Preliminary data

Table 1

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

**Biliary diseases** include gallbladder dysfunction, chronic acalculous cholecystitis without biliary sludge, and chronic acalculous cholecystitis with biliary sludge, chronic calculous cholecystitis, postcholecystectomy syndrome or condition after cholecystectomy.

**Concomitant functional disorders in the sphincter of Oddi includes:** 1. hypomotility of the sphincter of common bile duct [duodenogastric reflux: bile reflux gastritis (antral atrophic gastritis) and chronic «bland» intrahepatic cholestasis]; 2. spasm (hypertonus) of the sphincter of common bile duct [biliary type III of sphincter of Oddi dysfunction: chronic «bland» intragallbladder cholestasis (bile stasis) and chronic «bland» intrahepatic cholestasis]; 3. hypomotility of the sphincter of pancreatic duct [biliopancreatic reflux (length of the common channel (hepatopancreatic ampulla) > 5 mm): chronic biliary pancreatitis and chronic «bland» intrapancreatic pancreatostasis]; 4. spasm (hypertonus) of the sphincter of pancreatic duct [pancreatic type III of sphincter of Oddi dysfunction: chronic pancreatitis and chronic «bland» intrapancreatic pancreatostasis].

Chronic «bland» intragallbladder cholestasis is the decrease of secretion rate and volume of gallbladder bile. Chronic «bland» intrahepatic cholestasis is the decrease of secretion rate and volume of hepatic bile. Chronic «bland» intrapancreatic pancreatostasis is the decrease of secretion rate and volume of pancreatic juice.
Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction and sphincter of Oddi hypomotility and duodenogastric reflux (chronic bile reflux gastritis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile (low con GB).

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Gallbladder dysfunction

Fig. 1d. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction, sphincter of Oddi hypomotility and biliopancreatic reflux (chronic biliary pancreatitis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile (low con GB).

Fig. 1e. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction and small intestinal bacterial overgrowth syndrome (duodenal hypertension – the increase of intraluminal pressure in the duodenum). 1 = uncon HB; 2 = low concentrated GB.

Fig. 1f. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction after treatment with celecoxib and UDCA (normal motility of the sphincter of Oddi). 1 = unconcentrated hepatic bile; 2 = normal concentrated gallbladder bile.

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Increased COX-2 in the smooth muscle cells of cystic duct

Common bile duct (CBD)

Pressure in CBD – (+++)

Hypotonus of the sphincter of CBD

Pancreatic duct (PD)

Pressure in PD – (++)

Hypertonus or spasm of the sphincter of CBD

Sphincter of PD

Pressure in HPA – (++)

Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge, sphincter of Oddi hypomotility and duodenogastric reflux (chronic bile reflux gastritis). 1 = unconcentrated hepatic bile; 2 = low concentrated GB.

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Fig. 2d. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge, sphincter of Oddi hypermotility and biliopancreatic reflux (chronic biliary pancreatitis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 2e. Passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge and small intestinal bacterial overgrowth syndrome (duodenal hypertension – the increase of intraluminal pressure in the duodenum). 1 = uncon hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 2f. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge after treatment with celecoxib and UDCA (normal motility of the sphincter of Oddi). 1 = unconcentrated hepatic bile; 2 = normal concentrated gallbladder bile.

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Chronic acalculous cholecystitis. Biliary sludge.

Fig. 3a. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge, sphincter of Oddi hypomotility and duodenogastric reflux (chronic bile reflux gastritis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 3b. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge and biliary type III of sphincter of Oddi dysfunction (chronic spastic aseptic cholecystitis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 3c. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge and pancreatic type III of sphincter of Oddi dysfunction (chronic spastic aseptic pancreatitis). 1 = unconcentrated hepatic bile; 2 = low concentrated GB.

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Chronic acalculous cholecystitis. Biliary sludge.

Fig. 3d. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge, sphincter of Oddi hypomotility and biliopancreatic reflux (chronic biliary pancreatitis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 3e. Passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge and small intestinal bacterial overgrowth syndrome (duodenal hypertension – the increase of intraluminal pressure in the duodenum). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 3f. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge after treatment with celecoxib and UDCA (normal motility of the sphincter of Oddi). 1 = unconcentrated hepatic bile; 2 = normal concentrated gallbladder bile.

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Fig. 4a. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis, sphincter of Oddi hypomotility and duodenogastric reflux (chronic bile reflux gastritis). 1 = unconcentrated hepatic bile; 2 = low concentrated GB.

Fig. 4b. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis and biliary type III of sphincter of Oddi dysfunction (chronic spastic aseptic cholecystitis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 4c. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis and pancreatic type III of sphincter of Oddi dysfunction (chronic spastic aseptic pancreatitis). 1 = unconcentrated hepatic bile; 2 = low concentrated GB.

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Chronic calculous cholecystitis. Gallstone disease.

Increased COX-2 in the smooth muscle cells of cystic duct.

