J.L. Turumin, MD, PhD, DMSci.

Preliminary Data

Table 1.

Combinations of Biliary Diseases and Concomitant Functional Disorders in the Sphincter of Oddi

		Gallbladder and Cystic Duct			Concomitant Functional Disorders in the Sphincter of Oddi			
	Localization	gallbladder wall	gallbladder wall	cystic duct	sphincter of common bile duct		sphincter of pancreatic duct	
	Mechanism	COX-2 expression	COX-2 expression	COX-2 expression	hypomotility	spasm	hypomotility	spasm
		smooth muscle cells	epithelial cells	increased cystic duct resistance	duodenogastric reflux	biliary type III of Oddi dysfunction	biliopancreatic reflux	pancreatic type III of Oddi dysfunction
	Manifestation	gallbladder hypomotility	hypersecretion of biliary mucin	chronic «bland» intragallbladder cholestasis	chronic «bland» intrahepatic cholestasis	chronic «bland» intrahepatic cholestasis	chronic «bland» intrapancreatic pancreatostasis	chronic «bland» intrapancreatic pancreatostasis
	Disease	gallbladder stasis	gallbladder stasis	gallbladder stasis	antral atrophic gastritis	gallbladder stasis	chronic biliary pancreatitis	chronic pancreatitis
	Main symptom	pain in the right hypochondrium	biliary mucin in gallbladder	pain in the right hypochondrium	bitterness in one's mouth	pain in the right hypochondrium	pain in the left hypochondrium	pain in the left hypochondrium
	Biliary Diseases							
1	Gallbladder dysfunction	+		31%	5%	28%	14%	
2	Chronic acalculous cholecystitis without biliary sludge	++	++	42%	15%	55%	16%	
3	Chronic acalculous cholecystitis with biliary sludge	+++	+++	35%	25%	65%	21%	
4	Chronic calculous cholecystitis	++	++	28%	25%	61%	25%	
5	Postcholecystectomy syndrome or Condition after Cholecystectomy				32%	25%	30%	

The algorithm of the pathogenetic treatment of symptomatic (with biliary pain)
Biliary Diseases and Concomitant Functional Disorders in the Sphincter of Oddi

Biliary Diseases includes 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.

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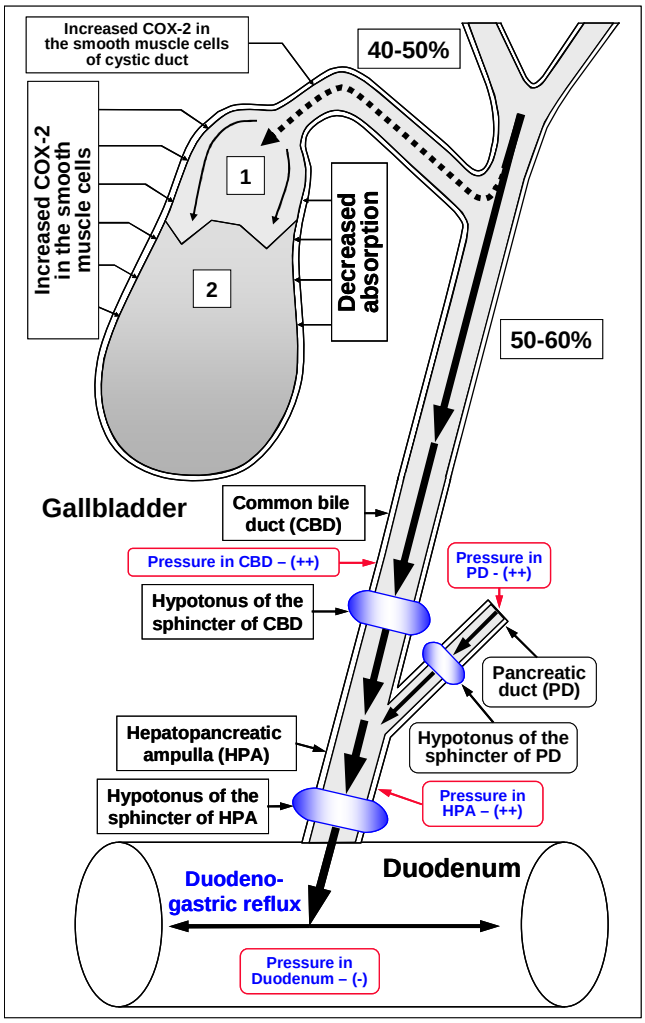
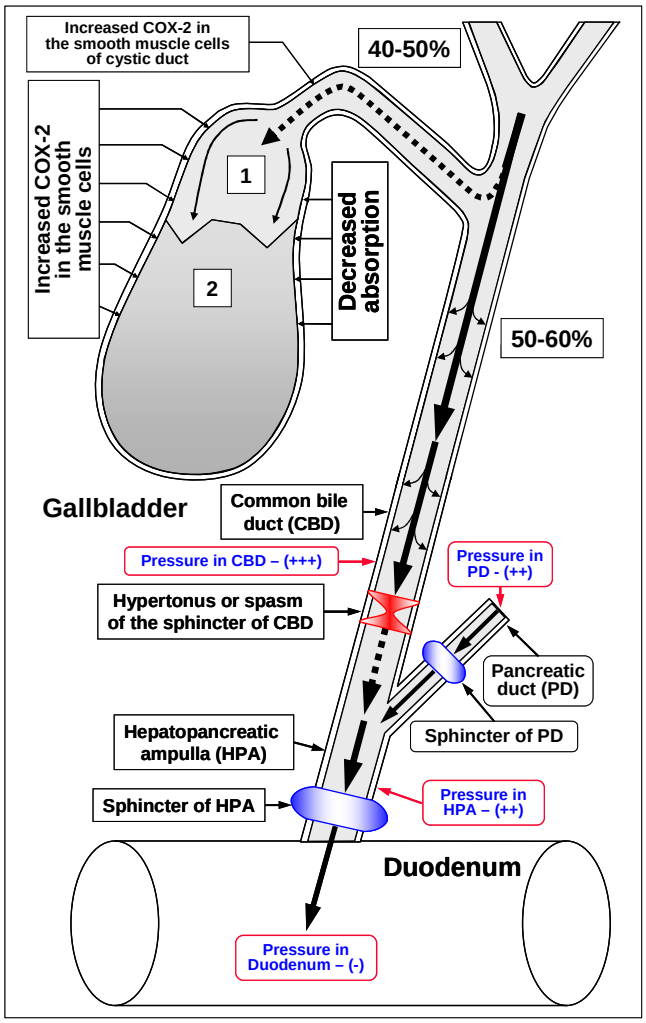
The algorithm of the pathogenetic treatment of symptomatic (with biliary pain) Biliary Diseases and Concomitant Functional Disorders in the Sphincter of Oddi Gallbladder Dysfunction



Gallbladder dysfunction and sphincter of Oddi hypomotility and duodenogastric reflux

Fig. 1. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) and duodenogastric reflux.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective prokinetics (domperidone, cizapride, metoclopramide, etc.) and ursodeoxycholic acid (UDCA).



