forming organisms.
Calcification in the gallbladder wall (the so-called porcelain gallbladder) is indicative of severe chronic cholecystitis. The main role of plain films in evaluating patients with suspected gallstone disease is to exclude other causes of acute abdominal pain, such as intestinal obstruction, visceral perforation, renal stones, or chronic calcific pancreatitis.
Others of imaging methods
Ultrasonography; Endoscopic ultrasound (noninvasive technique to identify stones in the distal common bile duct).
Computed tomography (CT); Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) has emerged for the noninvasive identification of gallstones anywhere in the biliary tract, including the common bile duct.
Magnetic resonance imaging with magnetic resonance cholangiopancreatography (for the noninvasive identification of gallstones anywhere in the biliary tract, including the common bile duct). Scintigraphy: Technetium-99m (99m Tc) hepatoiminodiacetic acid scintigraphy (for differential diagnosis of acute abdominal pain). Endoscopic retrograde cholangiopancreatography (ERSP) permits radiographic imaging of the bile ducts. Percutaneous transhepatic cholangiography may be the modality of choice in patients in whom ERCP is difficult.
End

Medical dissolution of gallstones

- Ursodeoxycholic acid (ursodiol) is a gallstone dissolution agent [Douglas M Heuman, Anastasios A Mihas, Anastasios A Mihas, Jeff Allen Cholelithiasis. Medscape. https://emedicine.medscape.com/article/175667-overview]. In humans, long-term administration of ursodeoxycholic acid reduces cholesterol saturation of bile, both by reducing liver cholesterol secretion and by reducing the detergent effect of bile salts in the gallbladder (thereby preserving vesicles that have a high cholesterol carrying capacity) [https://emedicine.medscape.com/article/175667-overview]. Desaturation of bile prevents crystals from forming and, in fact, may allow gradual extraction of cholesterol from existing stones [https://emedicine.medscape.com/article/175667-overview].

Medical dissolution of gallstones

- In patients with established cholesterol gallstones, treatment with ursodeoxycholic acid at a dose of 8-10 mg/kg/d PO divided bid/tid may result in gradual gallstone dissolution [https://emedicine.medscape.com/article/175667-overview]. This intervention typically requires 6-18 months and is successful only with small, purely cholesterol stones [https://emedicine.medscape.com/article/175667-overview]. Patients remain at risk for gallstone complications until dissolution is completed [https://emedicine.medscape.com/article/175667-overview]. The recurrence rate is 50% within 5 years [https://emedicine.medscape.com/article/175667-overview]. Moreover, after discontinuation of treatment, most patients form new gallstones over the subsequent 5-10 years [https://emedicine.medscape.com/article/175667-overview].

Treatment of Patients with Symptomatic Gallstones

- Cholecystectomy;
- Open versus laparoscopic cholecystectomy;
- Cholecystostomy;
- Endoscopic sphincterotomy.

Chronic cholecystitis

- Chronic cholecystitis refers to inflammation of a gallbladder of bacterial origin mainly, that occurs under presence of biliary dyskinesia, gallstones, parasite infections.

  Etiology:

  Main causes: Opportunistic pathogenic infections (E.coli, coccal flora), other microbial causes (Proteus, Pseudomonas aeruginosa, etc.). Bacteria can get to gallbladder by contact path from the small intestine, or by hematogenic and lymphogenic path from any site of chronic inflammation.

Chronic cholecystitis

- Additional causes:
  Hypotonic and atonic biliary dyskinesias with stagnation of bile,
  hypodynamia + unbalanced diet, pancreatic reflux, genetic factors, parasite infections

Pathogenesis:

- Development of is gradual. Entry of microbial flora against a background of gallbladder hypotonia causes catarrhal inflammation of mucosa. Inflammation progresses to submucosa and muscular layer of gallbladder, where it causes infiltration and activation of connective tissue. These processes lead to deformation of gallbladder and pericholecystitis development. In case of different unfavourable circumstances chronic cholecystitis may get exacerbated up to acute cholecystitis.

