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Current Aspects of Prognosis, Differential Diagnosis, and Spasmolytic Therapy in Gallstone Disease

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Aim: to analyze current aspects of prognosis, differential diagnosis, and spasmolytic therapy in gallstone disease.
Key points. The prevalence of gallstone disease in the Russian Federation remains considerably high. Cholelithiasis is associated with cardiovascular disorders and an increased risk of malignancies, including gastric, hepatic, renal, and gallbladder cancer. Several studies emphasize the correlation between the presence and size of gallbladder polyps and the development of gallbladder carcinoma. The current paradigm of biliary pathology postulates that the combined influence of *Lith* gene polymorphisms, motility disorders, chronic inflammation, and metabolic factors initiates lithogenesis, which in turn promotes chronic cholecystitis and may contribute to gallbladder carcinogenesis. Abdominal pain predominantly localized in the right upper quadrant is the leading clinical manifestation of biliary dyskinesia, chronic cholecystitis, and cholelithiasis. Spasmolytic therapy is considered appropriate for the relief of biliary pain. Clinical studies have demonstrated that the use of the selective spasmolytic agent mebeverine in patients with biliary tract disorders effectively alleviates right upper quadrant pain, improves functional status of the biliary tract, and indirectly facilitates the elimination of biliary sludge.
Conclusion. Gallstone disease represents a key nosological entity within the biliary continuum, characterized by the sequential development of pathogenetically related disorders of the biliary tract. Management of biliary system disorders should focus on relieving biliary pain, restoring motility of the biliary tract, and normalizing the physicochemical properties of bile.
Keywords: cholelithiasis, gallstone disease, gallbladder polyps, gallbladder cancer, spasmolytics, mebeverine
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Актуальные аспекты прогноза, дифференциального диагноза и спазмолитической терапии при желчнокаменной болезни

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Цель: проанализировать актуальные аспекты прогноза, дифференциального диагноза и спазмолитической терапии при желчнокаменной болезни.
Основные положения. Распространенность желчнокаменной болезни в Российской Федерации остается достаточно высокой. Холелитиаз ассоциирован с сердечно-сосудистыми заболеваниями и с высоким риском онкологических заболеваний, в том числе рака желудка, печени, почек и рака желчного пузыря. Ряд исследований подчеркивает ассоциацию наличия и размеров полипов в желчном пузыре с раком желчного пузыря. Современная парадигма билиарной патологии постулирует, что сочетанное действие полиморфизма *Lith*-генов, нарушений моторики, хронического воспаления и метаболических факторов инициируют холелитогенез, в свою очередь, стимулирующий развитие хронического холецистита, что способно приводить к канцерогенезу в желчном пузыре. Абдоминальная боль с преимущественной локализацией в правом подреберье служит ведущим проявлением дискинезии желчевыводящих путей, хронического холецистита и холелитиаза. Для купирования билиарной боли целесообразно назначение спазмолитиков. В клинических исследованиях было показано, что применение селективного спазмолитика мебеверина у больных с заболеваниями желчевыводящих путей эффективно купирует боль в правом подреберье, улучшает функциональное состояние билиарного тракта и, опосредованно, приводит к элиминации билиарного сладжа.

Заключение. Желчнокаменная болезнь служит ключевой нозологической формой билиарного континуума, с последовательным развитием патогенетически связанных заболеваний билиарного тракта. Лечение заболеваний билиарной системы должно быть направлено на купирование билиарной боли, восстановление моторики желчевыводящих путей и нормализацию физико-химических свойств желчи.
Ключевые слова: холелитиаз, желчнокаменная болезнь, полипы желчного пузыря, рак желчного пузыря, спазмолитики, мебеверин
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Introduction

Concepts regarding the prognosis of gallstone disease (GSD) have undergone significant changes. On the one hand, this is related to the development of complications, particularly in certain patient groups; on the other hand, it is driven by evidence of an increased risk of cardiovascular disease and malignancies of various localizations [1]. A 32-year follow-up of 86,000 women and 44,000 men demonstrated higher overall mortality from cancer of different sites and cardiovascular disease among individuals with biliary pathology [2]. In a long-term cohort study involving 239,799 participants, the presence of gallstones was associated with a markedly increased risk of gastric cancer (odds ratio (OR) — 2.54), liver and biliary tract cancer (OR — 2.46), renal cancer (OR — 2.04), and gallbladder cancer (OR — 2.23) [3]. A meta-analysis of 51 studies comprising 13 million patients confirmed a significant increase in cancer risk among those with cholelithiasis (OR— 1.43), including gastric and colorectal cancer (OR — 1.28), as well as liver, pancreatic, and biliary tract cancer (OR — 1.84) [4].