Gallbladder dysfunction and biliary type III of sphincter of Oddi dysfunction

Fig. 2. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction and hypertonus (spasm) of the sphincter of common bile duct (biliary type III of sphincter of Oddi dysfunction). The increase of COX-2 activity in the smooth muscle cells of the sphincter of common bile duct may be accompanied by hypertonus (spasm) formation.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, etc.) and ursodeoxycholic acid (UDCA).

Decrease in the evacuation function of the gallbladder to less than 40% results in the decrease in the "active" and "passive" passage of the hepatic bile into the gallbladder and in the concentration of total bile acids in the gallbladder bile (fig. 1, 2). The decrease of the "active" and "passive" passage of the hepatic bile into the gallbladder results in the increase of the passage of the hepatic bile into duodenum (fig. 1, 2).

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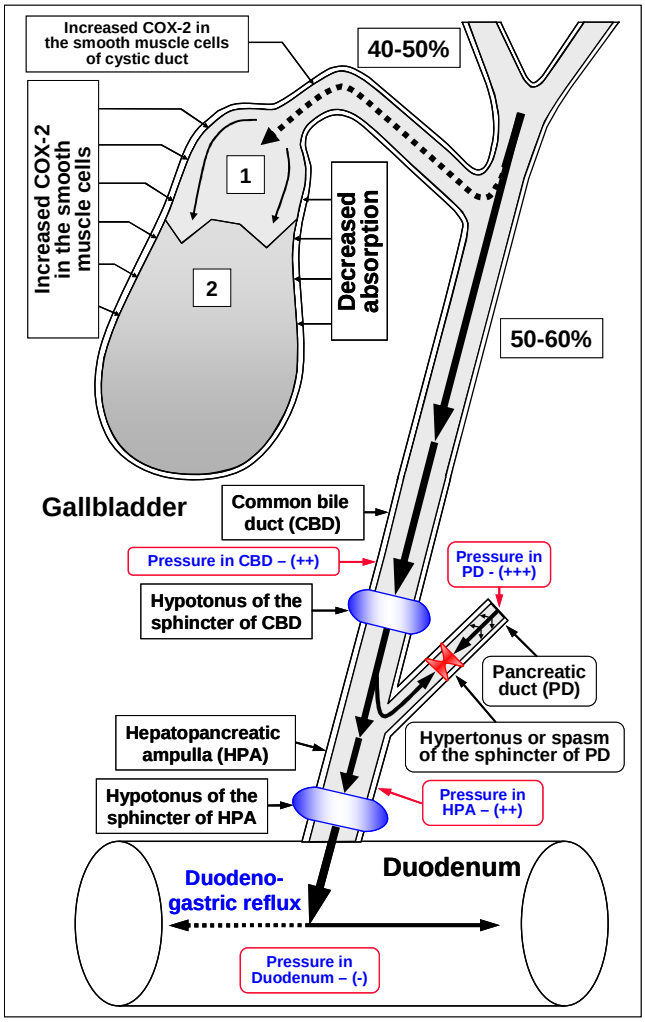
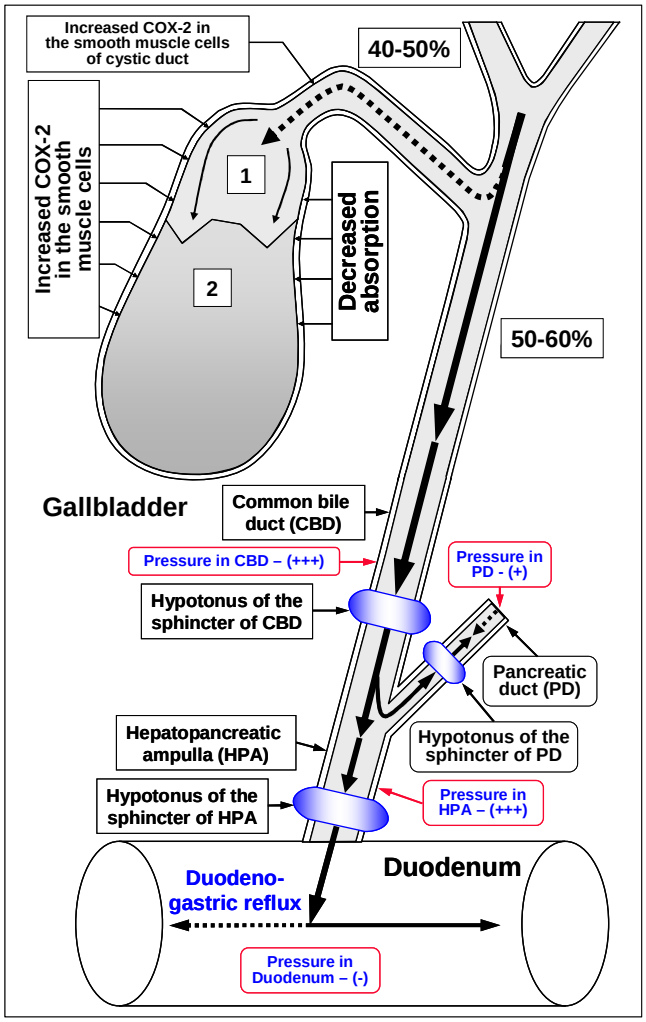
Gallbladder Dysfunction



Gallbladder dysfunction and pancreatic type III of sphincter of Oddi dysfunction (chronic pancreatitis)

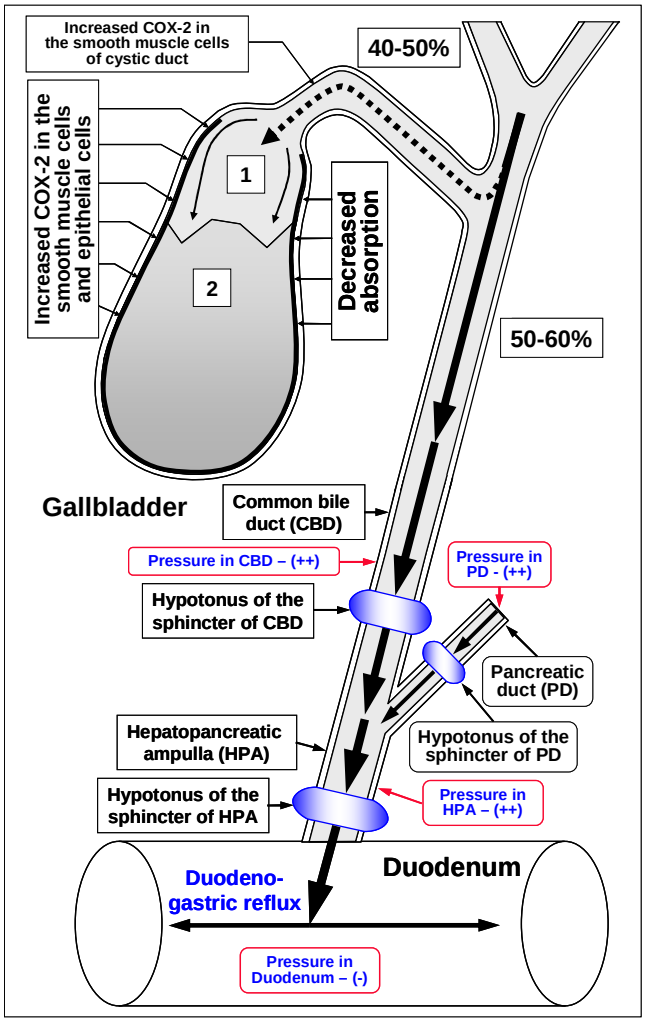
Fig. 3. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction and pancreatic type III of sphincter of Oddi dysfunction (hypomotility of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla, hypertonus (spasm) of the sphincter of pancreatic duct). The increase of COX-2 activity in the smooth muscle cells of the sphincter of pancreatic duct may be accompanied by hypertonus (spasm) formation.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.
Treatment: COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).