Clinical Data

- Pain in right hypochondrium zone and and epigastrium, can last for hours, increases after fatty, fried, spicy food, eggs, wine, beer. Pain radiates to right scapula or shoulder.
  Upper abdominal tenderness may be present, but usually fever is not. Fever suggests acute cholecystitis. However, subfebrile body temperature may be present. Once episodes begin, they are likely to recur.
  Bitter taste in mouth in the morning. Nausea, belching, bloating.
  Bowel movement disorders – alternation of constipations and diarrheas

Diagnosis by additional data:

- *Ultrasonography.*
  Ultrasonographic criteria of inflammation in GB:
  o Thickness of wall of gallbladder > 4 mm in the absence of liver and kidney pathology, and congestive heart failure;
  o Increase of gallbladder size over 5 cm above the normal for the corresponding age;

Diagnosis by additional data:

- o Presence of sonographic Murphy's sign;
  o Presence of paracystic hypoechogenic limbus (edema of GB wall).
  Next: Cholecystography.
  The following symptoms are characteristicfor patients with Chronic cholecystitis:
  o Absence of gallbladder shadow;
  o Derangements of concentration ability and motility of gallbladder (delayed emptying);
  o Deformation of gallbladder wall.

Diagnosis by additional data:

- *Duodenal investigation* – can be conducted only if gallstones are absent! Helps to access motor function of Chronic cholecystitis
  Provides 3 portions of bile for further studying of bile characteristics:
  o Microscopy – signs of inflammation and lithogenicity of bile;
  o Culture – determination of bacterial flora;
  o Biochemical analysis – determination of cholesterol, bile acids, phospholipids in bile.

Treatment (phase of exacerbation)

- *Antibiotics.* Indications for antibiotic therapy: presence of clinical and laboratory signs of inflammation, positive results of bile culture, cholangitis.
  - Ciprofloxacin
  - Cefotaxime
  - Doxycycline
  - Amoxicillin
  - Tinidazole

Treatment (phase of exacerbation)

- *Symptomatic therapy:*

  1. Prokinetic agents – domperidone
  2. Spasmolytics:

  - mebeverine

  3. Bile-expelling medications (cholagogues):

  - Preparations that stimulate cholepoietic function of liver (choleretics):

  - Preparations of bile acids: cholenzym, liobilum
  - Synthetic preparations: oxaphenamide, cyclovalone

The Inflammatory Cascade in IBD

- Preparations of herbal origin: strawflower extract, peppermint extract, corn stigmas
  - Preparations that improve secretion of bile by increasing of its aqueous component (hydrocholeretics) – mineral waters
  Preparations that stimulate biliary excretion:
  - Cholekinetics (inrease tonus of gallbladder and decrease tonus of bile ducts): xylite, sorbite, magnesium sulfate
- - Cholespasmolytics: anticholinergic drugs, aminophylline.
  - UDCA – 8-10 mg/kg/day (if microlites and/or stagnation of bile are present);
  - Herbal hepatoprotectors with bile-expelling properties.

Treatment (phase of ***remission)***

- Diet – meals 5-6 times a day, exclude fatty, fried, spicy, smoked food, pickles, alcohol.
- Phytotherapy. Mineral water. Physiotherapy. Exercise therapy.

Functional biliary disorders

- **Biliary dyskinesia** is a symptomatic functional disorder of the gallbladder whose precise etiology is unknown. It may be due to metabolic disorders that affect the motility of the GI tract, including the gallbladder, or to a primary alteration in the motility of the gallbladder itself. Biliary dyskinesia presents with a ***symptom complex*** that is similar to those with biliary colic:
  - Episodes of right upper quadrant pain
  - Severe pain that limits activities of daily living
  - Nausea associated with episodes of pain

The presumed mechanism

- ***The presumed mechanism*** for biliary pain is obstruction leading to distension and inflammation. This might result from incoordination between the gall bladder and either the cystic duct or the sphincter Oddi due to increased resistance or tone. Central projections from visceral nociceptors to the thalamus and cortex might lead to a more excitable state with hyperalgesia (severe pain evoked by mildly painful stimuli).
  Persistent central excitability might then result in allodynia where innocuous stimuli produce pain

Diagnosis

- In order to diagnose biliary dyskinesia, the patient should have right upper quadrant pains similar to biliary colic but have a normal ultrasound examination of the gallbladder (no stones, sludge, microlithiasis, gallbladder wall thickening or common bile duct dilation). For patients who are suspected to have biliary dyskinesia, the ***Rome IV diagnostic criteria*** for functional gallbladder disorders should be considered.

