Functional disorders in the sphincter of Oddi and possibly reflux-associated diseases in the hepato-biliary-cholecysto-pancreatico-duodeno-gastro-esophageal region

Functional disorders in the sphincter of Oddi	Possibly reflux associated diseases
Type of reflux or dysfunction	Target organ – Gallbladder
Pancreaticobiliary reflux (pancreatic juice)	Chronic (enzymatic) cholecystitis. Chronic calculous cholecystitis. Intestinal metaplasia. Dysplasia. Gallbladder cancer.
Biliary type III of sphincter of Oddi dysfunction (spasm of sphincter of common bile duct)	Chronic (spastic aseptic) cholecystitis. Cholesterol gallstone disease. Chronic calculous cholecystitis. Metaplasia.
Duodenal-biliary reflux (duodenal juice) (± *Salmonella enterica* serovar Typhi)	Chronic (infectious) cholecystitis. Mixed or Pigment (brown) gallstone disease. Chronic calculous cholecystitis. Metaplasia.
Duodenal-biliary (acidic) reflux (duodenal juice and gastric juice) (± *Helicobacter pylori*)	Chronic (infectious) cholecystitis. Mixed or Pigment (brown) gallstone disease. Chronic calculous cholecystitis. Gastric metaplasia.
Type of reflux or dysfunction	Target organ – Pancreas
Biliopancreatic reflux (lithogenic bile)	Chronic biliary pancreatitis. Biliary metaplasia. Dysplasia. Pancreatic cancer.
Pancreatic type III of sphincter of Oddi dysfunction (spasm of sphincter of pancreatic duct)	Chronic (spastic aseptic) pancreatitis.
Duodenal-pancreatic alcohol reflux (duodenal juice and gastric juice and alcohol)	Chronic (alcoholic infectious) pancreatitis.
Duodenal-pancreatic reflux (duodenal juice) (± *Salmonella enterica* serovar Typhi)	Chronic (infectious) pancreatitis.
Duodenal-pancreatic (acidic) reflux (duodenal juice and gastric juice) (± *Helicobacter pylori*)	Chronic (acidic) pancreatitis. Metaplasia. Dysplasia. Pancreatic cancer.
Type of reflux or dysfunction	Target organ – Duodenum – Stomach – Esophagus
Duodenogastric reflux (duodenal juice)	Bile reflux gastritis. Atrophic antral gastritis. Intestinal metaplasia.
Duodenogastroesophageal reflux (duodenal juice and gastric juice)	Bile reflux gastritis. Gastroesophageal reflux disease. Chronic esophagitis. Gastric metaplasia. Dysplasia. Esophageal cancer.
Small intestinal bacterial overgrowth syndrome (duodenum) (duodenal hypertension)	Gallstone disease. Chronic calculous cholecystitis. Chronic pancreatitis.

Absorption function of a gallbladder, a functional status of the sphincter of Oddi, an anatomic configuration of hepatopancreatic ampulla of the sphincter of Oddi (Y-type, V-type or U-type) define development and prevalence of the certain type of pathology in each concrete patient with biliary diseases and pancreatic diseases.

Therefore, depending on dysfunction (hyper tonus) or relaxation (hypo tonus) of the human sphincter of Oddi, depending on anatomic configurations of the human sphincter of Oddi (Y-type, V-type or U-type) and length of common channel (>5 mm, 2-5 mm or <2 mm) of the human sphincter of Oddi, different pathology will form in patients with biliary diseases after cholecystectomy in hepato-biliary-pancreatico-duodenal-gastric zone.

Correction of pathological processes

Inactivation of chronic aseptic inflammation – Selective or nonselective COX-2 inhibitors.
Inactivation of spasm – Selective or nonselective spasmolytics.
Inactivation of *Helicobacter pylori* – Antibacterial drugs (Eradication).
Inactivation of *Salmonella enterica* serovar Typhi – Antibacterial drugs (Eradication).
Inactivation of lithogenic bile and toxic secondary hydrophobic bile acids – Ursodeoxycholic acid.
Inactivation of pancreatic juice – Pancreatic enzymes (?) and/or Ursodeoxycholic acid (?).
Inactivation of gastric juice (HCl) – Proton pump inhibitor (PPI) agents. Selective prokinetics.