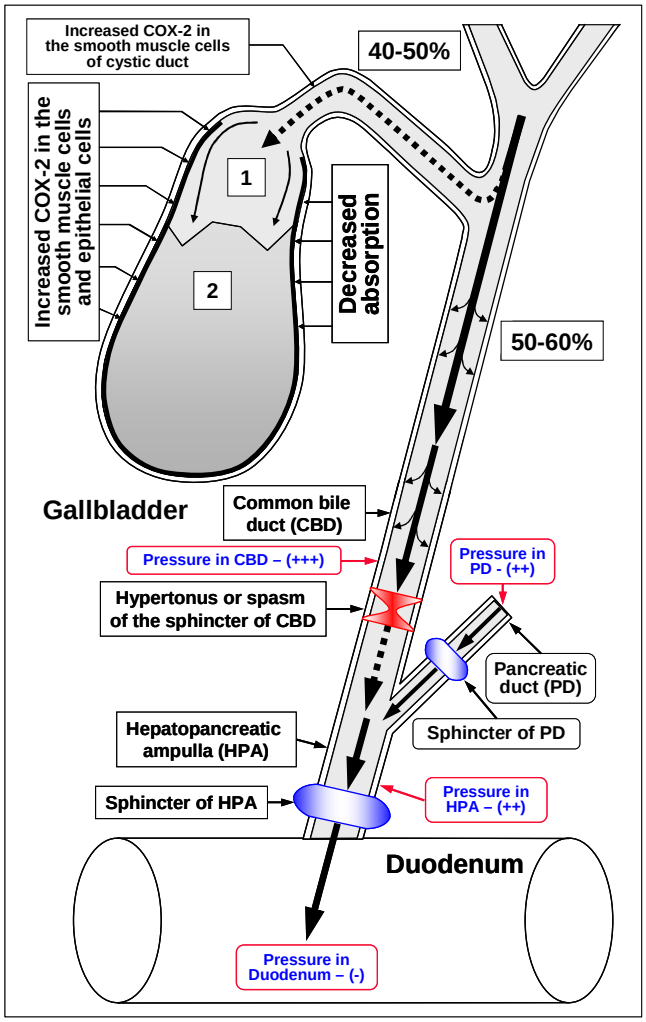
Gallbladder dysfunction and sphincter of Oddi hypomotility with biliopancreatic reflux (chronic biliary pancreatitis)

Fig. 4. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with gallbladder dysfunction, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) with biliopancreatic reflux.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.
Treatment:
COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective prokinetics (domperidone, cizapride, metoclopramide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Chronic acalculous cholecystitis without biliary sludge



Chronic acalculous cholecystitis without biliary sludge, sphincter of Oddi hypomotility and duodenogastric reflux



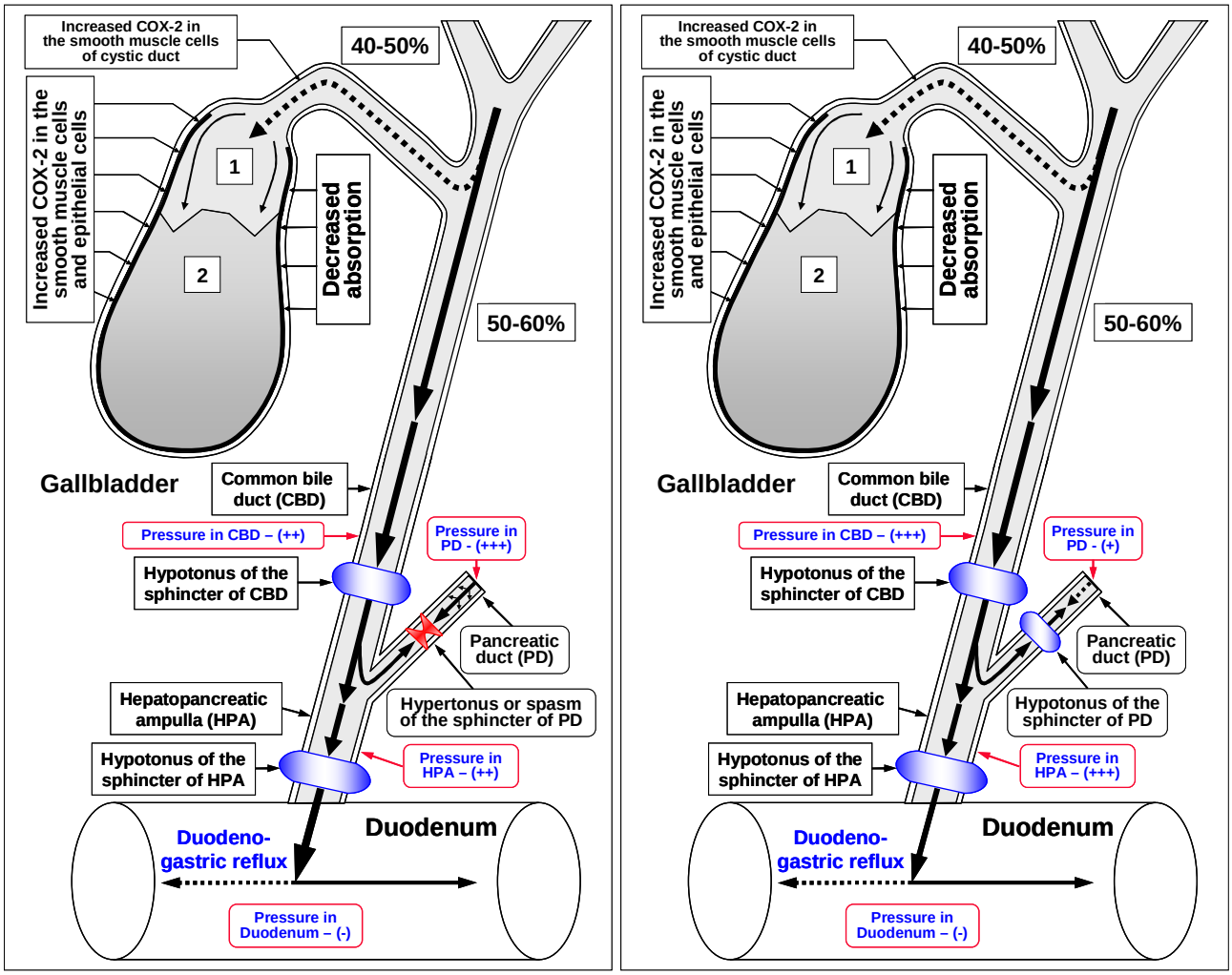
Chronic acalculous cholecystitis without biliary sludge and biliary type III of sphincter of Oddi dysfunction

Fig. 5. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) and duodenogastric reflux.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective prokinetics (domperidone, cizapride, metoclopramide, etc.) and ursodeoxycholic acid (UDCA).

