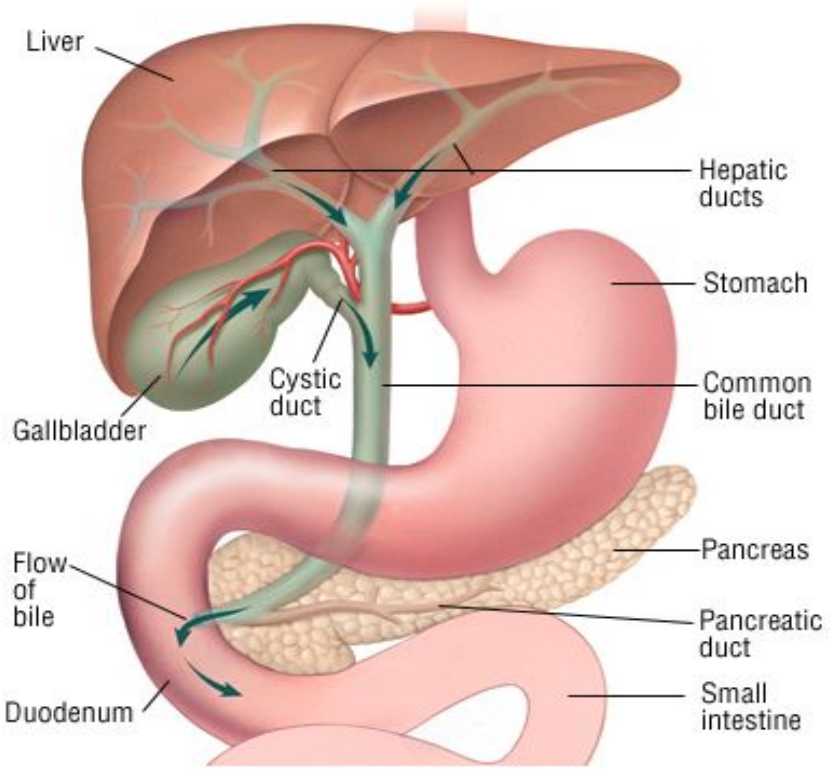
Obstructive jaundice and cholangitis

Professor Eduard I. Galperin

Anatomy of the bile ducts



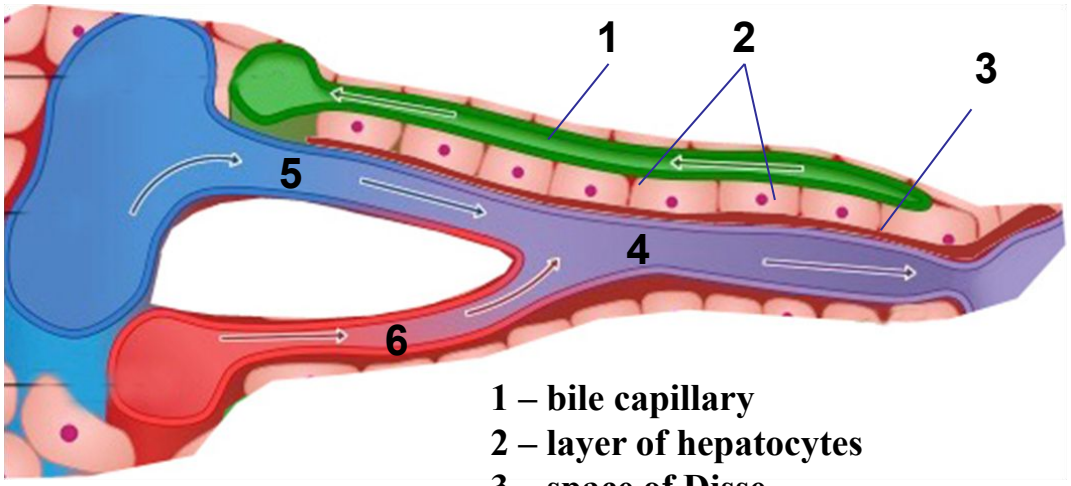
- **Anatomy and flow of bile. Sphincter of Oddi regulates bile flow. Liver secretes bile constantly, closed sphincter of Oddi ensures filling of gallbladder, open sphincter is followed by bile drainage from the gallbladder towards duodenum.**

  Bile duct obstruction causes biliary hypertension.

  Reliability of biliary system – bile duct lumen of 1 mm is enough for daily bile passage.

Bile Duct Diseases - Harvard Health

Anatomy of hepatic lobule



1 – bile capillary
2 – layer of hepatocytes
3 – space of Disse
4 – sinusoid
5 – portal vein branch
6 – hepatic artery branch

Substrates from sinusoid normally pass into the hepatocytes. After metabolic transformation, some metabolites (bile, bile acids, etc.) pass into the bile capillary. A part of metabolized substrates return to sinusoid and pass into systemic circulation.

Cholestasis

- **Definition: any impairment of secretion and release of bile from the hepatocyte to the major duodenal papilla is called cholestasis. Thus, this concept includes both biochemical and mechanical disorders.**
- **Cholestasis is a universal liver reaction against any type of lesion (ischemic, toxic, obstructive, metabolic, autoimmune).**
- **Types of cholestasis: extrahepatic (biliary hypertension, obstructive jaundice), intrahepatic, combined.**

Cholemia

- **Homeostasis disorders: vascular dilatation, reduced peripheral vascular resistance and total blood volume, bradycardia, vagal effects, reduced renal glomerular filtration.**
- **Dysfunction of RES (80% of cells in liver), Kupffer cells, inflammatory cytokine release (TNFα, IL6, IL8, etc.), endothelial dysfunction.**

Acholia

- **Acholia is followed by advanced bacterial colonization of bowel, release of toxins and their translocation into portal blood. One microbe decays to form 3 million molecules of lipopolysaccharide toxin (LPS).**
- **Functional overload of Kupffer cells associated with cholemia and advanced flow of microbes and toxins causes their partial dysfunction that leads to translocation of bacteria and toxins into systemic circulation, development of systemic inflammatory response and multiple organ failure.**

Jaundice is a universal liver response to adverse effects resulting dramatic changes in various systems.

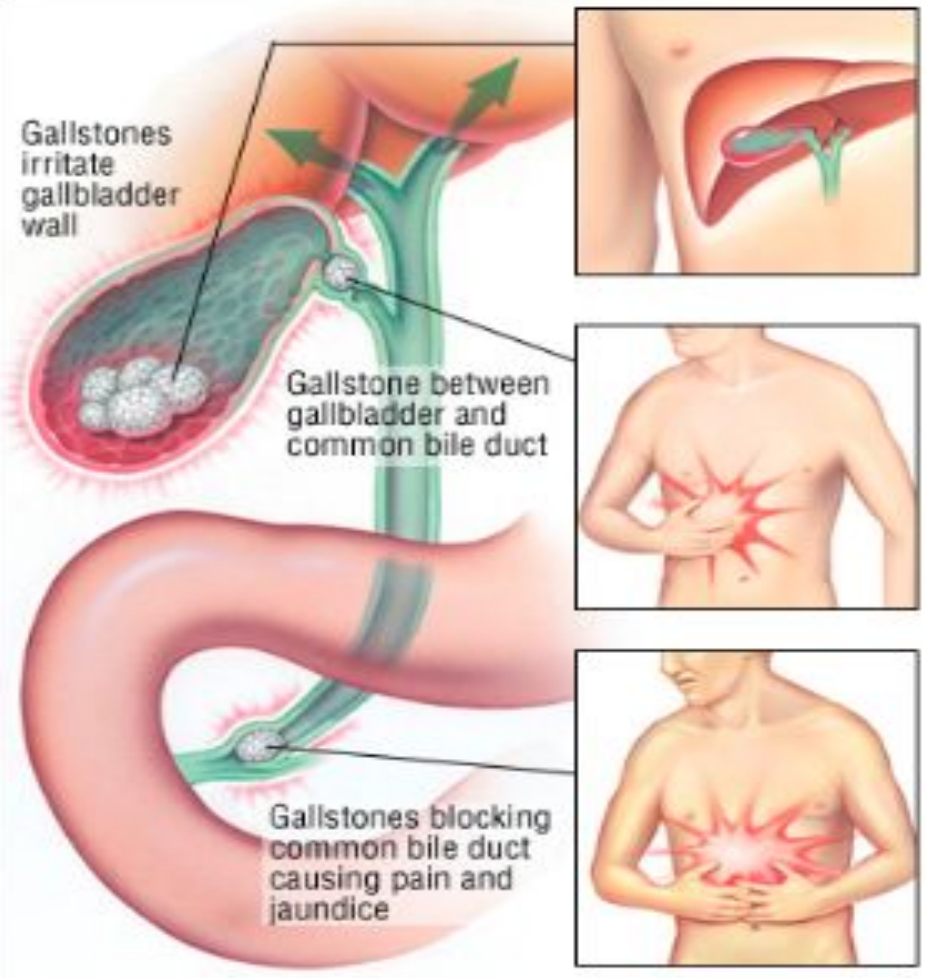
Painful and painless obstructive jaundice

Various rates of biliary hypertension development (fast, sudden or slow, gradual) determine occurrence of painful or painless obstructive jaundice. Sudden biliary hypertension is followed by acute pain in the right upper abdominal quadrant. Slow progression of biliary hypertension determines painless jaundice. Fast development of biliary hypertension is mainly observed in cholangiolithiasis, a slow one – in patients with bile duct tumors.

PAINFUL OBSTRUCTIVE JAUNDICE

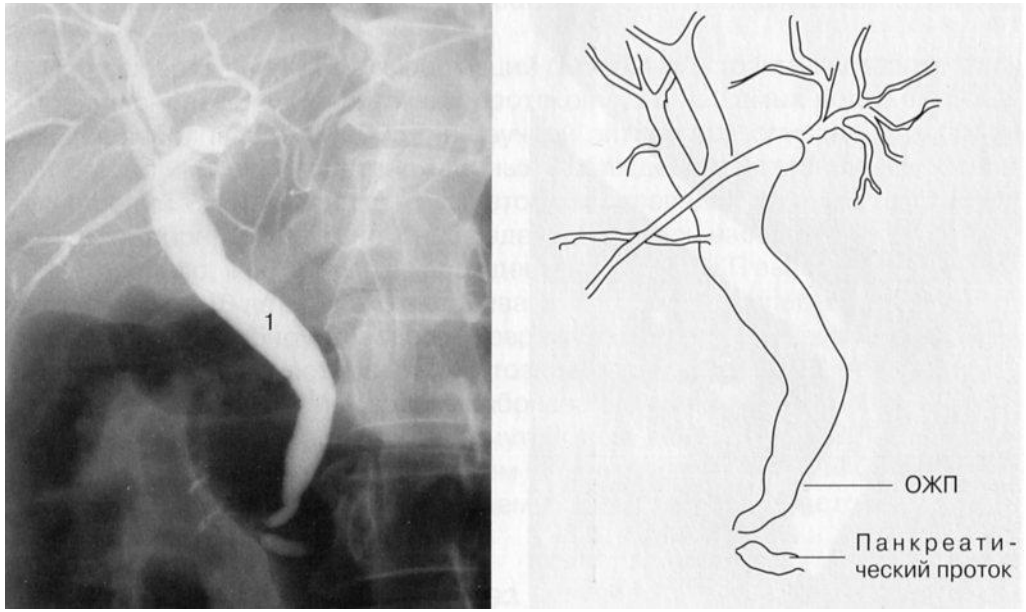
Cholangiolithiasis

1. Gallstone migration from the gallbladder.
2. Obstruction of common hepatic duct and common bile duct.
3. Obstruction of major duodenal papilla.