CLINICAL EVALUATION
Screening tests

- ***Laboratory***
  Tests of liver biochemistries and pancreatic enzymes must be normal.
  The following tests are necessary to eliminate calculous biliary disease, which can produce similar symptoms.
  Ultrasonography
  Transabdominal ultrasonography of the upper abdomen is mandatory. The biliary tract and pancreas should be normal and gallstones or sludge absent.
  Ultrasonography readily detects stones equal to or greater than 3–5 mm in diameter or biliary sludge within the gall bladder, but it has a low sensitivity for smaller stones or biliary microcrystals.

CLINICAL EVALUATION
Screening tests

- Endoscopic ultrasonography seems to be more sensitive than traditional transabdominal ultrasonography in detecting microlithiasis (tiny stones <3 mm) and sludge within the biliary tract, but the recommendation for its inclusion in standard workups requires further evaluation.

CLINICAL EVALUATION
Screening tests

- ***Microscopic bile examination***
  This procedure is necessary to exclude microlithiasis as a cause. Gallbladder bile can be obtained directly at the time of endoscopic retrograde cholangiopancreatography (ERCP) or by aspiration from the duodenum following stimulation (e.g., cholecystokinin (CCK)-8 5 ng/kg i.v. over 10 minutes, or 50 ml $MgSO_4$ instilled into the duodenum). Two types of deposits may be evident: (1) cholesterol microcrystals, which are birefringent and rhomboid shaped, best visualized by polarizing microscopy. Their presence provides a high diagnostic accuracy for microlithiasis; and (2) bilirubinate granules, which appear as red-brown deposits under conventional light microscopy.

Role of infection

- ***Endoscopy***
  In the presence of normal laboratory and ultrasonographic findings, endoscopy is usually indicated to exclude upper gastrointestinal diseases.
- **Tests for gall bladder dysfunction**
  CCK–cholescintigraphy assessment of gall bladder emptying
  This study continuously monitors the hepatic excretion of a radiopharmaceutical into the gall bladder and duodenum, using computer assistance to quantitate changes in radioactivity over the gall bladder. Filling of the gall bladder with radionuclide indicates patency of the cystic duct. Gall bladder emptying is expressed as the gall bladder ejection fraction, the percentage decrease in net gall bladder counts following CCK infusion (CCK-8 slowly infused at 20 ng/kg over 30 minutes).

- Reduced emptying, which defines gall bladder dysfunction, can arise from either depressed gall bladder contraction or increased resistance such as elevated tone in the sphincter Oddi. Furthermore, several other conditions that do not necessarily present with biliary colic can be associated with reduced gall bladder emptying. These range from intrinsic gall bladder disease (stones, cholecystitis) to neural and metabolic disorders, drugs, and even the irritable bowel syndrome. Although biliary-type pain is rarely elicited, the test appears to be a marker of this biliary disorder, based on evidence of the beneficial effect of cholecystectomy.

Transabdominal ultrasonography

This test measures gall bladder volume, which if followed serially after a stimulus (meal or CCK), reflects emptying. The technique is operator dependent and the results may not be reproducible in different centers. Ultrasonographic assessment of gall bladder emptying is currently not the standard for gall bladder dysfunction.