Fig. 6. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge and hypertonus (spasm) of the sphincter of common bile duct (biliary type III of sphincter of Oddi dysfunction). The increase of COX-2 activity in the smooth muscle cells of the sphincter of common bile duct may be accompanied by hypertonus (spasm) formation.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, etc.) and ursodeoxycholic acid (UDCA).

High COX-2 expression in the epithelial cells of the gallbladder mucosa causes decrease of the absorption function of the gallbladder (decrease of water and biliary cholesterol absorption) and "passive" passage of the hepatic bile into the gallbladder (fig. 5, 6). Decrease in "active" and "passive" passage of the hepatic bile into the gallbladder causes increase in passage of hepatic bile into the duodenum (fig. 5, 6).

Chronic acalculous cholecystitis without biliary sludge



Chronic acalculous cholecystitis without biliary sludge and pancreatic type III of sphincter of Oddi dysfunction (chronic pancreatitis)

Chronic acalculous cholecystitis without biliary sludge and sphincter of Oddi hypomotility with biliopancreatic reflux (chronic biliary pancreatitis)

Fig. 7. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge and pancreatic type III of sphincter of Oddi dysfunction (hypomotility of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla, hypertonus (spasm) of the sphincter of pancreatic duct). The increase of COX-2 activity in the smooth muscle cells of the sphincter of pancreatic duct may be accompanied by hypertonus (spasm) formation.

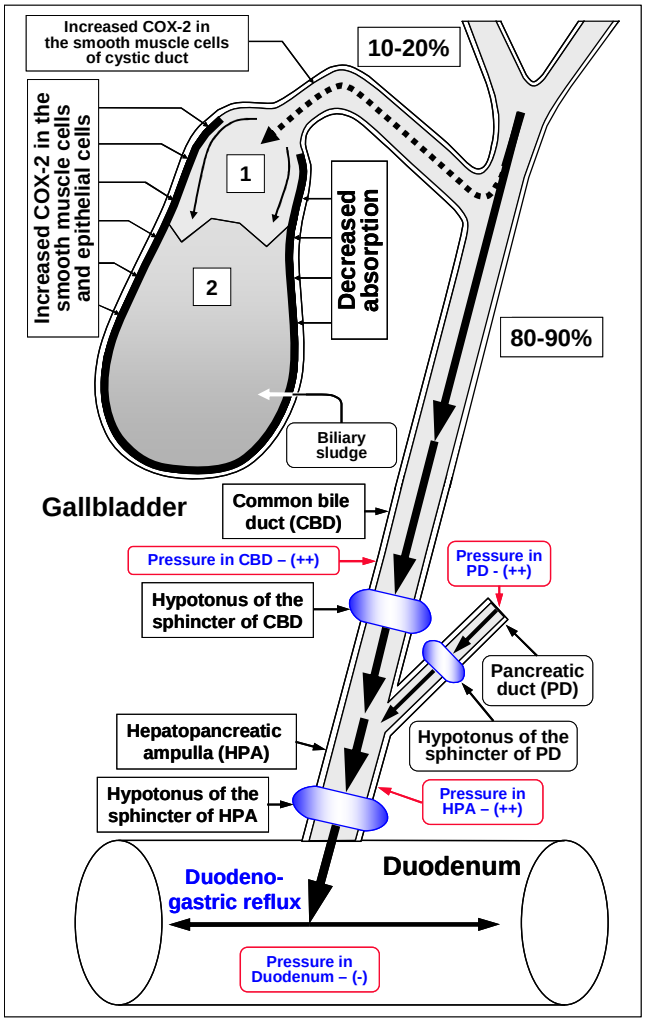
Treatment: COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Fig. 8. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis without biliary sludge and sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) with biliopancreatic reflux.

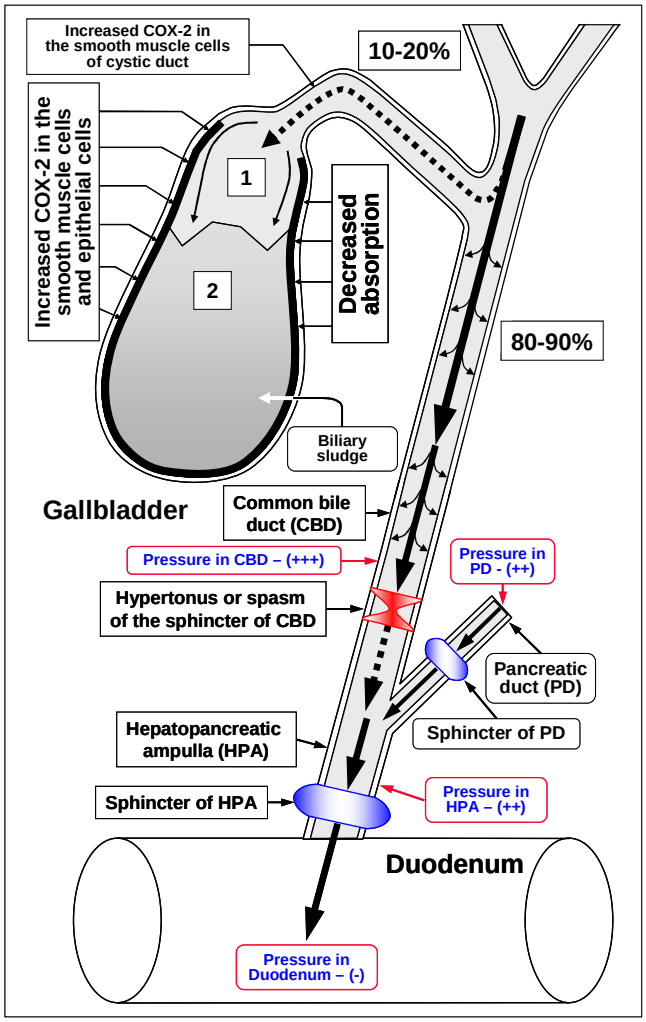
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.