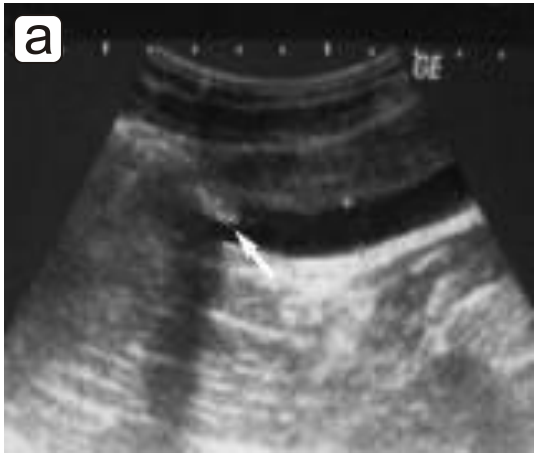


Stenosis of major duodenal papilla

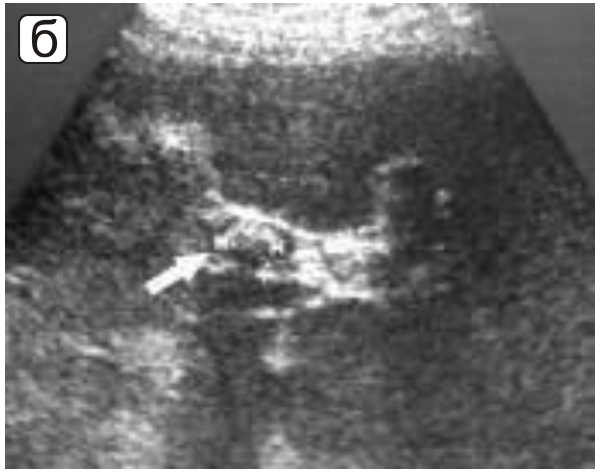
- **Causes:** cholangitis, pancreatitis, instrumental injury, gallstone passage, parapapillary diverticulum, functional disorders of the sphincter of Oddi.
- **Morphological changes:** fibrosclerotic disorders.
- **Symptoms:** pain, intermittent jaundice, urine and stool discoloration.
- **Diagnosis:** endoscopic examination of major duodenal papilla, ERCP, PTC, manometry.
- **Treatment:** endoscopic or surgical intervention for severe stenosis.



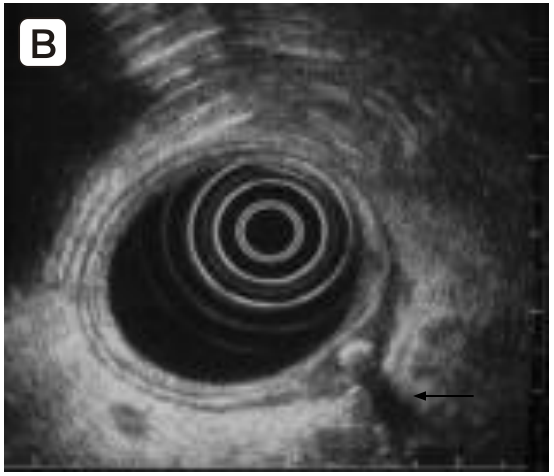
Choledocholithiasis. Ultrasound



а – ultrasound: common bile duct enlargement and calculus (arrow).



б – ultrasound: calculus inside the common bile duct (arrow).

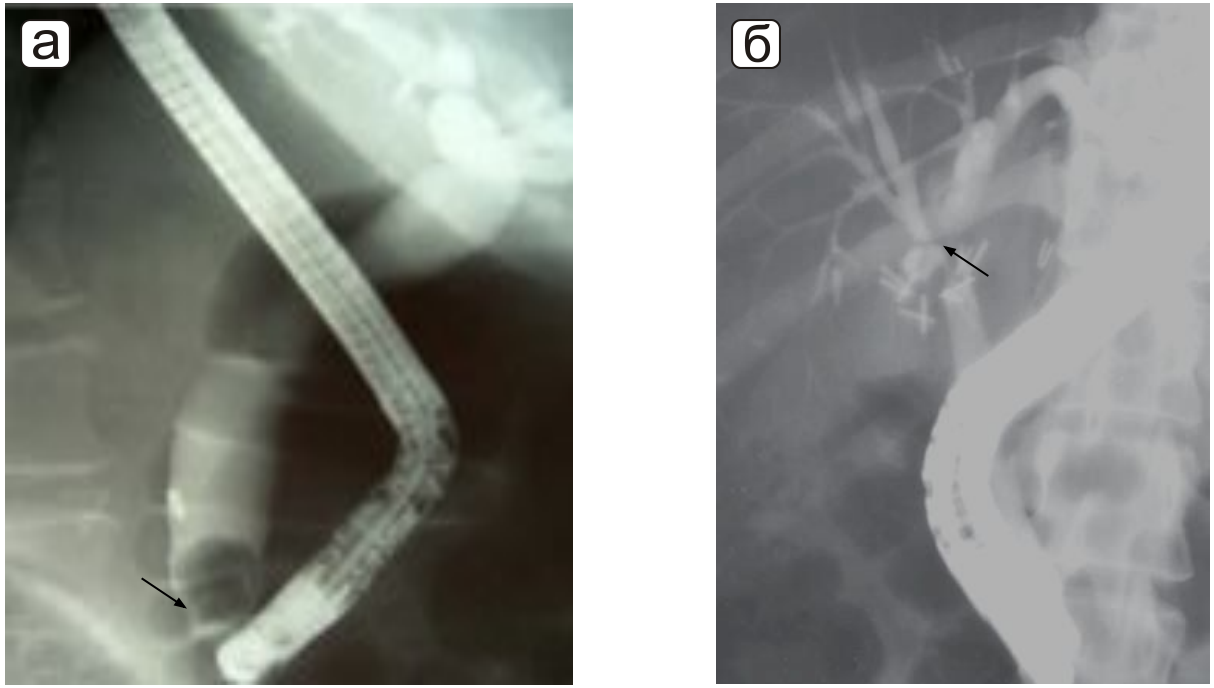


в – endoscopic ultrasound: a small calculus is visualized (arrow).

- **Dilatation of the bile ducts, doubling of the tubular structure**
- **Calculi in the bile ducts**
- **Endoscopic ultrasound – small calculi**

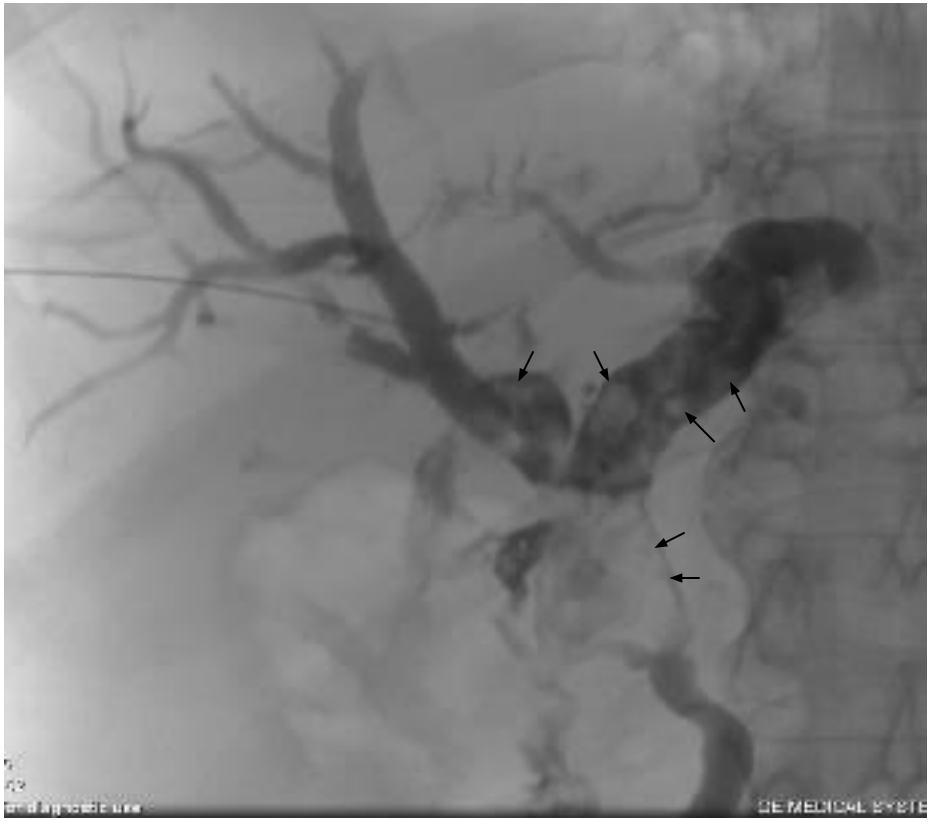
Sensitivity of ultrasound – 28-50%, endoscopic ultrasound– 98%.

ERCP



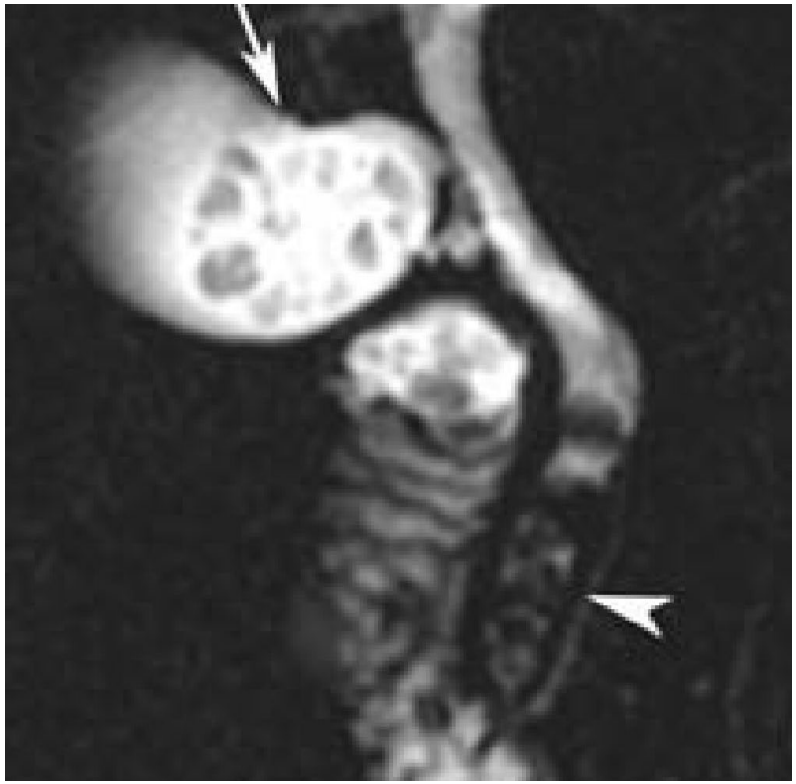
ERCP – diagnosis of calculi (а, arrow), hepatic duct injury after laparoscopic surgery (б, arrow).
Sensitivity – 89-98%.