Elderly and comorbid patients with biliary tract disorders represent a special category, and the choice of management strategy for GSD complications in these individuals remains a challenging issue [5–7].

Prevalence of gallstone disease

The prevalence of GSD in Western Europe and North America ranges from approximately 15 to 20 % [8, 9]. A 2024 meta-analysis on global epidemiology of cholelithiasis, which included 115 studies and over 32 million patients, reported a worldwide prevalence of gallstones of 6.1 % (7.6 % in women and 5.4 % in men). The frequency of GSD is consistently higher among older individuals [10]. Our epidemiological studies revealed that the prevalence of cholelithiasis among Caucasian populations in Evenkia and Khakassia was 8.8 and 7.2 %, respectively, whereas among indigenous populations it was 1.5 % in Evenkia, 3.4 % in Khakassia, and 7.3 % in Tuva. These findings underscore the significant influence of genetic factors on disease occurrence [11–13].

Gallstone disease as a risk factor for cardiovascular disorders

Recent studies have explored the association between cholelithiasis and cardiovascular disease. Elevated cardiometabolic index values are significantly correlated with a higher incidence of gallstones [14]. A 2025 meta-analysis of 22 studies involving approximately 7.5 million patients concluded that GSD is associated with a significantly increased risk of cardiovascular disease ($p < 0.001$) [15]. Another 2025 meta-analysis (21 studies, > 2 million participants) demonstrated that gallstone disease confers a relative risk of cardiovascular disease of 1.46 (95 % confidence interval (95% CI): 1.32–1.63; $p < 0.001$) [16].

Gallstone disease as a risk factor for gallbladder cancer

Considerable attention has been directed toward the relationship between cholelithiasis and biliary tract cancer. A meta-analysis of 23 cohort studies conducted in Asia, Europe, and the Americas demonstrated that the presence of gallstones increases the risk of gallbladder cancer by 7.3 times. Stone size greater than 1 cm and the number of calculi are directly associated with biliary tract malignancy [17]. Another meta-analysis of 10 studies revealed that gallbladder cancer is often detected incidentally following cholecystectomy performed

for benign biliary disease, occurring in 0.19–1.6 % of laparoscopic cholecystectomies (mean incidence — 0.365 %). Gallbladder carcinoma is more frequently observed in patients with solitary or large stones and in cases of gallbladder wall thickening, particularly localized thickening. These findings underscore the need for thorough preoperative evaluation [18].

Several studies also highlight the association between the presence and size of gallbladder polyps and gallbladder cancer [19, 20].

Gallbladder cancer is relatively uncommon: in terms of primary incidence, it ranks 22nd globally, with a rate of 2.1 per 100,000 population (https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf). According to cancer registries from 68 countries, the highest incidence rates are reported among indigenous populations of the Americas (Chile: 27 per 100,000) [21], Northern India (21.5 per 100,000) [22], and Southern Pakistan (11.3 per 100,000) [23]. In Russia, according to the Federal State Statistics Service, gallbladder cancer incidence in 2019 was 1.4 per 100,000 among men and 2.5 per 100,000 among women [24]. Investigating the contribution of GSD to gallbladder cancer incidence in Russia remains an important research priority.

Pathogenesis of gallstone disease

The most widely accepted pathogenetic concept of GSD is the model of cholesterol cholelithiasis. A landmark study by W.H. Admirand and D.M. Small proposed the physicochemical theory, which states that gallstones form when bile is supersaturated with cholesterol and deficient in bile acids and phospholipids [25]. By the mid-1990s, it became evident that lithogenesis cannot be explained solely by metabolic processes. It was shown that the initial stage of stone formation involves protein precipitation, largely driven by gallbladder inflammation and impaired motility of the biliary tract. By the late 1990s, metabolic and infectious theories of cholelithiasis pathogenesis had converged [26].

In 2005, a study of 43,141 twin pairs demonstrated that genetic factors contribute significantly to the development of cholelithiasis compared to phenotypic influences [27]. That same year, F. Lammert and D.Q. Wang proposed a paradigm for cholesterol cholelithiasis pathogenesis: the combined effect of specific gene polymorphisms (*Lith* genes), altered biliary motility, chronic inflammation, and metabolic factors initiates lithogenesis, which in turn promotes chronic cholecystitis and may lead to gallbladder carcinogenesis [28]. Around the same time, a concept introduced by Kh.Kh. Mansurov gained momentum in Russia, suggesting that cholelithiasis develops through sequential stages: biliary dyskinesia (involving the gallbladder and sphincter of Oddi), chronic cholecystitis, pre-stone formation of lithogenic bile, and eventual gallstone formation [29]. In our view, these perspectives are complementary rather than contradictory.