Treatment:
COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective prokinetics (domperidone, cizapride, metoclopramide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Chronic acalculous cholecystitis with biliary sludge



Chronic acalculous cholecystitis with biliary sludge, sphincter of Oddi hypomotility and duodenogastric reflux



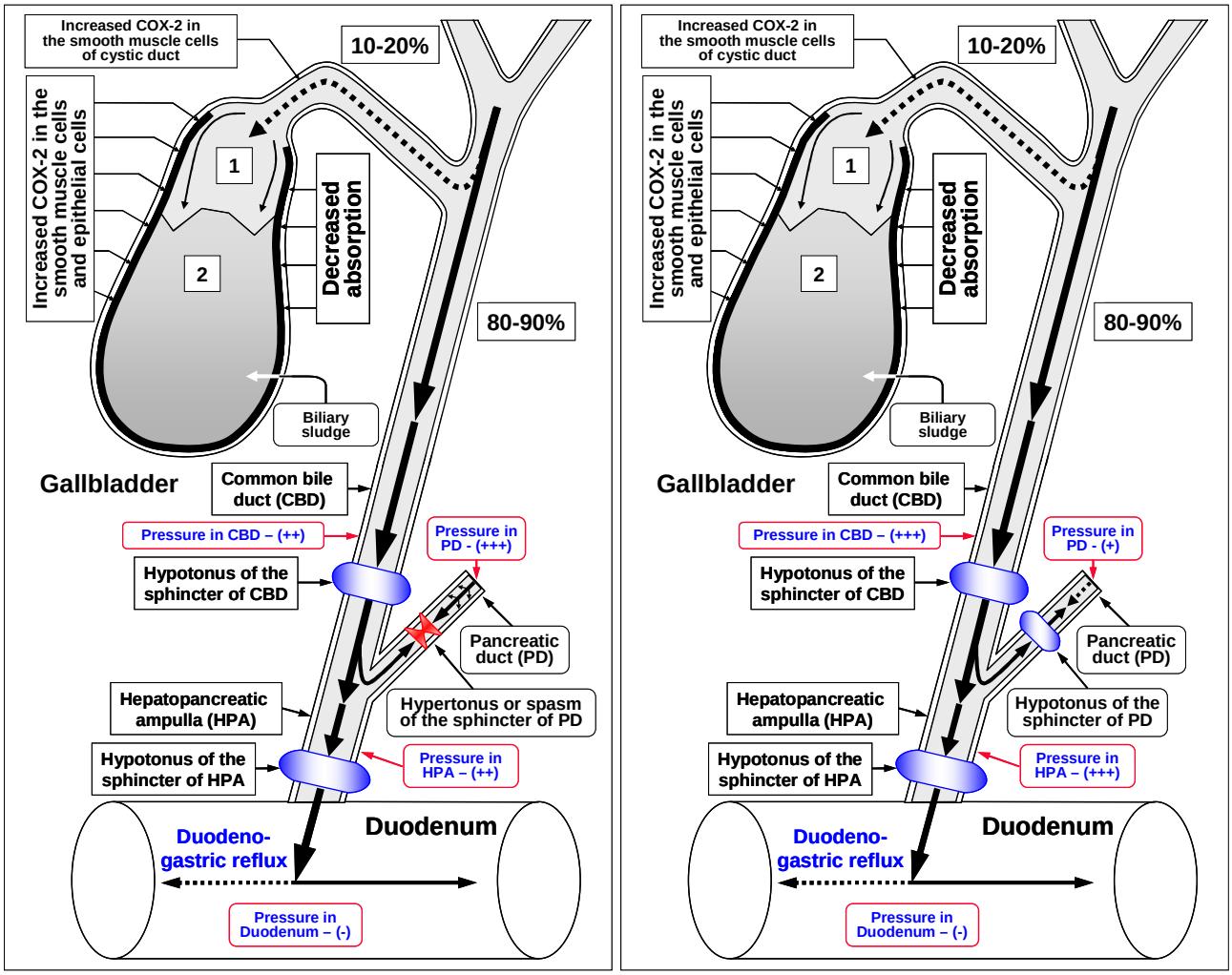
Chronic acalculous cholecystitis with biliary sludge and biliary type III of sphincter of Oddi dysfunction

Fig. 9. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) and duodenogastric reflux.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective prokinetics (domperidone, cizapride, metoclopramide, etc.) and ursodeoxycholic acid (UDCA).

Fig. 10. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge and hypertonus (spasm) of the sphincter of common bile duct (biliary type III of sphincter of Oddi dysfunction). The increase of COX-2 activity in the smooth muscle cells of the sphincter of common bile duct may be accompanied by hypertonus (spasm) formation. **Treatment:** selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, etc.) and ursodeoxycholic acid (UDCA).

Surplus COX-2 expression in the epithelial cells of the gallbladder mucosa causes decrease in the absorption function of the gallbladder (decrease of water and biliary cholesterol absorption) and "passive" passage of the hepatic bile into the gallbladder (fig. 9, 10). Decrease in "active" and "passive" passage of the hepatic bile into the gallbladder causes increase in passage of hepatic bile into the duodenum (fig. 9, 10).

Chronic acalculous cholecystitis with biliary sludge



Chronic acalculous cholecystitis with biliary sludge and pancreatic type III of sphincter of Oddi dysfunction (chronic pancreatitis)

Chronic acalculous cholecystitis with biliary sludge and sphincter of Oddi hypomotility with biliopancreatic reflux (chronic biliary pancreatitis)

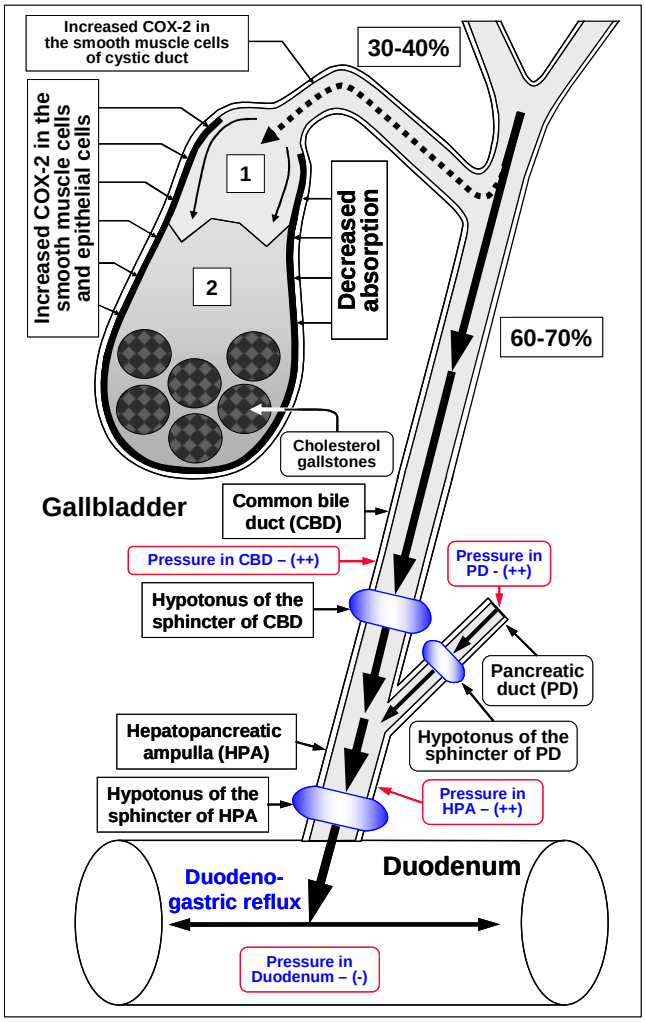
Fig. 11. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge and pancreatic type III of sphincter of Oddi dysfunction (hypomotility of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla, hypertonus (spasm) of the sphincter of pancreatic duct). The increase of COX-2 activity in the smooth muscle cells of the sphincter of pancreatic duct may be accompanied by hypertonus (spasm) formation.