PTC



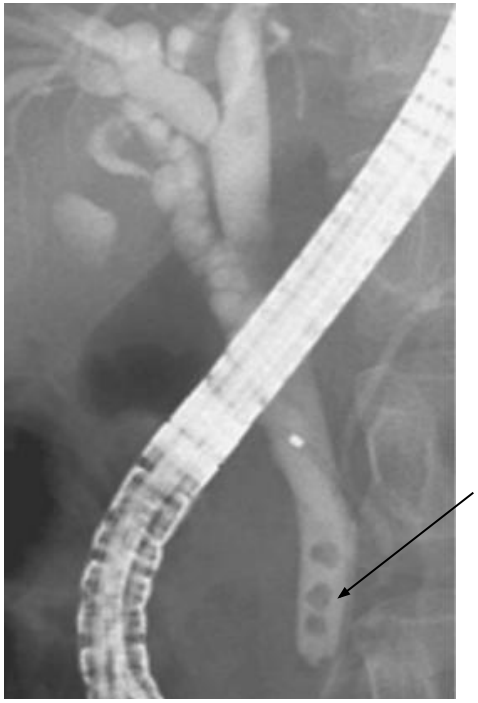
Mirizzi syndrome. Hepatic duct calculi.
Sensitivity - 90-100%.

MRCP. MR-cholangiography



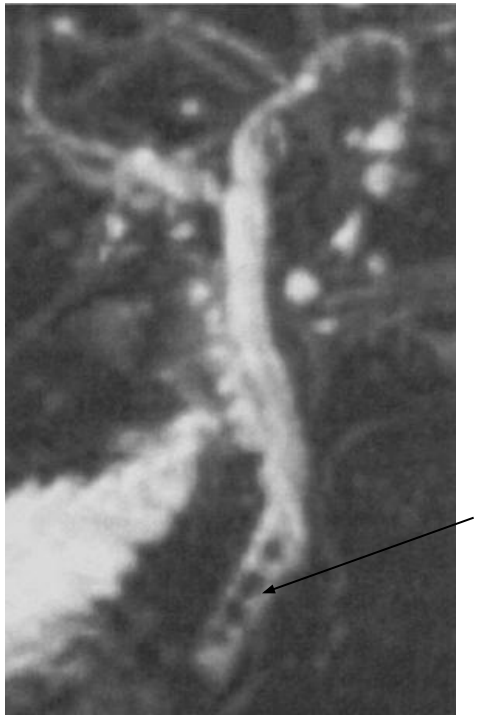
Imaging of gallbladder, bile ducts and calculi (arrows) without contrast enhancement. Sensitivity 85–88%.

ERCP vs. MRCP



ERCP

A relatively invasive method requires contrast agent injection into the bile ducts, biliary hypertension and irradiation.

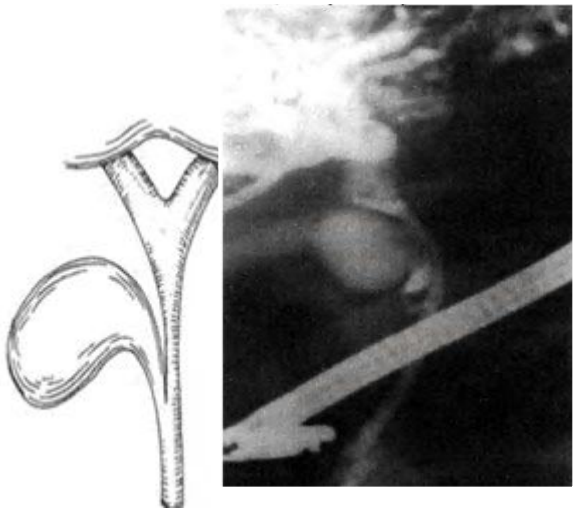


MRCP

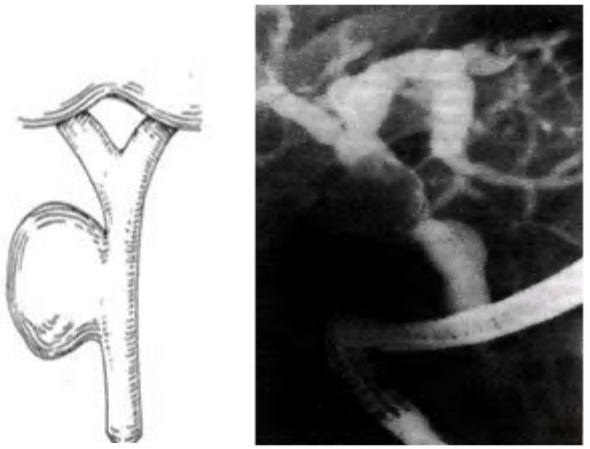
Non-invasive method without the need for direct contrast enhancement of the bile ducts.
Less clear image, but no irradiation.

Images were obtained from the same patient. Calculi were removed via endoscopic approach.

Mirizzi syndrome

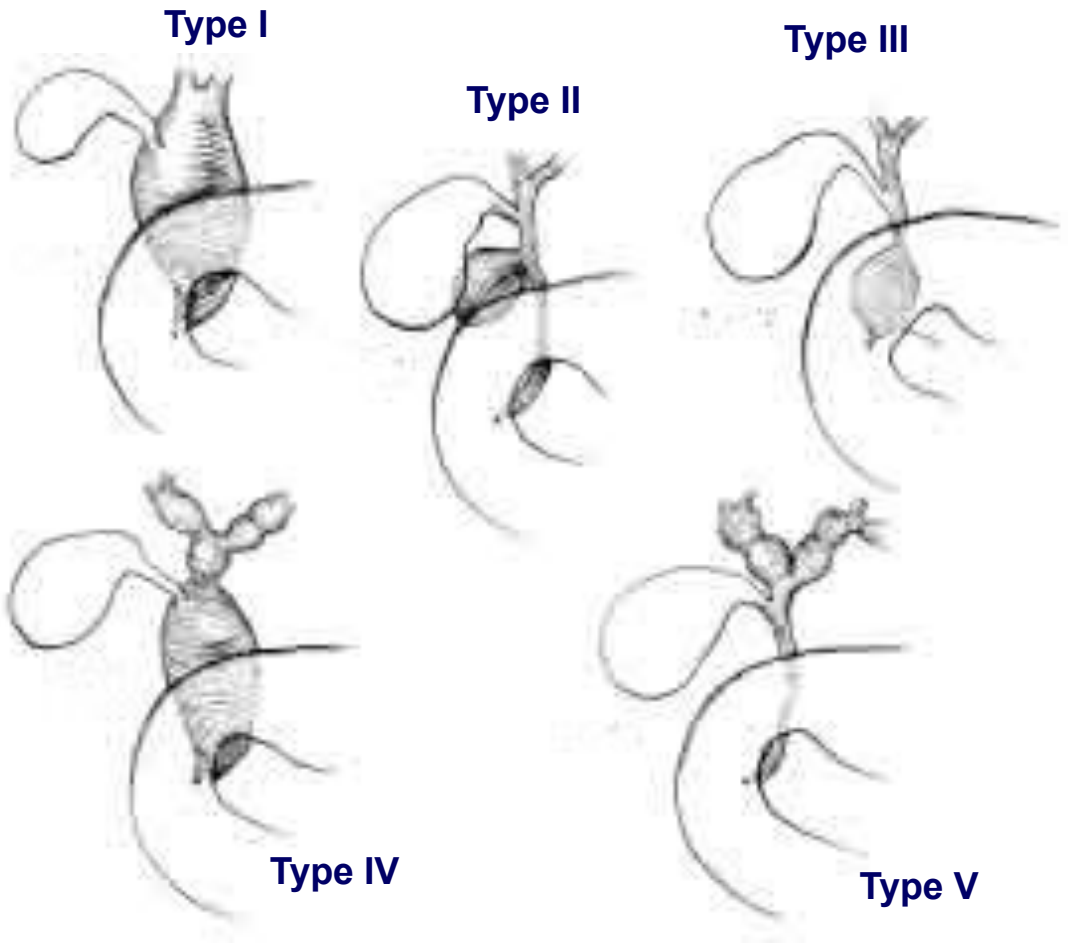


Type I - narrowing of common hepatic duct caused by calculus-induced compression of Hartmann's pouch



Type II - fistula between the gallbladder and hepatic duct. Hypertension of lobar hepatic ducts