Pain provocation test

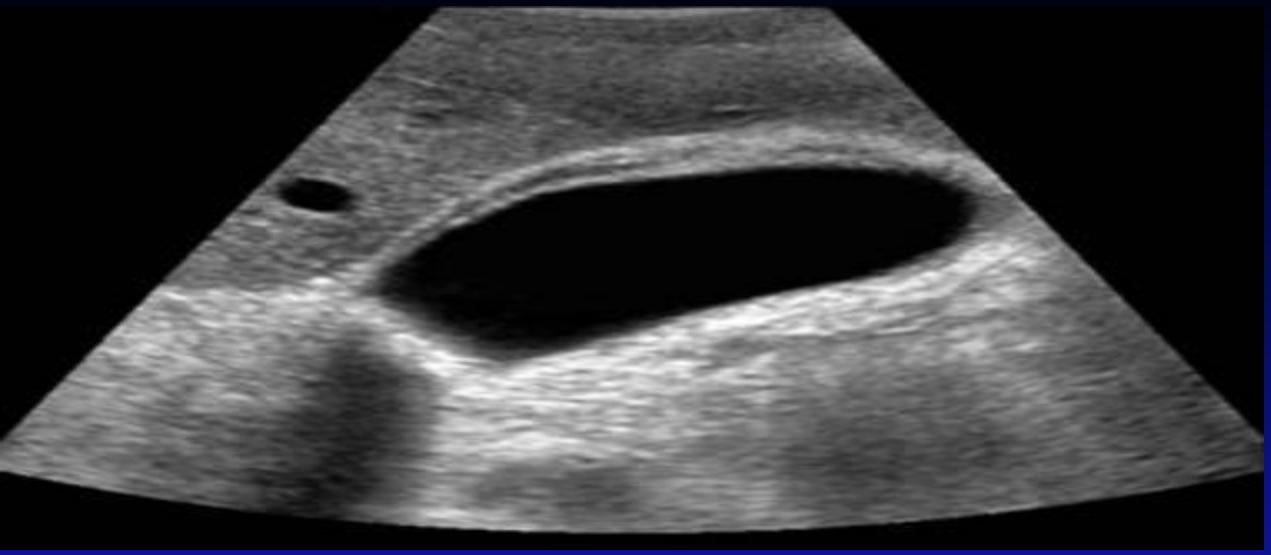
Stimulation tests with CCK to duplicate biliary pain have been used historically as a diagnostic investigation. Such tests have low sensitivity and specificity in selecting patients with gall bladder dysfunction who respond to therapy. This may relate to problems in the subjective assessment of pain and the use of bolus injections of CCK, which can induce intestinal contractions.

Diagnostic workup

- Biliary tract symptoms should be evaluated by liver biochemistry, pancreatic enzymes, and ultrasound examination of the abdomen. As a general recommendation we suggest that invasive investigations should be withheld in those patients in whom episodes are infrequent and not accompanied by increased liver function tests.
  - If no abnormal findings are detected, CCK–cholescintigraphy should be used to assess gall bladder emptying. Abnormal gall bladder emptying (<40% ejection) indicates gall bladder dysfunction.
  - If there is no obvious cause for impaired emptying, cholecystectomy is appropriate treatment.
  - If gall bladder emptying is normal, bile for microscopic examination to detect cholesterol microcrystals and bilirubinate can be obtained by duodenal drainage, at the time of gastrointestinal endoscopy or during ERCP. Magnetic resonance cholangiography or endoscopic ultrasound, where available, can be performed to detect lithiasis.
  - If gall bladder emptying is normal, ERCP should be considered. In the absence of common bile duct stones or other abnormalities, SO manometry should be considered if clinically indicated. Evidence of SO dysfunction is an indication for treatment, which may include sphincterotomy.

Treatment strategies

- 1. Altering gall bladder motor function (use of motility agents which enhance gall bladder contractility or ursodeoxycholic acid which worsens motility yet lessens the likelihood of biliary pain);
- 2. Reducing visceral hyperalgesia or inflammation (non-steroidal antiinflammatory drugs)
- 3. Cholecystectomy. Laparascopic cholecystectomy retains a role in the treatment of gall bladder dysfunction



Cholecystitis with small stones in the gallbladder neck. Classic acoustic shadowing is seen beneath the gallstones.
The gallbladder wall is greater than 4 mm. Image courtesy of DT Schwartz. (Douglas M Heuman, Anastasios A Mihas, Anastasios A Mihas, Jeff Allen Cholelithiasis. Medscape. https://emedicine.medscape.com/article/175667-overview)