Treatment: COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Fig. 12. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic acalculous cholecystitis with biliary sludge and sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) with biliopancreatic reflux.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.

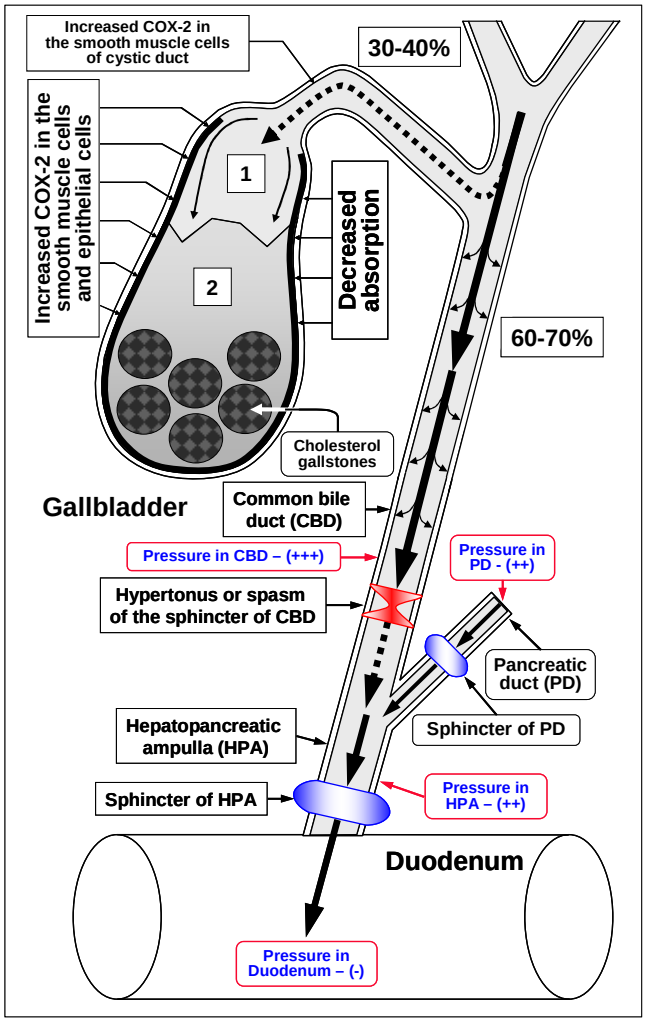
Treatment:
COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective prokinetics (domperidone, cizapride, metoclopramide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Gallstone Disease or Chronic calculous cholecystitis



Chronic calculous cholecystitis, sphincter of Oddi hypomotility and duodenogastric reflux

Fig. 13. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) and duodenogastric reflux.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective prokinetics (domperidone, cizapride, metoclopramide, etc.) and ursodeoxycholic acid (UDCA).

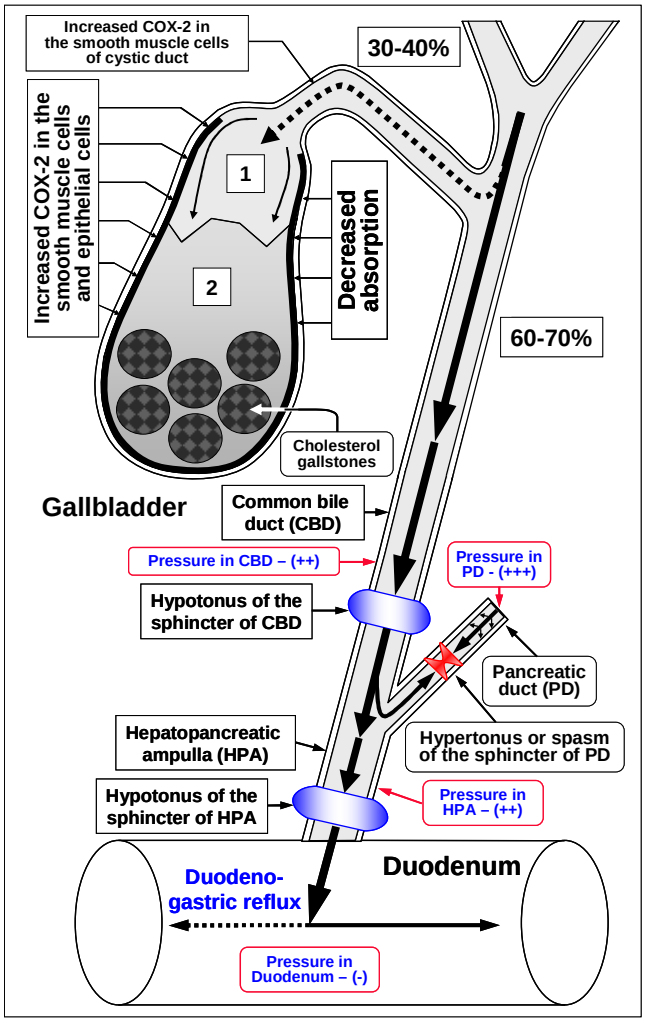


Chronic calculous cholecystitis and biliary type III of sphincter of Oddi dysfunction

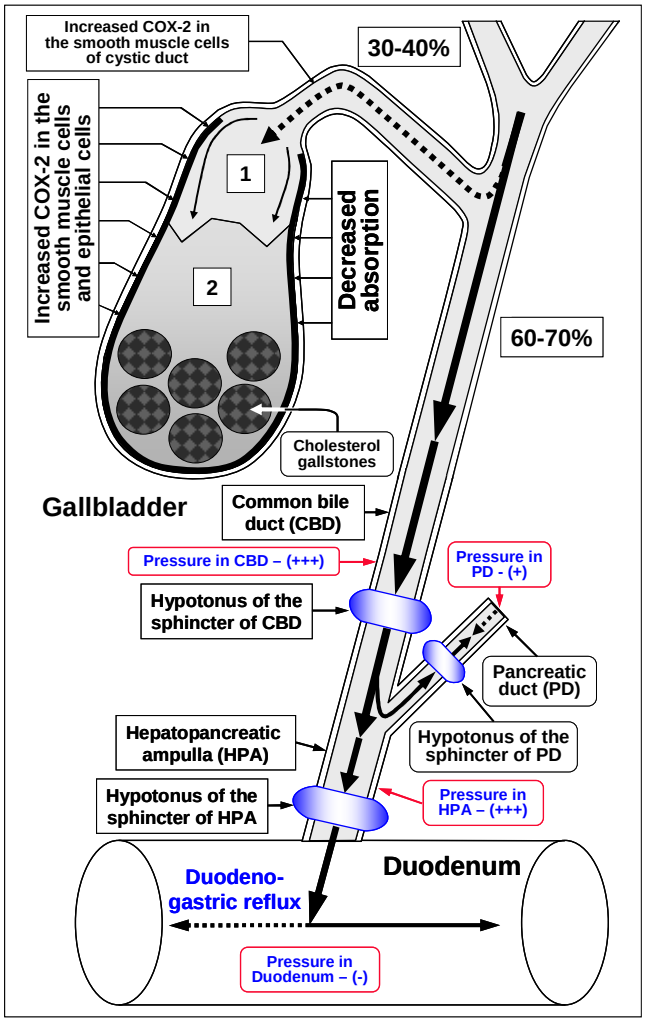
Fig. 14. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis and hypertonus (spasm) of the sphincter of common bile duct (biliary type III of sphincter of Oddi dysfunction).
The increase of COX-2 activity in the smooth muscle cells of the sphincter of common bile duct may be accompanied by hypertonus (spasm) formation. **Treatment:** selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, etc.) and ursodeoxycholic acid (UDCA).