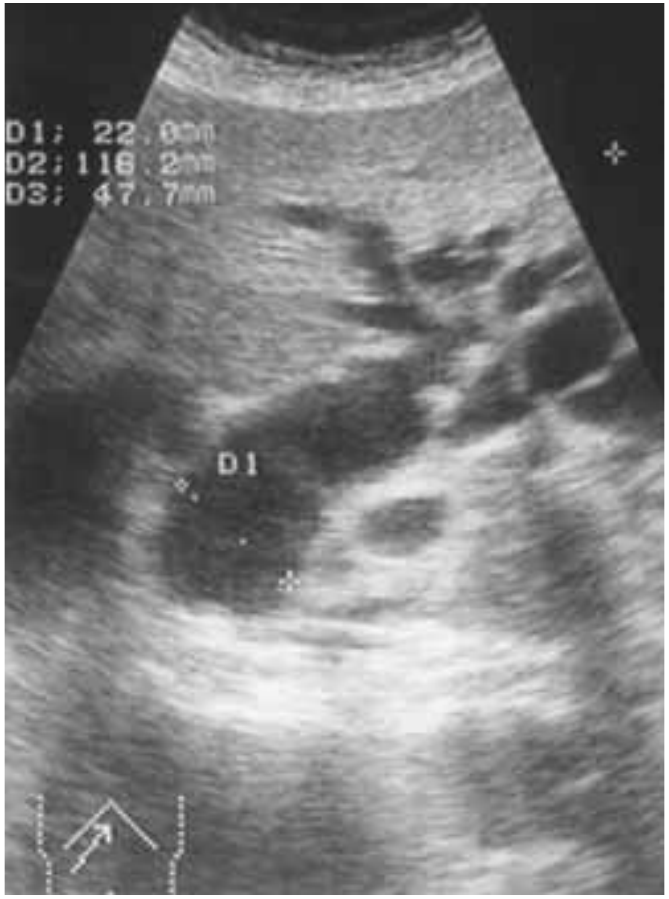
Bile duct cysts. Classification

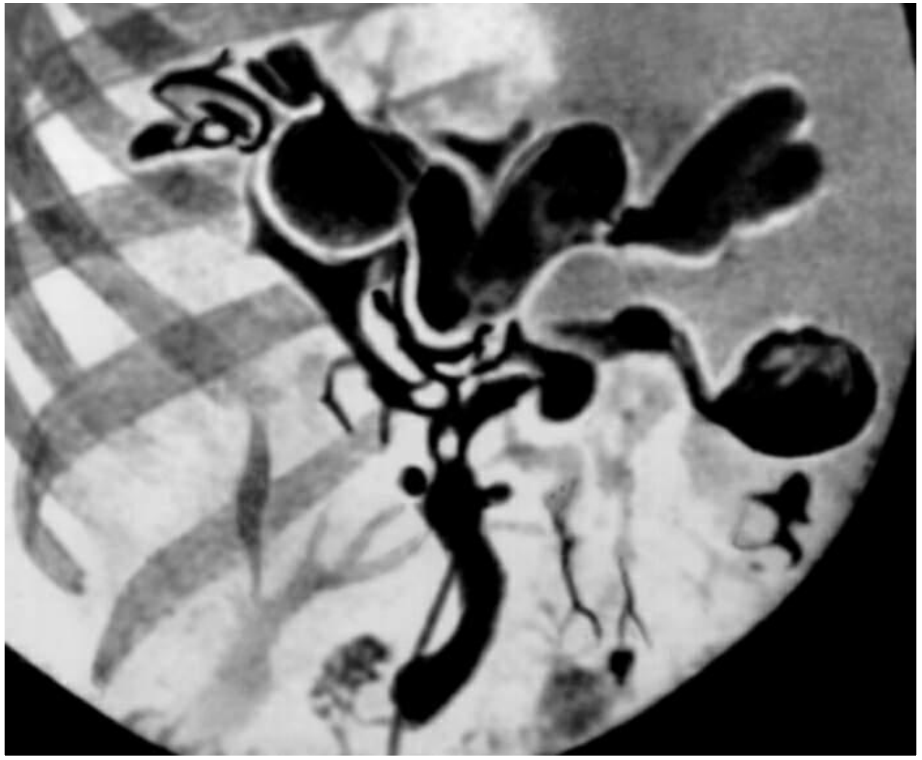


- Cysts are diagnosed in patients aged 3 months - 16 years and often cause obstruction of the bile ducts
- Hereditary disease
- No muscle layer and collagen fibers. Liver fibrosis
- Periductal eosinophilic infiltration

Todani classification

Caroli disease (cystic lesion type V)
Surgery – liver resection

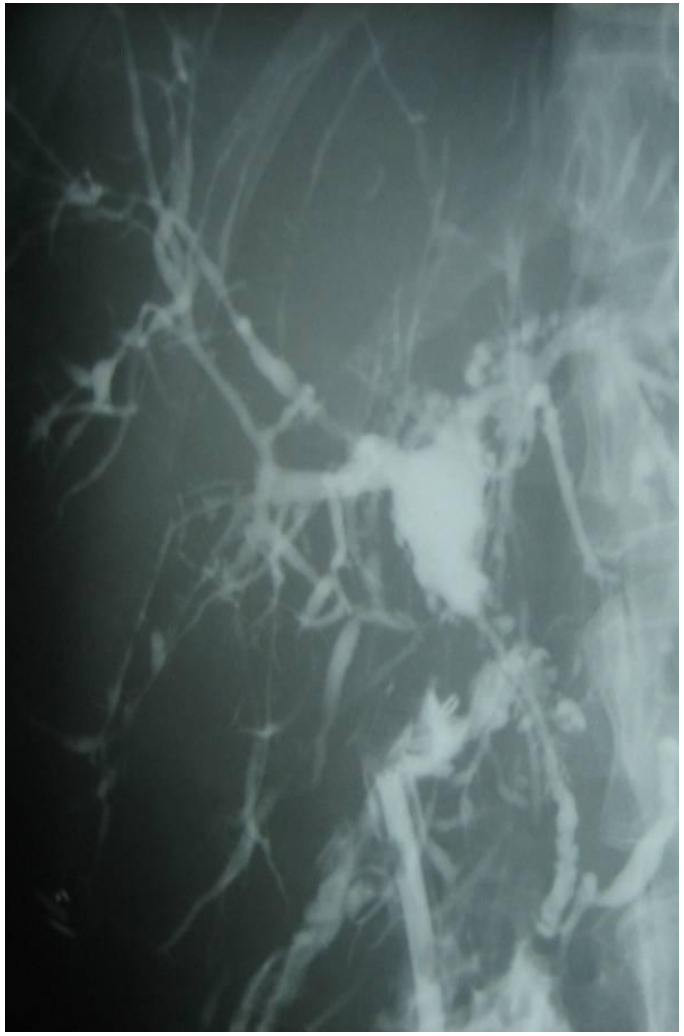




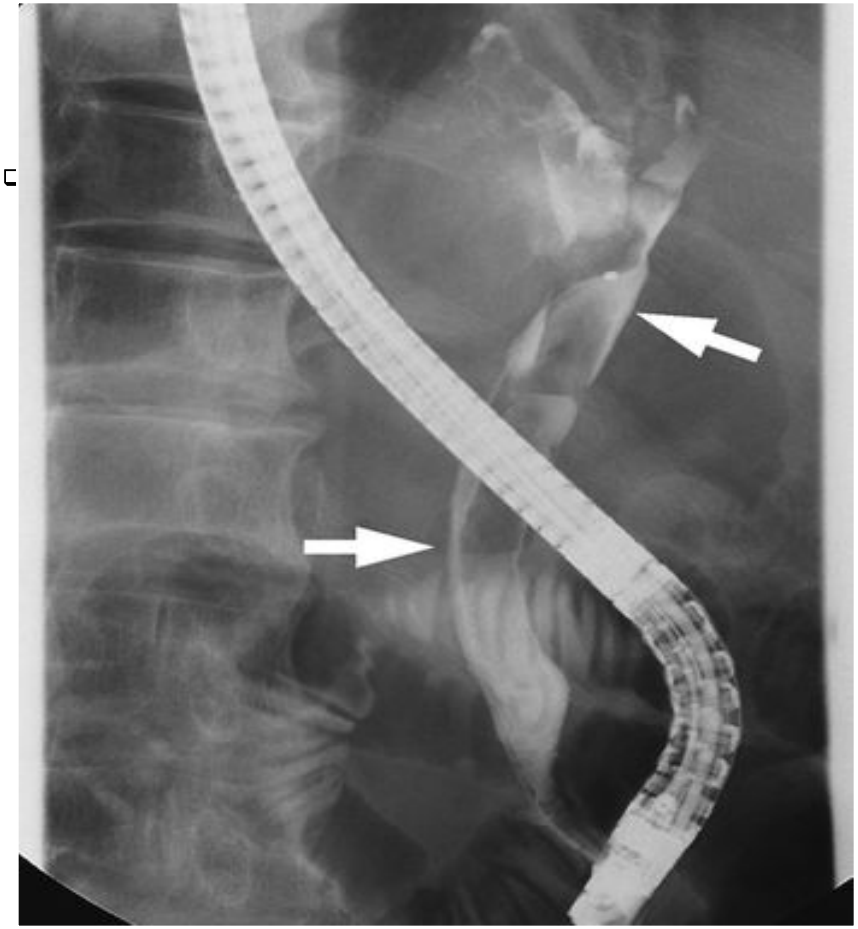
Primary sclerosing cholangitis

Idiopathic gallbladder obliteration, autoimmune disease, frequent combination with ulcerative colitis, Crohn's disease.
Higher-than-normal levels of AST and ALP.

- **Chronic course**
- **Cause is unclear**
- **Multiple strictures and dilatations of intrahepatic bile ducts**
- **Outcome: liver cirrhosis, cholangiocarcinoma is rarer**
- **Diagnosis: direct contrast enhanced methods, MRCP**
- **Radical approach – liver transplantation**



Haemobilia



- Damage to the liver or intrahepatic bile ducts, local liver necrosis. Haemobilia is a secondary sign of the underlying disease.
- Right upper quadrant abdominal pain, melena, transient jaundice.
- Endoscopic examination of major duodenal papilla, ERCP, angiography, ultrasound, CT, MRI
- Mortality rate 32–50%.

Parasitic invasion

- Opisthorchiasis (Ob, Volga basin, East Asia)
- Echinococcosis, alveococcosis, ascariasis,
- Fascioliasis– Fasciola gigantica
- Schistosomiasis – tropical helminth

Parasites penetrate into the bile ducts from the duodenum

Symptoms and diagnosis of painful obstructive jaundice

- Acute onset
- Scleral icterus
- Pain attack
- Dark urine, stool discoloration

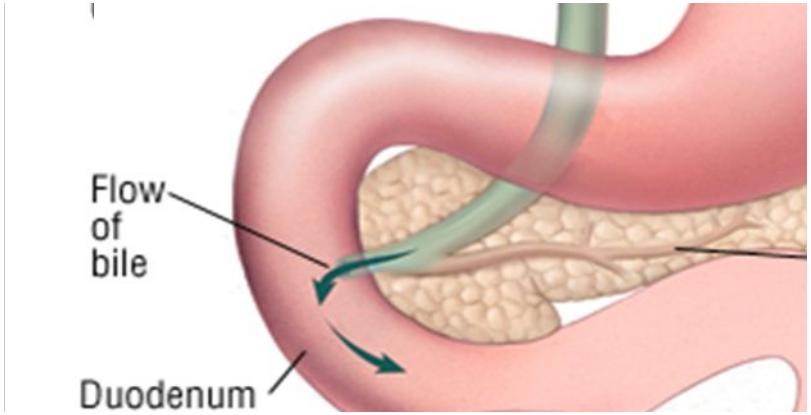
- Common previous cholelithiasis
- Ultrasound, ERCP, PTC, MRCP, CT, endoscopic ultrasound.
- Laboratory survey.