A significant role in the pathogenesis of biliary tract diseases is played by bile microbiota and gut microbiota. Studies indicate that impaired intestinal permeability, altered microbial composition, and reduced biodiversity are key factors in GSD and other biliary disorders, including gallbladder cancer and cholangiocarcinoma [30, 31]. Compared to healthy individuals, patients with asymptomatic GSD exhibit quantitatively increased fecal microbiota but reduced diversity, with a relative predominance of *Firmicutes* and decreased representation of *Bacteroidetes* and *Proteobacteria*. In patients with gallstones, hypertension, non-alcoholic fatty liver disease, and BMI ≥ 24, compared to BMI-matched controls, differences were observed across 15 microbial species, including reduced abundance of unclassified *Lactobacillales* [32]. Alongside decreased *Bacteroidetes*, an increased presence of *Desulfovibrionales* was noted in GSD patients. Fecal transplantation of *Desulfovibrionales* from cholelithiasis patients into laboratory mice resulted in gallstone formation in 73 % of animals. High levels of *Desulfovibrionales* were associated with increased production of secondary bile acids in the cecum and enhanced hydrophobicity, promoting intestinal cholesterol reabsorption. Metabolic products of *Desulfovibrionales* (H_2S) activate hepatic farnesoid X receptors (FXR) and inhibit CYP7A1 expression, leading to increased bile acid synthesis, cholesterol supersaturation, and gallstone formation. In mice harboring *Desulfovibrionales*, hepatic expression of cholesterol transporters Abcg5/g8 was induced, further facilitating biliary cholesterol secretion [33].

Diagnosis and differential diagnosis of gallstone disease

Modern principles of diagnosing biliary tract disorders are outlined in the clinical guidelines of the Russian Gastroenterological Association (RGA) for the management of patients with

biliary dyskinesia [34], gallstone disease [35], and cholecystitis [36], published in 2024 under the auspices of the RGA, the Russian Society of Surgeons, and the Endoscopic Society "REndO".

The diagnosis of biliary tract diseases is based on a combination of various tests, including clinical, laboratory, and imaging studies.

The hallmark clinical manifestation of biliary tract disorders is biliary pain, most localized in the right upper quadrant. Key features of biliary pain in functional gallbladder and sphincter of Oddi dyskinesia include: intensity exceeding 5 points on the visual analog scale; localization in the epigastrium and right hypochondrium; occurrence independent of body position or defecation; lack of response to antacids and antisecretory drugs; absence of a direct relationship with food intake; frequent nocturnal episodes; associated nausea and vomiting that do not relieve pain; radiation to the right shoulder and arm [37]. Classic biliary colic does not occur in functional biliary disorders. It is hypothesized that gallbladder dyskinesia may serve as a background for GSD development. Similarity of risk factors, pathophysiological mechanisms (including the role of lithogenic bile), and symptoms makes this plausible, although objective clinical evidence is lacking [38].

A differential diagnosis, which allows the functional nature of pain to be determined only after organic causes have been ruled out, is essential [35–38]. The addition of inflammation in patients with acalculous or calculous cholecystitis is accompanied by changes in pain intensity and timing, its association with gallbladder morphological alterations, and the presence of complications.

Thus, it is essential to determine the presence of inflammation in the biliary system. Laboratory confirmation includes elevated erythrocyte sedimentation rate and leukocytosis in the complete blood count. A biochemical marker of inflammation is an increased level of C-reactive protein. Biliary obstruction manifests as a pronounced cholestatic syndrome with jaundice, hyperbilirubinemia, and elevated alkaline phosphatase and gamma-glutamyl transpeptidase. Ultrasound signs of inflammation in cholecystitis include gallbladder wall thickening beyond normal values (> 3–4 mm), irregular thickening, edema, stratification or consolidation, and impaired contractile function [35, 36]. According to a meta-analysis of 40 studies involving 8,652 patients, ultrasound is a reliable method for diagnosing acute cholecystitis, with a sensitivity of 71 % (95% CI: 69–72 %) and specificity of 85 % (95% CI: 84–86 %) [39].

We consider it reasonable to highlight diagnostic features of gallbladder cancer and polyps.