1. **Selective COX-2 inhibitors** (celecoxib, nimesulide, etc.): celecoxib – 100 mg or 200 mg * 2 times per day during 5-7 days;
2. **Nonselective COX-2 inhibitors** (ibuprofen, diclofenac sodium, indomethacin, naproxen sodium, ketoprofen, flurbiprofen, etc.): ibuprofen – 200 mg or 300 mg or 400 mg * 3 times per day during 5-7 days;
3. **Selective spasmolytics** (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, etc.): hymecromone – 200 mg or 400 mg or 600 mg * 3 times per day during 5-7 days;
4. **Nonselective spasmolytics** (drotaverine hydrochloride, papaverine hydrochloride, fenpiverinium, etc.): drotaverine hydrochloride – 40 mg or 60 mg or 80 mg * 3 times per day during 5-7 days;
5. **Antibacterial drugs** (ciprofloxacin, clarithromycin, amoxicillin, metronidazole, erythromycin, doxycycline, co-trimoxazole, etc.): ciprofloxacin – 500 mg * 2 times per day during 5 days;
6. **Ursodeoxycholic acid:** ursodeoxycholic acid – 750 mg * 1 time before going to bed – 14-30-45 days.
7. **Pancreatic enzymes** (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.): kreon 10000 – 1 capsule or 2 capsules * 2-4 times per day during meal during 7-14-30 days;
8. **Proton pump inhibitor (PPI) agents** (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, dexlansoprazole): rabeprazole – 20 mg * once daily – during 4-8 weeks.
9. **Selective prokinetics** (domperidone, cizapride, metoclopramide, etc.): domperidone – 10 mg * 3-4 times per day before meal and at bedtime during 14 days.

The universal algorithm of the pathogenetic treatment of symptomatic (with biliary pain) biliary diseases with concomitant functional disorders in the sphincter of Oddi:

1) selective COX-2 inhibitors (celecoxib or nimesulide, etc.):
celecoxib – 100 mg or 200 mg * 2 times per day during 5-7 days,
+
2) selective spasmolytics (hymecromone or mebeverine hydrochloride or hyoscine butylbromide or pinaverium bromide, etc.):
hymecromone – 200 mg or 400 mg or 600 mg * 3 times per day during 5-7 days;
+
3) antibacterial drugs (ciprofloxacin [for eradication of *Salmonella enterica ser. Typhi*]) or clarithromycin + amoxicillin or metronidazole [for eradication of *Helicobacter pylori*], etc.):
ciprofloxacin – 500 mg * 2 times per day during 5 days,

4) after 5 days of treatment (1+2+3):
ursodeoxycholic acid – 750 mg 1 time before going to bed – 30-45 days.

The presented data and this algorithm of pathogenetic treatment of biliary diseases with concomitant functional disorders in sphincter of Oddi may help diminish the duration of disease period and the quantity of patients with biliary diseases by 30-40%. Also, the remission period will be increased up to 24-48 months.

The pathogenetic correction of metabolic and morpho-functional disturbances in the gallbladder and liver:

- in patients with gallbladder dysfunction helps decrease the risk of appearance of the chronic acalculous cholecystitis without biliary sludge,
- in patients with chronic acalculous cholecystitis without biliary sludge helps decrease the risk of appearance of the chronic acalculous cholecystitis with biliary sludge,
- in patients with chronic acalculous cholecystitis with biliary sludge helps decrease the risk of appearance of the chronic calculous cholecystitis,
- in patients with chronic calculous cholecystitis helps decrease the risk of appearance of the acute calculous cholecystitis,
- in patients after cholecystectomy helps decrease the risk of appearance of the choledocholithiasis,