ACUTE CHOLANGITIS

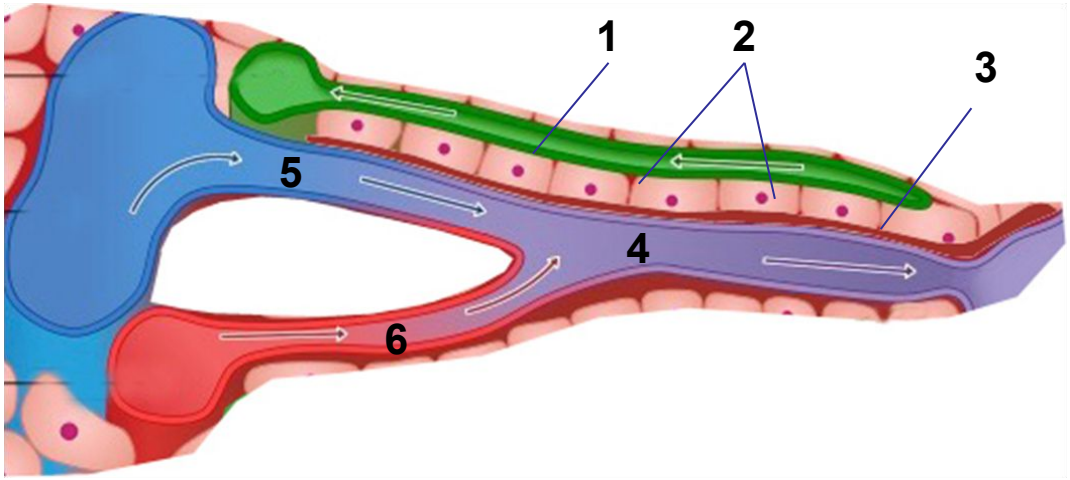
Acute cholangitis (AC)

AC is an infectious inflammation of the bile ducts. Most often, AC develops on the background of obstructive jaundice and biliary hypertension. AC is associated with penetration of microbes (Escherichia coli, Klebsiella, Proteus) from the duodenum into the bile ducts.

Metabolic products of microbial cells cause acute biliary hypertension.



Cholangiovenous reflux



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6 – hepatic artery branch

Corrosion casting. Scanning electron microscopy

Ductal pressure, mm H2O	Penetration of corrosive particles (1,7 μm)*
200	Intact bile ducts
200–500	Particles achieve sinusoids
500–800	Particles achieve central veins

* Particle of 1,7 μm – is a size of microbe

Secretory pressure. Microbial metabolite pressure. L., Pellegrini C.A., Way L.W. Am. J. Surg., 1988; 155: 23–28.

Symptoms of acute cholangitis

- Chills, fever
- Leukocytosis
- Infection
- Symptoms associated with biliary hypertension and obstructive jaundice
- Recurrent systemic inflammatory response with organ dysfunction

Charcot's triad:
fever, rigors, jaundice

Reynolds' pentad :
Charcot's triad +
altered mental status, hypotension

Causes of short-term SIRS and symptoms of sepsis

Two factors:

1. **Large purulent surface of gallbladder, direct biliovenous reflux - sinusoidal endotoxemia**
2. **Kupffer cell failure caused by cholemia - systemic endotoxemia, increased release of pro-inflammatory cytokines – systemic inflammatory response, sepsis.**

The difference between cholangitis and other purulent diseases is high sinusoidal endotoxemia combined with Kupffer cell failure.

Criteria of SIRS and sepsis

- **Body temperature > 38ºC or < 36ºC**
- **Heart rate > 90 beats per minute**
- **Tachypnea > 20 breaths per minute or $PaCO_2$ < 32 mm Hg**
- **Leukocyte count >12 000 or < 4000**
- **SIRS = 2 criteria**
- **SIRS + infection = sepsis**

Consensus conference of ACCP and SCCM, 1991

Severe sepsis: oliguria <500 ml/day, encephalopathy

Septic shock: BP < 90 mm Hg or reduction by 40 mm Hg

Organ dysfunction criteria

- CVS – hypotension requiring dopamine support
- CNS – impaired consciousness
- Respiratory system – tachypnea >20 or $PaCO_2$ < 32 mm Hg
- Kidney – serum creatinine > 2,0
- Liver – hypoalbuminemia, prothrombin index↓
- Coagulation – platelets < 100 000
- Severe systemic dysfunction – multiple organ failure

Renal failure in acute cholangitis

- **Kidney is a main organ secreting bile components – cholemic nephropathy.**
- **Cholemia and endotoxemia cause renin and aldosterone release, increased level of atrial natriuretic peptide, vasodilation, reducing total blood volume, renal and glomerular blood flow, arterial and venous thrombosis.**
- **Renal failure is more common in patients with jaundice and cholangitis compared to those without jaundice.**

The difference of cholangitis from other purulent diseases is high incidence of renal failure

Management of acute cholangitis (choledocholithiasis, n = 613)

Objective: to interrupt the course of cholangitis, to prevent sepsis.
Main measures: decompression and antimicrobial therapy.
Minimally invasive techniques (ERCP, PTC) reduced morbidity and mortality.
Data of the Hepatobiliary Surgery Department

Variable	Medication, conventional surgery (n = 157) (1972–1982)	Conventional surgery and endoscopic treatment (n = 94) (1983–1994)	Endoscopic treatment predominantly (n = 362) (1995–2008)
Effective medication (without surgery)	84 (51%)		
Conventional surgery	67 (42,7%) including cholecystostomy in 13 cases	44 (46,8%)	31 (8,5%)
Endoscopic treatment: Successful lithoextraction other procedures complications mortality		52 out of 74 (70%) NBD 11 (11,5%) 4 (4,25%)	329 (90,8%) Stents - 12, NBD 20 (5,5%) 2 (0,55%)
Severe sepsis	28 (17,8%) 13 (46,4%) died	20 (16,3%) 9 (45%) died	28 (7,7%) 9 (32,1%) died
Septic shock	15 (9,5%) 8 (53,3%) died	11 (9%) 7 (63,6%) died	12 (3,3%) 5 (41,6%) died
Overall mortality	21 (13,4%)	16 out of 122 (13,1%)	17 (4,6%)

Treatment of pyogenic liver abscesses in acute cholangitis (n = 19)

The main requirement is biliary decompression + puncture or drainage of the abscess.

Mean duration of acute cholangitis – 8 days. Solitary – 7, multiple – 2, miliary – 10. Symptoms are significantly determined by severity of cholangitis.

- **Percutaneous puncture (abscess volume – 15–120 ml):**

  ≤80 ml – efficacy 80%, >80 ml – efficacy 33%
- **Percutaneous drainage (abscess volume 30–160 ml).**

  Volume < 120 ml – efficiency is 15 times higher than for volume > 120 ml.

  Duration of drainage – 10–55 days.
- **Surgery: drainage, liver lobe resection – 3.**
- **Miliary abscesses – antimicrobial therapy without surgery – 10, 4 patients died.**
- **Severe sepsis – 5, 2 patients died.**
- **Septic shock – 7, 4 patients died.**

Risk factors: miliary abscesses, septic shock, inadequate drainage, high creatinine.

Stages of acute cholangitis and Tokyo Guidelines (2007)

Criterion	Stage of acute cholangitis		
	mild (I)	moderate (II)	severe (III)
Organ dysfunction	no	no	yes
Response to therapy*	yes	no	no

*Overall and antimicrobial therapy

- **Emergency biliary decompression is required for severe acute cholangitis (stage III)**
- **In mild stages, it is important to determine response to therapy. Emergency biliary decompression is required if there is no response (moderate, stage II).**
- **Antibiotics enter the bile only after medical or surgical decompression. An importance of decompression in emergency surgery.**

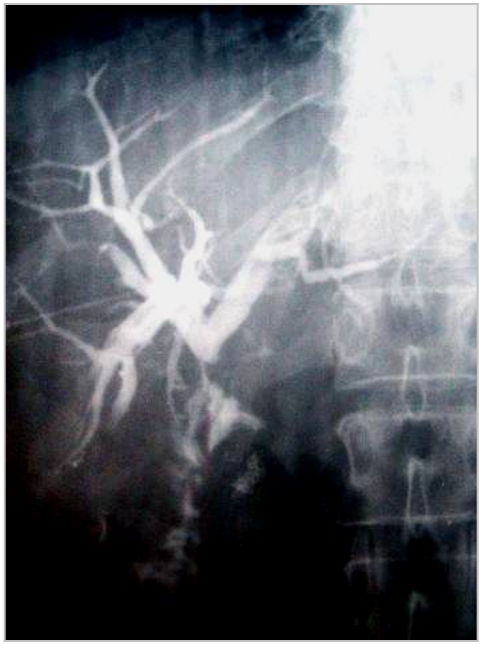
Chronic cholangitis

Chronic cholangitis may be diagnosed in patients with:

- **post-traumatic strictures;**
- **primary sclerosing cholangitis;**
- **Klatskin tumors with vascular lesion;**
- **AIDS-associated cholangitis.**

Chronic cholangitis in post-traumatic stricture

- **Long-term course**
- **Persistent infection**
- **Recurrent biliary obstruction**
- **Secondary immune deficiency (impaired response of lymphocytes to concanavalin, reduced number of NK cells, CD4/CD8 <0.5)**
- **Secondary biliary cirrhosis is common**



Chronic cholangitis in patients with AIDS

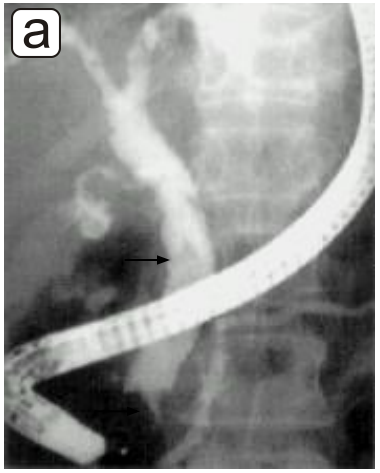
Causative agents : ***Cryptosporidium*** **and** ***Cytomegalovirus*****.**

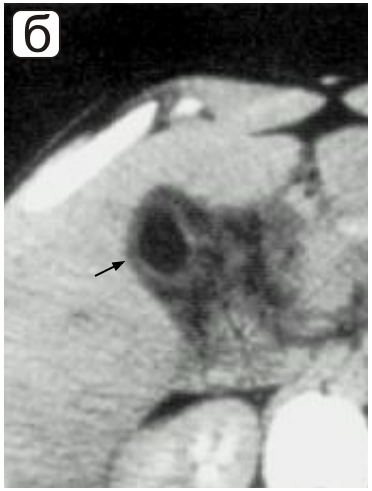
Features: stenosis of major duodenal papilla and bile duct enlargement, thickened walls of common bile duct (a, arrow) and gallbladder (б, arrow).

Symptoms: right upper quadrant abdominal pain and fever without jaundice and itching.

