

Review

Gallstone disease: From genes to evidence-based therapy[☆]

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The number of gallstone patients is increasing in ageing populations with a high prevalence of metabolic syndrome and obesity. Recently variants of hepatic ATP binding cassette transporters have been identified as genetic susceptibility factors for gallstone disease, pointing to novel means for risk assessment and prevention. Although laparoscopic cholecystectomy is the mainstay of therapy for symptomatic gallbladder stones, the clinical management of gallstone disease is changing rapidly, with an increase in day case surgery and the advent of transluminal endoscopic surgery. Here, we summarize the molecular and genetic mechanisms of gallstone formation as well as the current evidence-based algorithms for diagnosis and therapy of gallbladder and bile duct stones.

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1. Introduction

In Europe, 10–20% of the population carry gallbladder stones [1,2]. Many gallstones are silent, but symptoms and severe complications ensue in more than 40% of patients above the age of 40 years, necessitating laparoscopic cholecystectomy [2]. In a recent study from Germany [2], the highest prevalence rate of gallstones was observed in women between 70 and 79 years of age: 57% had either a history of cholecystectomy or current sonographic evidence for gallstones. The prevalence of cholelithiasis is even higher in most Hispanic populations of Central and South America, and in American Hispanics with Native

American ancestry [3–6]. Native populations from North and South America represent the groups at highest risk in the world. In these populations, gallstone disease appears earlier in life [4,7], reaching prevalence rates at the age of 50 years over 50% and 70% in male and women, respectively [6,8,9]. Overall, gallstone disease represents a serious burden for our healthcare systems: Each year, an estimated 700,000 cholecystectomies are performed in the US, more than 190,000 in Germany, and more than 40,000 in Chile [1,10,11].

2. Molecular mechanisms

2.1. Cholesterol stones

Gallstones are classified as cholesterol and pigment stones. More than 90% of gallstones consist mainly of cholesterol and are formed within the gallbladder [12]. Cholesterol stones form mainly if bile contains more cholesterol than can be solubilized by mixed micelles of bile salts and phosphatidylcholine (lecithin). Additional factors such as biliary mucin and impaired

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Abbreviations: ABC, ATP-binding cassette; ERC, endoscopic retrograde cholangiography; ESWL, extracorporeal shock-wave lithotripsy; FXR, farnesoid X receptor; GT, glutamyltransferase; MRC, magnetic resonance cholangiography; RCT, randomised controlled trial; UDCA, ursodeoxycholic acid.

gallbladder motility allow cholesterol microcrystals to be retained and to grow into macroscopic gallstones [13,14]. Whether gallbladder hypomotility is a primary defect or secondary to excess cholesterol accumulation in gallbladder smooth muscle is debatable [14]. Recent studies in mouse models [15] indicate that cholesterol monohydrate crystals induce expression of inflammatory cytokines in a T-cell-dependent fashion. There appears to be a link between gallstones and intestinal hypomotility, since gallstone patients display slower intestinal transit [16], thereby increasing bacterial formation of the secondary bile salt deoxycholate in the colon, which in turn, increases biliary cholesterol secretion and saturation [17].

In principle, cholesterol supersaturation of gallbladder bile can result from hepatic hypersecretion of cholesterol, or from hyposecretion of bile salts or lecithin. The open question as to which defect might be primary in gallstone pathogenesis has driven genetic studies in animal models [18–20] and, more recently, in humans. A large study within the framework of the Swedish Twin Registry provided conclusive evidence for a role of genetic factors in gallstone pathogenesis [21]. Based on data from 43,141 twin pairs, concordance rates were significantly higher in monozygotic compared with dizygotic twins, and we calculated that genetic factors accounted for 25% (95% confidence interval 9–40%) of the phenotypic variation among the twins [21]. A similar analysis in 358 families in Wisconsin, each of which contained at least two obese siblings, determined that the heritability of symptomatic gallstones is $29 \pm 14\%$ [22], which is similar to the figure obtained in the Swedish twin study.