Surplus COX-2 expression in the epithelial cells of the gallbladder mucosa makes for decrease of the absorption function of the gallbladder (decrease of water and biliary cholesterol absorption) and "passive" passage of the hepatic bile into the gallbladder (fig. 13, 14). Also, gallstones volume in the gallbladder lumen may be the cause of decreased "active" and "passive" passage of the hepatic bile into the gallbladder (from 50% to 5%). The decrease in "active" and "passive" passage of the hepatic bile into the gallbladder causes increase of passage of hepatic bile into duodenum (fig. 13, 14).

Gallstone Disease or Chronic calculous cholecystitis



Chronic calculous cholecystitis and pancreatic type III of sphincter of Oddi dysfunction (chronic pancreatitis)



Chronic calculous cholecystitis and sphincter of Oddi hypomotility with biliopancreatic reflux (chronic biliary pancreatitis)

Fig. 15. 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 (hypomotility of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla, hypertonus (spasm) of the sphincter of pancreatic duct). The increase of COX-2 activity in the smooth muscle cells of the sphincter of pancreatic duct may be accompanied by hypertonus (spasm) formation.

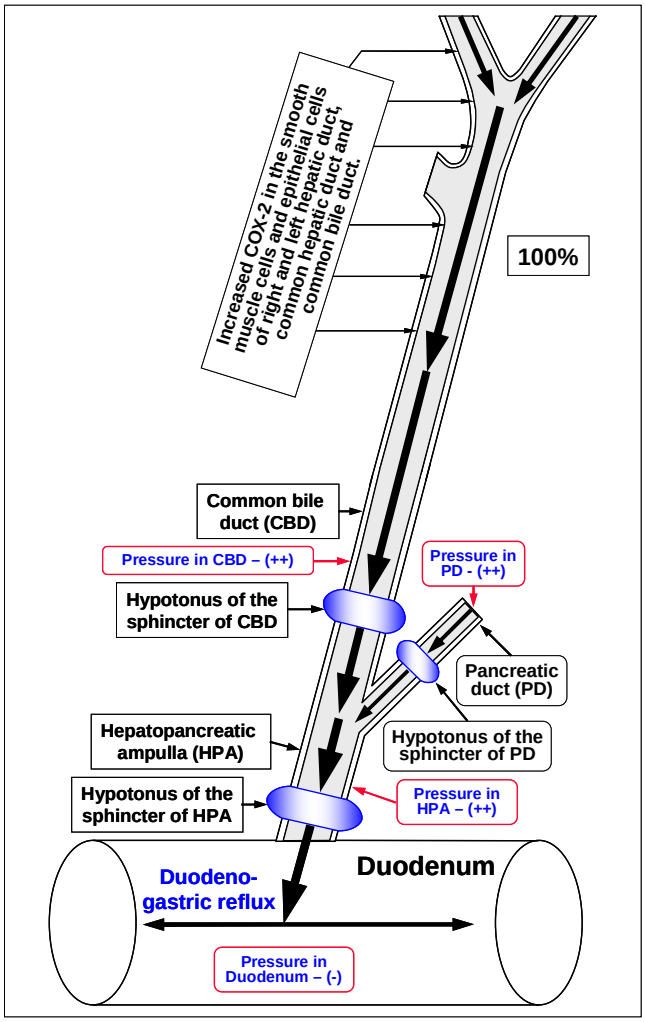
Treatment: COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Fig. 16. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients with chronic calculous cholecystitis, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) with biliopancreatic reflux.

1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.

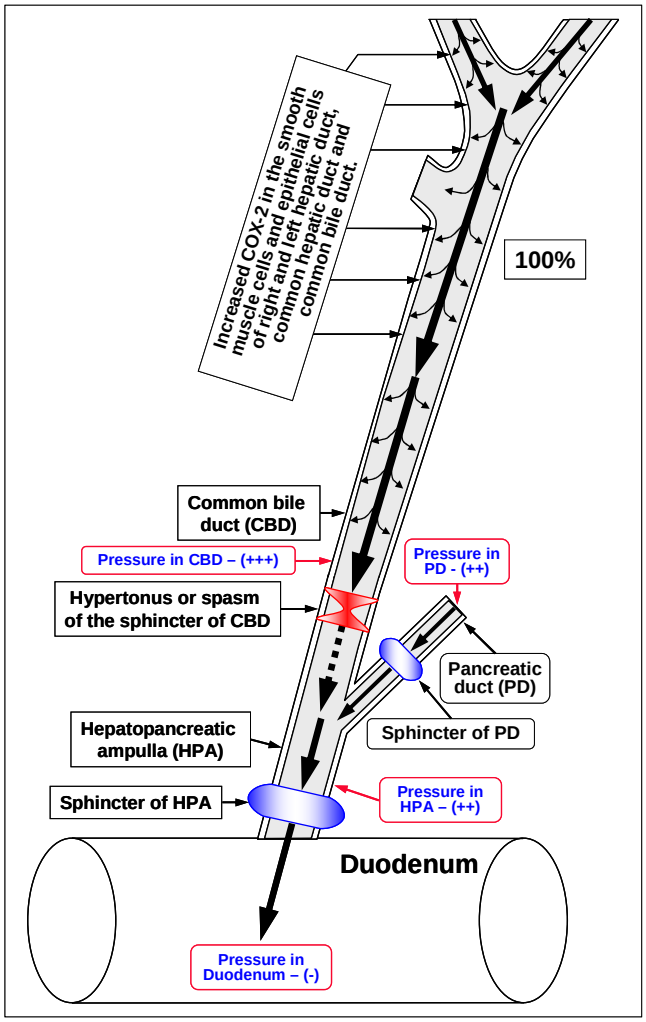
Treatment:
COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective prokinetics (domperidone, cizapride, metoclopramide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Postcholecystectomy Syndrome or Condition after Cholecystectomy (Gallbladder Removal)



Postcholecystectomy Syndrome or Condition after Cholecystectomy, sphincter of Oddi hypomotility and duodenogastric reflux

Fig. 17. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) and duodeno-gastric reflux.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective prokinetics (domperidone, cizapride, metoclopramide, etc.) and ursodeoxycholic acid (UDCA).