Diagnosis: ultrasound, ERCP, CT

Prognosis: life expectancy after manifestation of biliary symptoms – near 7 months





Nash J.A., Cohen S.A. Gastroenterol. Clin. N. Am. 1997; 26: 2

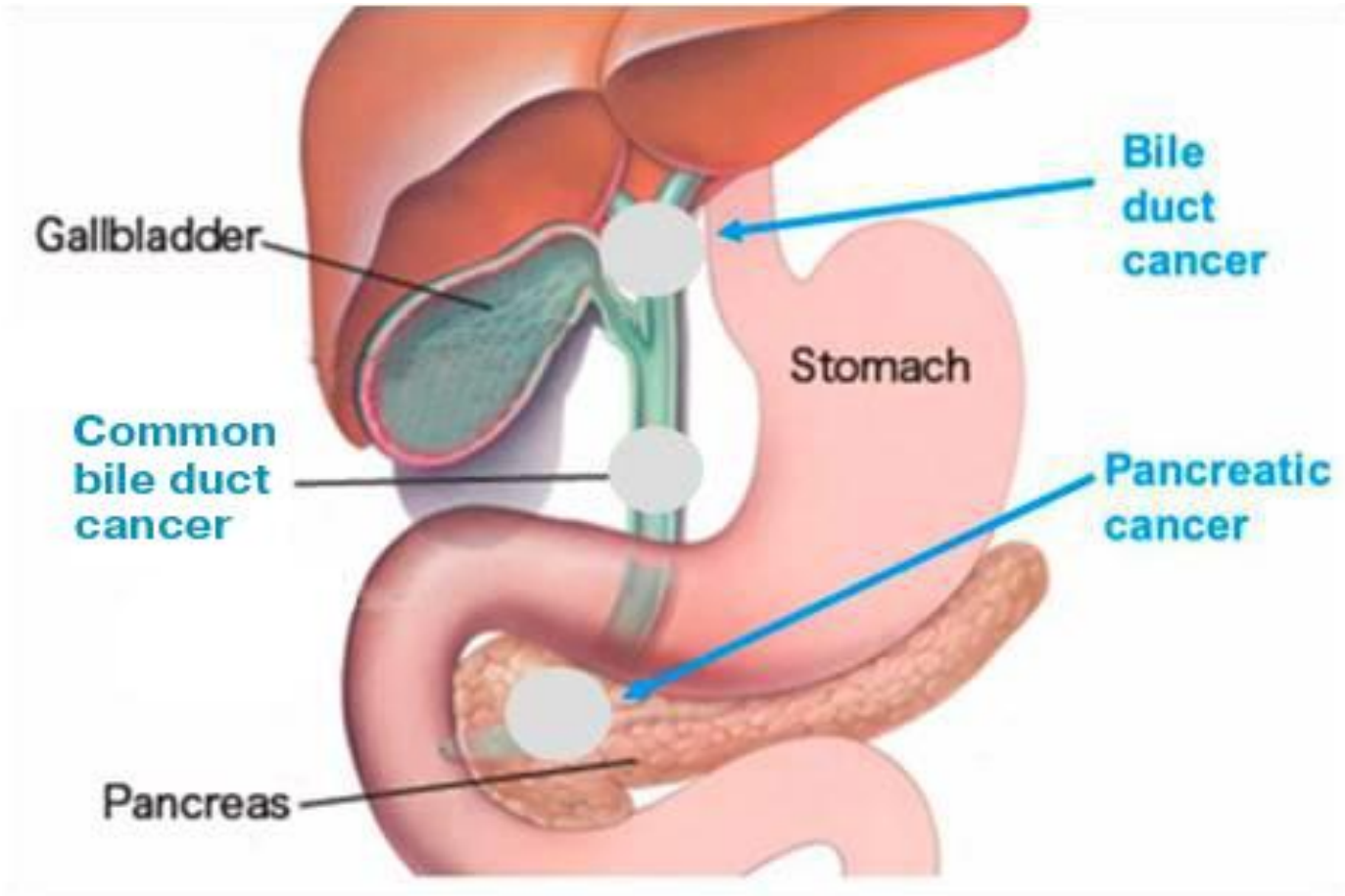
3+

Conclusion

- **Acute cholangitis is characterized by purulent process proceeding on the background of cholemia and acholia caused by obstructive jaundice. This determines the features of course in comparison with other purulent diseases.**
- **Features of acute cholangitis:**
  - **Large purulent surface of gallbladder. Cholangiovenous reflux.**
  - **Advanced portal endotoxemia combined with cholemia-induced Kupffer cell failure. Systemic endotoxemia. Short-term SIRS and organ failure.**
  - **High incidence of renal failure.**
- **Endoscopic methods ensure simultaneous diagnosis and treatment of acute cholangitis, early decompression of gallbladder in critically ill patients, and lithoextraction in 90% of patients. Endoscopic treatment reduces the risk of severe sepsis and septic shock, results low mortality and is currently preferable treatment strategy.**
- **A distinctive feature of chronic cholangitis is recurrent gallbladder obstruction and secondary immune deficiency.**

PAINLESS OBSTRUCTIVE JAUNDICE

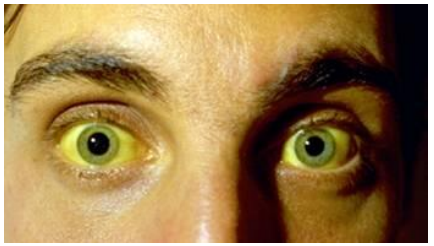
Tumors of bile ducts



Progressive biliary obstruction. Jaundice is the first, but not an early symptom. Features of Klatskin tumor and pancreatic cancer.

Symptoms of painless obstructive jaundice

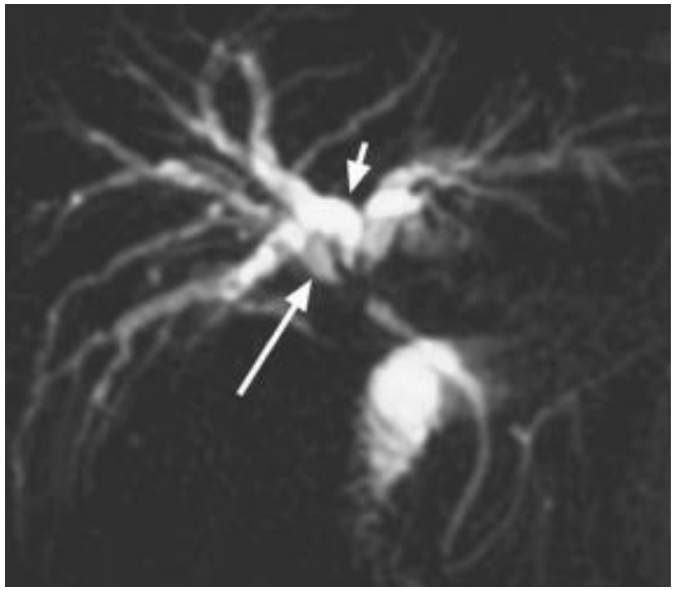
- **Icteric sclera and skin**
- **Itching**
- **Dark urine and stool discoloration**
- **No pain as a rule**
- **Signs of tumor growth are sometimes observed: body mass loss, no appetite, weakness**



Cancer of hepatic and common bile ducts

Common hepatic duct (Klatskin tumor) 56%

- Obstructive jaundice following a small tumor
- No metastases for a long time (nodular and papillary forms as a rule)
- Proximal growth

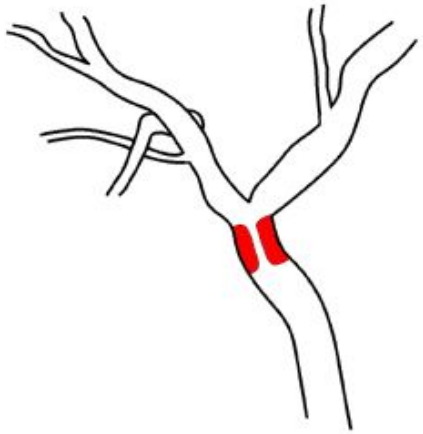


Common bile duct 44%

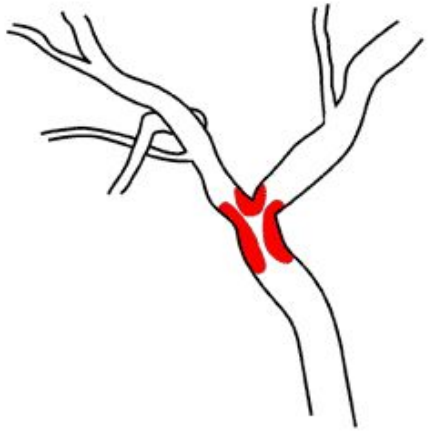
- Early local invasion
- Early lymphogenous metastasizing

Classification of hepatic duct cancer (Bismuth)