Pressure in CBD – (+)
Pressure in PD – (+)

Pressure in CBD – (-)
Pressure in PD – (-)

Pressure in Duodenum – (+)
Duodenal hypertension

PD - (+)
PD - (-)

Sphincter of CBD
Sphincter of PD
Sphincter of HPA

Normal tonus of the sphincter of CBD
Normal tonus of the sphincter of PD
Normal tonus of the sphincter of HPA

Duodenogastric reflux

Fig. 4d. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis, sphincter of Oddi hypomotility and biliopancreatic reflux (chronic biliary pancreatitis). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 4e. Passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis and small intestinal bacterial overgrowth syndrome (duodenal hypertension – the increase of intraluminal pressure in the duodenum). 1 = unconcentrated hepatic bile; 2 = low concentrated gallbladder bile.

Fig. 4f. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis after treatment with celecoxib and UDCA (normal motility of the sphincter of Oddi). 1 = unconcentrated hepatic bile; 2 = normal concentrated gallbladder bile.

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Postcholecystectomy syndrome.

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Fig. 5a. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy (postcholecystectomy syndrome), sphincter of Oddi hypomotility and duodeno-gastric reflux (chronic bile reflux gastritis).

Fig. 5b. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy (postcholecystectomy syndrome) and biliary type III of sphincter of Oddi dysfunction.

Fig. 5c. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy (postcholecystectomy syndrome) and pancreatic type III of sphincter of Oddi dysfunction (chronic spastic aseptic pancreatitis).

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Postcholecystectomy syndrome.

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Fig. 5d. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy (postcholecystectomy syndrome), sphincter of Oddi hypomotility and biliopancreatic reflux (chronic biliary pancreatitis).

Fig. 5e. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy (postcholecystectomy syndrome) and small intestinal bacterial overgrowth syndrome (duodenal hypertension – the increase of intraluminal pressure in the duodenum).

Fig. 5f. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy (postcholecystectomy syndrome) after treatment with celecoxib and UDCA (normal motility of the sphincter of Oddi).

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

<table>
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<tr>
<th>Type of reflux or dysfunction</th>
<th>Target organ – Gallbladder</th>
<th>Possibly reflux associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal-biliary reflux (duodenal juice) ± <em>Salmonella enterica</em> serovar Typhi</td>
<td>Chronic (infectious) cholecystitis. Mixed or Pigment (brown) gallstone disease. Chronic calculous cholecystitis. Metaplasia.</td>
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<tr>
<td>Duodenal-biliary (acidic) reflux (duodenal juice and gastric juice) ± <em>Helicobacter pylori</em></td>
<td>Chronic (infectious) cholecystitis. Mixed or Pigment (brown) gallstone disease. Chronic calculous cholecystitis. Gastric metaplasia.</td>
<td></td>
</tr>
<tr>
<td>Type of reflux or dysfunction</td>
<td>Target organ – Pancreas</td>
<td>Chronic biliary pancreatitis. Biliary metaplasia. Dysplasia. Pancreatic cancer.</td>
</tr>
<tr>
<td>Biliopancreatic reflux (liothigenic bile)</td>
<td>Chronic (spastic aseptic) pancreatitis.</td>
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<tr>
<td>Pancreatic type III of sphincter of Oddi dysfunction (spasm of sphincter of pancreatic duct)</td>
<td>Chronic (alcoholic infectious) pancreatitis.</td>
<td></td>
</tr>
<tr>
<td>Duodenal-pancreatic alcohol reflux (duodenal juice and gastric juice and alcohol)</td>
<td>Chronic (alcoholic infectious) pancreatitis.</td>
<td></td>
</tr>
<tr>
<td>Duodenal-pancreatic reflux (duodenal juice) ± <em>Salmonella enterica</em> serovar Typhi</td>
<td>Chronic (infectious) pancreatitis.</td>
<td></td>
</tr>
<tr>
<td>Type of reflux or dysfunction</td>
<td>Target organ – Duodenum – Stomach – Esophagus</td>
<td>Gallstone disease. Chronic calculous cholecystitis. Chronic pancreatitis.</td>
</tr>
<tr>
<td>Duodenogastric reflux (duodenal juice)</td>
<td>Bile reflux gastritis. Atrophic antral gastritis. Intestinal metaplasia.</td>
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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 cholecystec-
Reflux associated diseases

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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 (cecloxib, nimesulide, etc.): cecloxib – 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 spasmyotics (pinaverium bromide, mebeverine hydrochloride, hycromecrine, hyoscine butylbromide, etc.): hycromecrine – 200 mg or 400 mg or 600 mg * 3 times per day during 5-7 days.
4. Nonselective spasmyotics (drotaverine hydrochloride, papaverine hydrochloride, fenpireverine, 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, panzy norm forte, pancreofilat, festrol, 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 (omeprazole, lansoprazole, esomeprazole, 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 presented data and this algorithm of pathogenetic treatment of biliary diseases with concomitant functional disorders in the 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 gall-bladder 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 cholecdocholithiasis,
- in patients with pancreaticobiliary reflux of pancreatic juice into common bile duct and the gallbladder (hypo mobility of the sphincter of Oddi) 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 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 (hypo motility of the sphincter of hepatopancreatic ampulla and sphincter of com-
Reflux associated diseases

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mon 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 (hymoptomity 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 I I 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 (hymoptomity 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 (acic) pancreatitis.

- in patients with duodenogastric bile reflux (hymoptomity 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 proximal gastritis (bile reflux gastritis),

- in patients with duodenogastroesophageal bile reflux (hymoptomity of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla, and hymoptomity 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 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 (acic) 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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Celcoxib and UDCA


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Reflux associated diseases


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