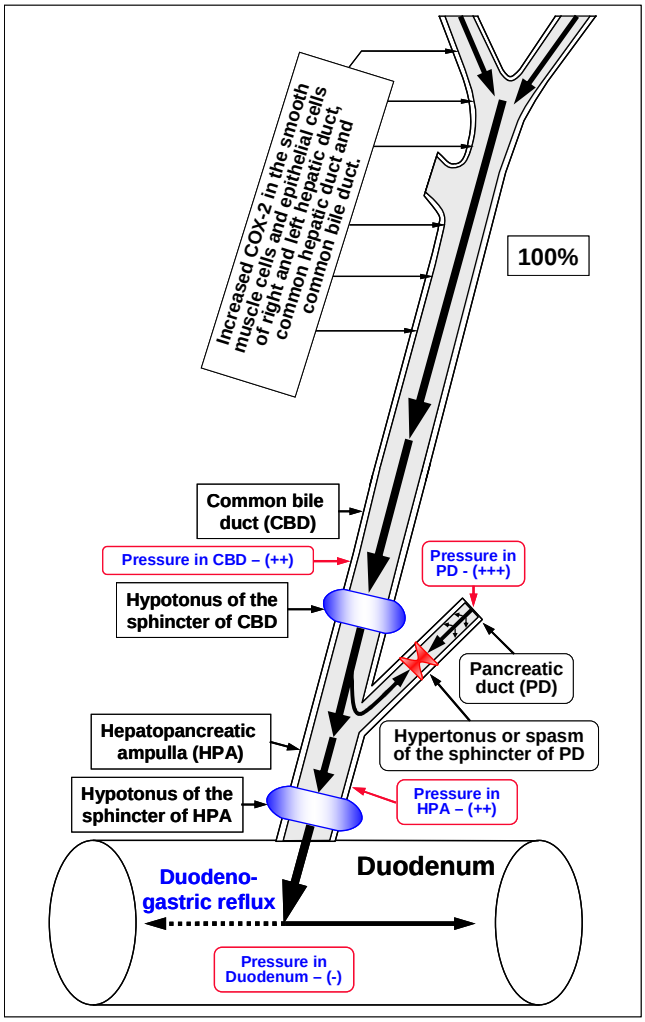


Postcholecystectomy Syndrome or Condition after Cholecystectomy and biliary type III of sphincter of Oddi dysfunction

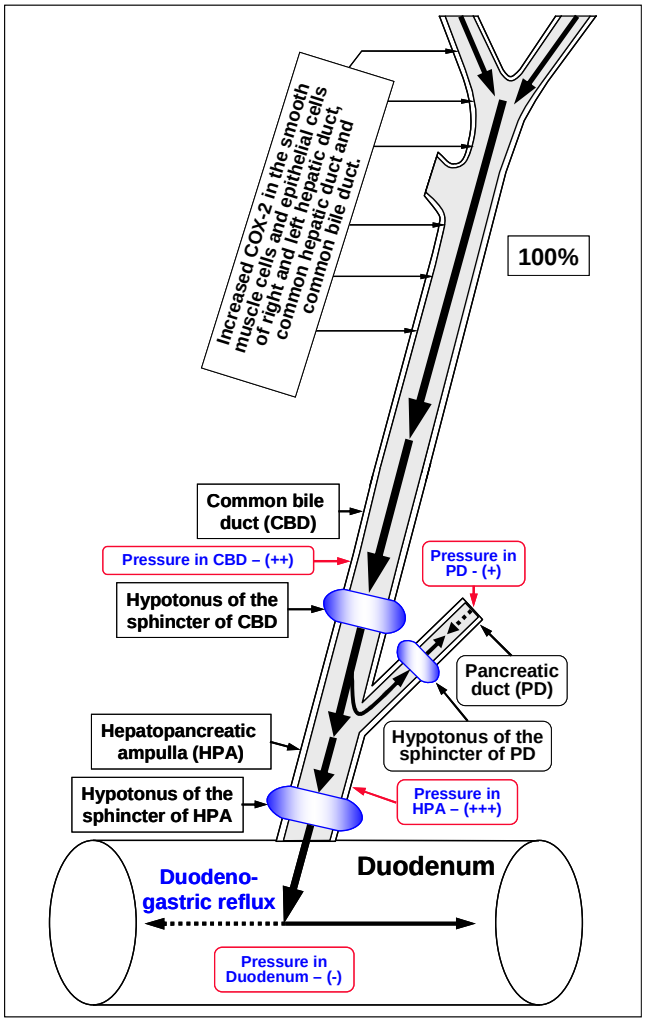
Fig. 18. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy and hypertonus (spasm) of the sphincter of common bile duct (biliary type III of sphincter of Oddi dysfunction). The increase of COX-2 activity in the smooth muscle cells of the sphincter of common bile duct may be accompanied by hypertonus (spasm) formation.
Treatment: selective COX-2 inhibitors (celecoxib, nimesulide, etc.), selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, etc.) and ursodeoxycholic acid (UDCA).

Absence of the gallbladder leads to surplus passage of hepatic bile only into the duodenum (fig. 17, 18). Due to dysfunction of the sphincter of Oddi (high degree of COX-2 expression in the smooth muscle and epithelial cells of the sphincter of Oddi), hindered passage of hepatic bile into the duodenum causes development of the functional biliary hypertension, dilating of the common hepatic duct and common bile duct, development of the biliary pain in epigastrium or right hypochondrium (high degree of COX-2 expression in the smooth muscle and epithelial cells of the biliary tract) (fig. 17, 18).

Postcholecystectomy Syndrome or Condition after Cholecystectomy (Gallbladder Removal)



Postcholecystectomy Syndrome or Condition after Cholecystectomy and pancreatic type III of sphincter of Oddi dysfunction (chronic pancreatitis)



Postcholecystectomy Syndrome or Condition after Cholecystectomy and sphincter of Oddi hypomotility with biliopancreatic reflux (chronic biliary pancreatitis)

Fig. 19. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy and pancreatic type III of sphincter of Oddi dysfunction (hypomotility of the sphincter of common bile duct and sphincter of hepatopancreatic ampulla, hypertonus (spasm) of the sphincter of pancreatic duct). The increase of COX-2 activity in the smooth muscle cells of the sphincter of pancreatic duct may be accompanied by hypertonus (spasm) formation.

Treatment: COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective spasmolytics (pinaverium bromide, mebeverine hydrochloride, hymecromone, hyoscine butylbromide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).

Fig. 20. Passage of hepatic bile and pancreatic juice into the duodenum lumen in patients after cholecystectomy, sphincter of Oddi hypomotility (hypomotility of the sphincter of common bile duct, sphincter of pancreatic duct and sphincter of hepatopancreatic ampulla) with biliopancreatic reflux.

1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.

Treatment:
COX-2 inhibitors (celecoxib, nimesulide, etc.),
selective prokinetics (domperidone, cizapride, metoclopramide, ets.),
pancreatic enzymes (mezym forte, panzynorm forte, pancreoflat, festal, kreon, etc.) and
ursodeoxycholic acid (UDCA).