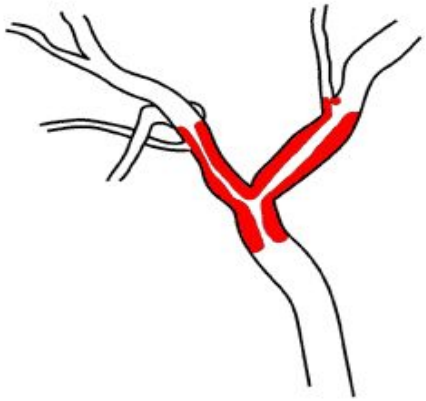
Type I



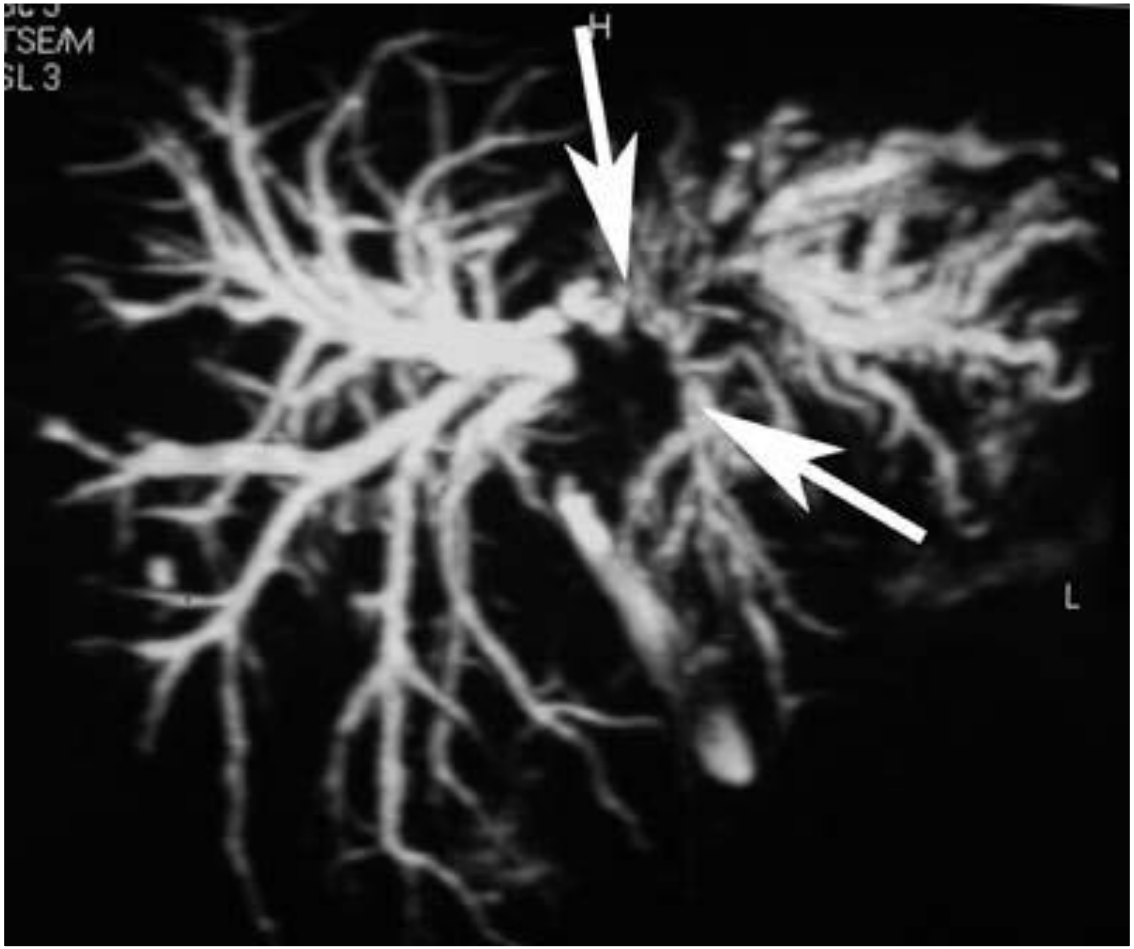
Type II



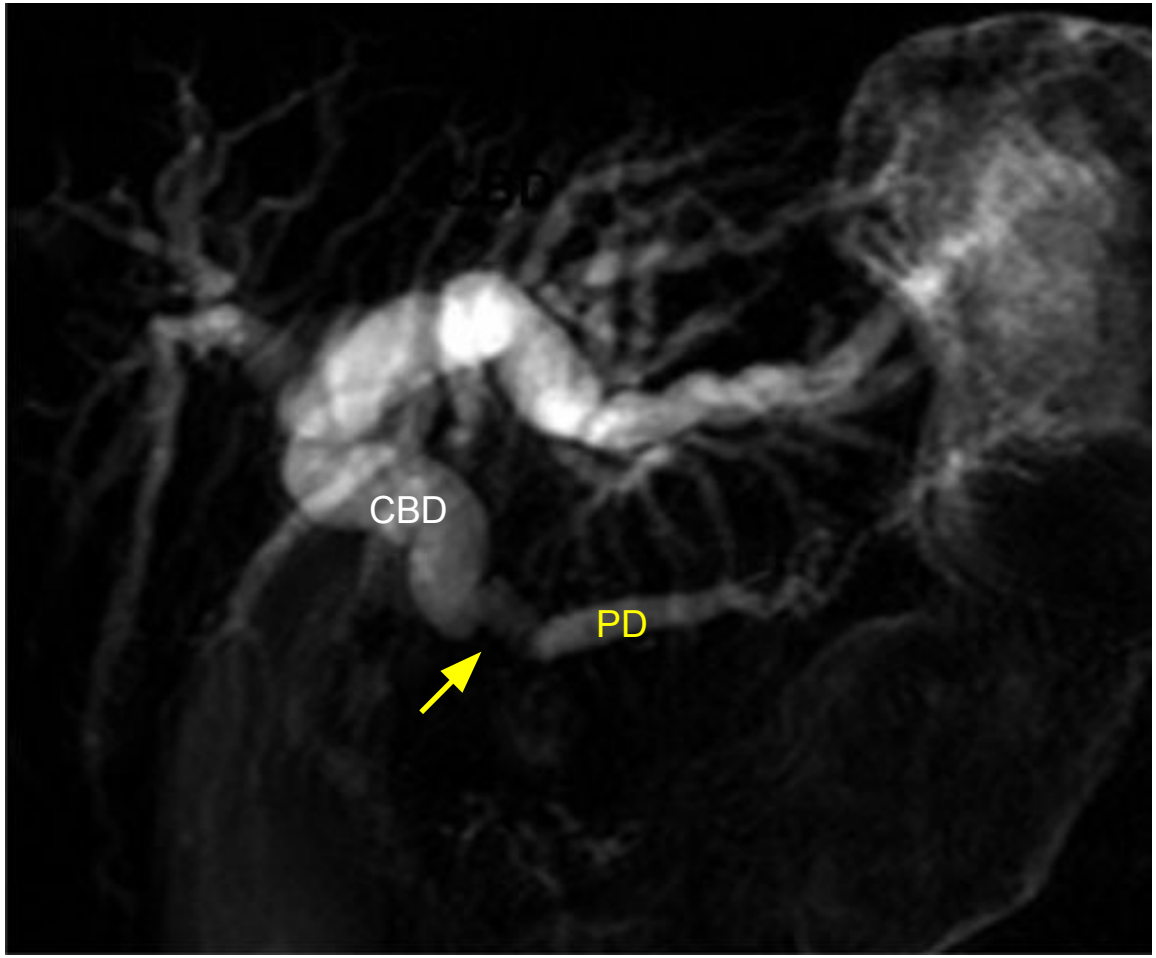
Type IV



MR-cholangiography in Klatskin tumor



Pancreatic head cancer. MRCP



Differential diagnosis of obstructive and parenchymatous jaundice

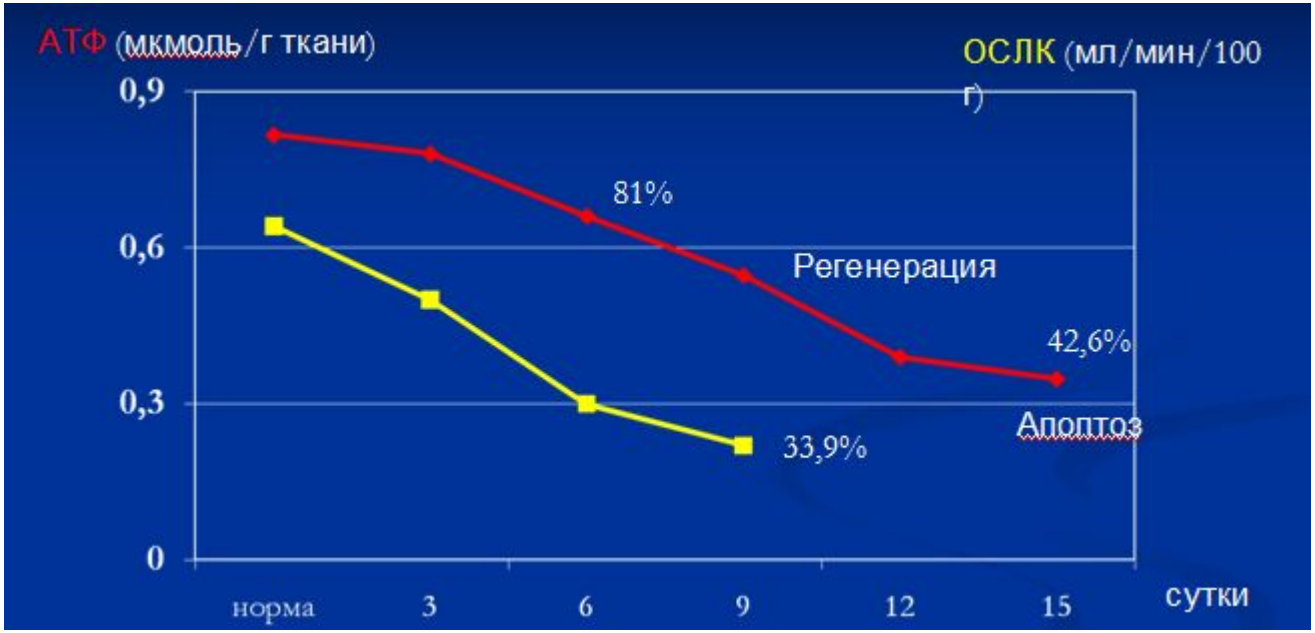
- **Patients with a painless obstructive jaundice do not notice anything for many days because severe symptoms are absent. Patients often admit to infectious disease departments with a diagnosis of hepatitis and undergo examination for a long time. Differential diagnosis is simple - DETECTION OF ENLARGED common bile duct during ultrasound or other surveys.**

Functional and morphological features of liver in painless obstructive jaundice

- **Increased levels of direct and indirect bilirubin and alkaline phosphatase. A slight increase in AST, ALT, LDH in some patients. No other biochemical disorders.**
- **Reduced prothrombin, platelets, rare signs of mild encephalopathy in long-standing obstructive jaundice (over 3-4 weeks).**
- **Hepatocyte proliferation is replaced by their wrinkling and degeneration after 2-3 days (foci, fields). After 4 - 5 weeks, hepatocyte dimensions are reduced by 30-40%, their volume decreases from 97% to 40%.**
- **Bile duct proliferation from the first day. After 4–5 weeks, their volume is increased from 2% to 40%,volume of stroma - from 1% to 20%.**
- **Phlebitis of portal vein branches, neutrophilic infiltration, increased permeability of intercellular junctions.**

Wu P.C. et al. – J. Pathol. 1981,133: 61–74.

Metabolic disorders in painless obstructive jaundice



Reduced ATP and local blood flow velocity are associated with long-standing obstructive jaundice and progressive hyperbilirubinemia (p <0.05)
HGF release - regeneration regulator (ATP interval 0.53-0.6 μmol/g of tissue) – the 9th day
TNF-α release - apoptosis factor (decrease in ATP below 0.365 μmol/g of tissue) - after the 12th day

Conclusion on disorders arising in painless obstructive jaundice

- **Painless obstructive jaundice causes severe functional and morphological disorders in liver associated with biliary hypertension, cholestasis, cholemia and acholia.**
- **These disturbances result extrahepatic disorders, microbial colonization of gastrointestinal tract, portal endotoxemia, RES dysfunction, especially Kupffer cells, systemic toxemia followed by organ dysfunction.**
- **Intra- and extrahepatic disorders together with persistent obstructive jaundice and progressive hyperbilirubinemia acquire a critical nature (fragile stability state), and additional effect ("second impact") can result SIRS and multiple organ failure.**

PREOPERATIVE DECOMPRESSION

Preoperative decompression of the bile ducts

Secondary obstructive jaundice is often more dangerous for the patient's life than the underlying disease that caused this syndrome. Therefore, minimally invasive correction of obstructive jaundice is essential in some patients. These patients undergo a two-stage surgery: stage 1 – bile duct decompression, correction of hyperbilirubinemia, stage 2 – total resection of tumor.