In 2021, the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) published guidelines for the management of biliary tract cancers. We present some of the provisions of this consensus [40]. Symptoms of gallbladder cancer are non-specific and include pain in the right hypochondrium, jaundice, nausea, vomiting, and weight loss. In many cases, cancer is detected incidentally during abdominal ultrasound or cholecystectomy for GSD. Ultrasound has high specificity and sensitivity and should be the first diagnostic step in suspected biliary tract cancer. As a second step, computerized tomography (CT) is useful for assessing tumor localization and extent, although its sensitivity for T1 tumors is relatively low. Magnetic resonance imaging (MRI), including MR cholangiopancreatography, helps evaluate tumor spread to the cystic duct and common bile duct. Endoscopic ultrasonography (EUS) is recommended as the third step, offering higher sensitivity, specificity, and accuracy than abdominal ultrasound and CT, and enabling precise assessment of tumor location and extent. Direct cholangiography via endoscopic retrograde cholangiopancreatography and peroral cholangioscopy assist in evaluating tumor involvement of the cystic and common bile ducts. Positron emission tomography (PET) and PET-CT are useful for detecting lymph node involvement, distant metastases, and recurrence [40].

Given that gallbladder polyps are among the predictors of gallbladder cancer, we present selected recommendations for managing patients with gallbladder polyps, developed by the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), the European Association for Endoscopic Surgery (EAES), the International Society of Digestive Surgery (EFISDS), and the European Society of Gastrointestinal Endoscopy (ESGE), published in 2022 [41]. Initial evaluation of gallbladder polyps should be performed using abdominal ultrasound. Routine use of other imaging

modalities is currently not recommended. In centers with appropriate expertise and resources, alternative imaging techniques (e.g., contrast-enhanced or endoscopic ultrasound) may be helpful in complex cases [41].

Spasmolytics in the management of patients with gallstone disease and functional biliary disorders

The use of spasmolytic agents for the relief of biliary pain is a well-founded strategy in the management of patients with gallstone disease (GSD) and functional biliary disorders [34–37].

Mebeverine is a selective agent that normalizes gastrointestinal and biliary motility through a dual mechanism of action. On the one hand, it acts as a myotropic spasmolytic by blocking sodium channels in smooth muscle cells; on the other, it exhibits moderate prokinetic properties by inhibiting Ca^{2+}, release from intracellular stores, limiting K^+ efflux, and preventing smooth muscle hypotonia. Mebeverine selectively targets the biliary tract and intestines without affecting the cholinergic system, thereby avoiding systemic side effects and allowing long-term use in various patient populations.

The efficacy and safety of mebeverine in GSD management have been demonstrated in domestic clinical studies. In patients with cholelithiasis, biliary pain completely resolved in 85 % and significantly decreased in duration and intensity in 15 % after a course of Duspatalin (mebeverine). Concurrently, symptoms such as nausea and bitter taste in the mouth disappeared or improved. Duodenogastric reflux, verified by 24-hour pH monitoring in two-thirds of patients, was reduced in half of these cases after mebeverine therapy [42]. Combination therapy with ursodeoxycholic acid (UDCA) and mebeverine for eight weeks showed superior efficacy compared to UDCA monotherapy in patients with biliary sludge and impaired gallbladder motility, achieving complete pain relief in all patients versus 70 % with UDCA alone and sludge elimination in 95 % versus 80 % [43]. In a mixed cohort of patients with cholelithiasis, prior cholecystectomy, and functional biliary disorders (one-third with GSD), biliary pain intensity was assessed using a four-point scale. The course of Duspatalin resulted in pain relief for all patients, and the duration of high-intensity pain relief was twice as short when mebeverine was prescribed compared to drotaverine. Positive functional changes were also confirmed by hepatobiliary scintigraphy [44].

One challenge in managing GSD patients is the persistence or emergence of gastrointestinal symptoms following cholecystectomy. Surgical treatment does not always eliminate preoperative abdominal symptoms (including irritable bowel syndrome features) and may lead to their appearance *de novo*. The multicenter “Odyssey” study, conducted in 14 Russian cities, evaluated 218 patients with abdominal spastic pain as part of post-cholecystectomy syndrome. Clinical response to mebeverine (200 mg twice daily) was assessed at 2 and 6 weeks using a five-point Likert scale (“no symptoms” or “marked improvement”). After two weeks, complete response was achieved in 50.5 % of patients, and after six weeks in 79 %. Significant improvements were also noted in stool frequency, stool form (Bristol scale), and quality of life [45].

The concept of the “biliary continuum” has been proposed, describing the sequential development of pathogenetically related biliary tract disorders. Motor dysfunction and alterations in bile physicochemical properties create conditions for inflammation, sludge formation, and gallstone development. Therefore, restoring biliary motility is a key therapeutic goal, for which spasmolytics with proven clinical efficacy are recommended. Mebeverine therapy is pathogenetically justified, as it normalizes biliary tract motility and indirectly improves bile properties. The optimal duration of mebeverine therapy for biliary disorders is at least eight weeks [46].

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All authors made an equal contribution to the development of the concept and formulation of the aim of the article, collection and processing of materials, writing and editing the text and proof checking.

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