♦ in patients with pancreaticobiliary reflux of pancreatic juice into common bile duct and the gallbladder (hypomotility of the sphincter of pancreatic duct and sphincter of common bile duct) helps decrease the risk of appearance of the chronic acalculous (enzymatic) cholecystitis and chronic calculous cholecystitis,
♦ in patients with spasm of the sphincter of common bile duct helps decrease the risk of appearance of the biliary type III of sphincter of Oddi dysfunction, the chronic acalculous (aseptic spastic) cholecystitis and chronic calculous cholecystitis,
♦ in patients with duodenal hypertension (the increase of intraluminal pressure in the duodenum – the small intestinal bacterial overgrowth syndrome) and duodenal-biliary reflux of duodenal juice into the

common bile duct (hypomotility of the sphincter of hepatopancreatic ampulla and sphincter of common bile duct) and into the gallbladder helps decrease the risk of appearance of the chronic cholangitis, chronic acalculous (infectious) cholecystitis and chronic calculous cholecystitis, mixed gallstone disease or pigment (brown) gallstone disease,

- in patients with biliopancreatic reflux of lithogenic bile into the pancreatic duct (hypomotility of the sphincter of common bile duct and sphincter of pancreatic duct) helps decrease the risk of appearance of the chronic biliary (bile) pancreatitis and pancreatic cancer,
- in patients with spasm of the sphincter of pancreatic duct helps decrease the risk of appearance of the pancreatic type III of sphincter of Oddi dysfunction and chronic (aseptic) pancreatitis,
- in patients with duodenal hypertension (the increase of intraluminal pressure in the duodenum – the small intestinal bacterial overgrowth syndrome) and duodenal-pancreatic reflux of duodenal juice into the pancreas (hypomotility of the sphincter of hepatopancreatic ampulla and sphincter of pancreatic duct) helps decrease the risk of appearance of the chronic alcoholic (infectious) pancreatitis, chronic (chymous infectious) pancreatitis, chronic (acidic) pancreatitis,

- in patients with duodenogastric bile reflux (hypomotility of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla) of duodenal juice (mixture of duodenal bile and pancreatic juice) helps decrease the risk of appearance of the atrophic antral gastritis (bile reflux gastritis),
- in patients with duodenogastroesophageal bile reflux (hypomotility of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla, and hypomotility of the lower esophageal sphincter) of duodenal juice (mixture of duodenal bile and pancreatic juice and gastric juice) helps decrease the risk of appearance of the esophagitis and gastro-esophageal-reflux-disease (bile reflux esophagitis),

- in patients with small intestinal bacterial overgrowth syndrome (duodenal hypertension) helps decrease the risk of appearance of the gallstone disease, chronic calculous cholecystitis and chronic pancreatitis.

This algorithm of pathogenetic treatment of biliary diseases with concomitant functional disorders in sphincter of Oddi may help:

1. Effectively to stop the biliary pain and dyspeptic syndrome within 1-3 days;
2. To block the intensity of chronic aseptic inflammation in the gallbladder wall within 7-10 days, i.e. to decrease the thickness of gallbladder wall from 4-5 mm up to 2 mm;
3. Complete disorganization and elimination of biliary sludge within 10-14 days;
4. To restore the accumulation function of liver and the excretion function of liver within 10-14 days;
5. To restore the absorption function and the concentrating function and the evacuation function of gallbladder within 10-14 days;
6. To increase the duration of complete clinical remission period up to 2-4 years.

These data will help diminish the quantity of patients with biliary diseases (the gallbladder dysfunction, the chronic acalculous cholecystitis (aseptic spastic) without biliary sludge, the chronic acalculous (enzymatic) cholecystitis, the chronic acalculous (infectious) cholecystitis, the chronic acalculous cholecystitis with biliary sludge, the chronic calculous cholecystitis, the acute calculous cholecystitis, the choledocholithiasis) and the quantity of patients with pancreatic diseases (the chronic biliary pancreatitis, the chronic (aseptic) pancreatitis, the chronic alcoholic (infectious) pancreatitis), the chronic (chymous infectious) pancreatitis, the chronic (acidic) pancreatitis and the quantity of patients with gastro-esophageal-reflux-disease, and, also, the quantity of patients after cholecystectomy by 30-40% after 18-24 months in different countries of the North America, Central America and South America, Europe and Asia Pacific, Africa and Middle East.

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Ursodeoxycholic acid: liver and gallbladder, hepatic and gallbladder bile, etc

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