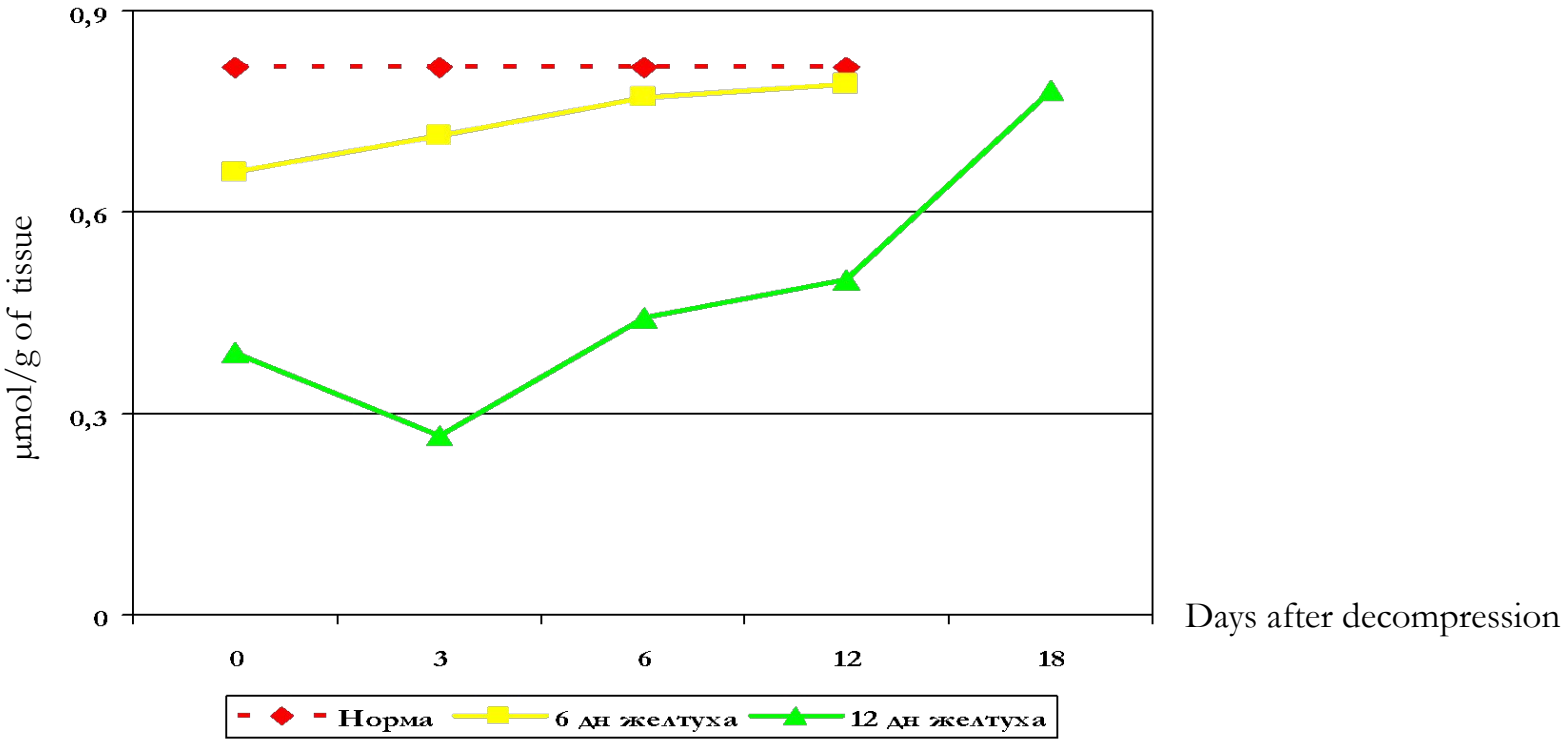
Methods of preoperative biliary decompression:

- **Percutaneous cholangiostomy.**
- **Endoscopic nasobiliary drainage or stenting.**
- **Cholecystostomy: open, ultrasound-assisted laparoscopic percutaneous.**
- **Open choledocho- or hepaticostomy.**

A fairly complete restoration of liver and other systems requires prolonged decompression of the bile ducts (3-4 weeks). Therefore, various stents are often used for this purpose. For short-term decompression, drainage tubes are used. The last ones may be later replaced with stents.

Can bile duct decompression per se impair liver function?

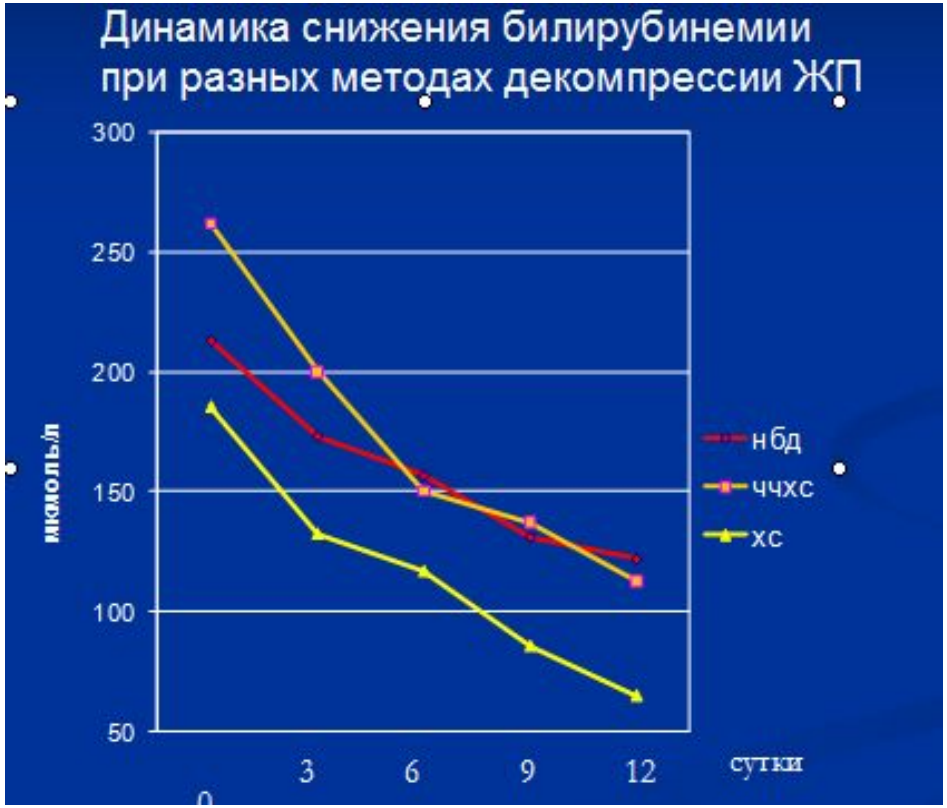
ATP restoration after decompression in 6- and 12-day obstructive jaundice



In a 12-day obstructive jaundice, decrease of ATP, progressive energy deficit of liver tissue and hyperbilirubinemia have been observed for 3 days. This the so-called post-decompression syndrome is probably associated with fast decompression of the bile ducts (similar to fast drainage of abdominal effusion).

Comparison of various methods of bile duct decompression (n = 205)

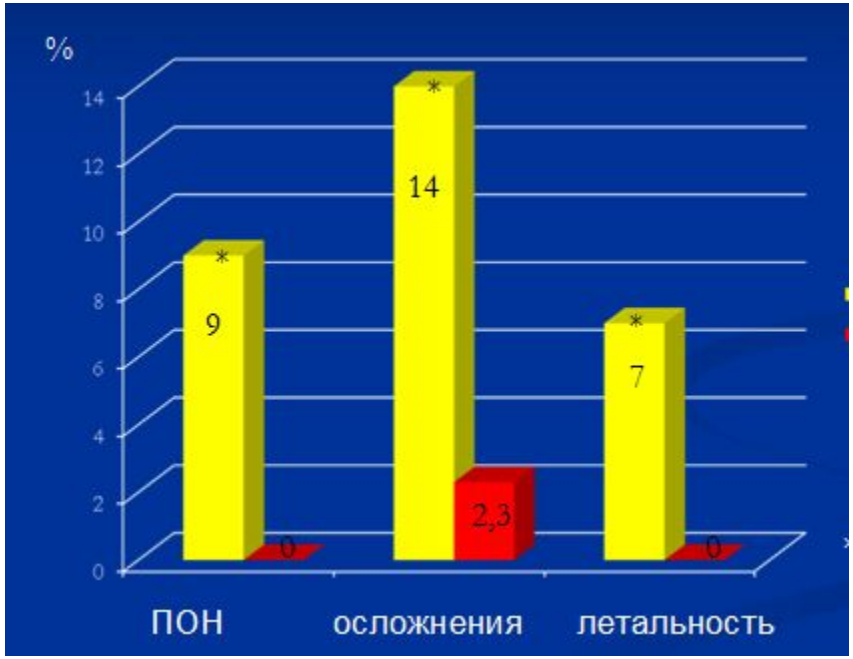
NBD-85, PTC-37, cholecystostomy-63, CBD decompression -20



NBD was followed by gradual decrease in biliary pressure throughout the entire period of decompression. An acceptable pressure was achieved by the 7th day. Other methods were characterized by faster decrease in biliary pressure. Decompression rate may be adjusted by raising or lowering the outer end of drainage tube.

NBD – B = 4,6; PTC – B = 10; cholecystostomy– B = 9

Morbidity and mortality in various rates of bile duct decompression



– fact decompression (PTC, CS)

– slow decompression (NBD)

* – p < 0,05

Slow decompression rate is associated with fewer complications and no mortality

Positive and negative aspects of preoperative biliary decompression

Advantages

- Improved function of liver and other organs and systems
- Improved immune status
- Improved liver microcirculation
- Restored energy potential of liver tissue

Drawbacks

- Enhanced microbial contamination of the bile ducts (18-97%)
- Chronic inflammation in bile ducts and gallbladder
- Stenting can cause some adverse events: acute pancreatitis, cholangitis, bleeding, stent obstruction, etc.

Opinions on stenting are still controversial. However, there are absolute indications for preoperative biliary decompression: cholangitis, neoadjuvant chemotherapy, inoperable tumor, risk of radical surgery.

Additional factors in favor of preoperative biliary decompression: serum bilirubin > 200 mmol / L and Klatskin tumor.

Features of preoperative biliary decompression in Klatskin tumor

1. Radical surgery for Klatskin tumor implies extended liver resection. Future liver remnant (preferably at least 30%) must be functionally adequate that is facilitated by preoperative decompression of the bile ducts.
2. Percutaneous transhepatic selective drainage of segmental bile duct of future liver remnant is of particular importance. This procedure together with increased portal blood flow facilitate fast regeneration and enlargement of liver remnant.

Conclusion on bile duct decompression

Opinions on preoperative biliary decompression are still controversial. Absolute indications for decompression are acute cholangitis, neoadjuvant chemotherapy, inoperable tumor and high risk of radical surgery.

Factors in favor of decompression are serum bilirubin > 200 mmol / L and scheduled total resection of Klatskin tumor.

Preoperative biliary decompression should be slow in patients with long-standing obstructive jaundice and serum bilirubin > 200 mmol/L. NBD with standard drainage tube (length 180 cm and diameter 2 mm), as well as its height in relation to common bile duct ensure gradual decompression.
Fast biliary decompression deteriorates liver disorders within 2–3 days in patients with high serum bilirubin and should not be used in these cases.