Data from several large epidemiological studies in the US, Europe, China and Japan implicate chronic overnutrition with refined carbohydrates and triglycerides as well as depletion of dietary fiber as environmental risk factors for cholesterol gallstones [23]. Hence, gallstone disease is likely to result from the complex interaction of genetic factors, high-carbohydrate, high-fat and low-fiber diets [24–28], and other not fully defined environmental factors including scarce [2,29,30] and postmenopausal estrogen therapy [31]. This hypothesis is supported by the profound increases of cholesterol gallstone prevalence rates in Native Americans, post-war European countries and current urban centers in East Asia, all of which are associated with the introduction of high-caloric “Westernized” diets [23]. Similar to atherosclerosis, the risk of cholesterol gallstone disease increases with obesity, type 2 diabetes, insulin resistance and dyslipidaemia (hypertriglyceridaemia and low-serum HDL cholesterol levels) [14]. These conditions are associated with the metabolic syndrome, of which cholesterol gallstone disease is deemed to be yet another “fellow traveller” [32,33].

In spite of a large number of candidate gallstone genes identified in mouse models, common genetic factors that

contribute to gallstone formation in humans have remained elusive until now [34]. Recently, the first genome wide association study in a large cohort of gallstone patients from Germany [35] and a linkage study in affected sib pairs [36] identified a common variant (p.D19H) of the hepato-canalicular cholesterol transporter *ABCG5/ABG8* as genetic risk factor for gallstones. Of note, this variant was also a susceptibility factor for gallstones in Chilean Hispanics [35]. Hepatocytes express specific transport proteins for biliary lipids – known as ATP-binding cassette (ABC) transporters – at the canalicular membrane domain. The ABCB11 transporter is the bile salt export pump, ABCB4 is the transporter for phosphatidylcholine, and ABCG5/ABCG8 form obligate heterodimers for biliary cholesterol secretion [37]. The p.D19H variant confers odds ratios of 2–3 and 7 for heterozygous and homozygous carriers, respectively, and 8–11% of the total gallstone risk can be attributed to this variant [35,36]. These studies identify the first common susceptibility factor for cholesterol gallstones in humans. Carriers of the lithogenic *ABCG8* variant 19H display lower serum plant sterol levels (sitosterol, lathosterol) and higher levels of cholesterol precursors (cholesterol, lathosterol) [38,39], indicating decreased cholesterol absorption and a reciprocally increased cholesterol biosynthesis. This might be clinically relevant, since we would predict that HMG-CoA reductase inhibitors could be particularly effective in lowering serum cholesterol concentrations [40] and biliary cholesterol levels in patients carrying the *ABCG8* 19H variant. Of note, a genome wide scan in experimental crosses of inbred strains identified the orthologous mouse gene as gallstone susceptibility gene [41], demonstrating that identical genes affect gallstone formation in both mice and men.

Since only 10% of the total gallstone risk is due to the *ABCG8* 19H variant, other genetic factors have yet to be discovered. Evidence for a single gene defect that causes gallstone formation in a defined subgroup – young patients with a recurring form of cholelithiasis – was provided by Rosmorduc et al. [42]. The group performed a mutation search in the *ABCB4* gene in patients with cholesterol gallbladder stones and intrahepatic sludge or microlithiasis, recurrence of biliary symptoms after cholecystectomy, positive family history, and mild chronic cholestasis and/or intrahepatic cholestasis of pregnancy; point mutations were identified in 18 out of 32 patients (56%) [42]. These findings are clinically relevant, since asymptomatic carriers might benefit from prevention with ursodeoxycholic acid (UDCA) [42]. Hence, genetic testing for *ABCB4* mutations may already be useful in young patients (onset of symptoms <40 years) with a positive family history, cholesterol gallbladder stones and intrahepatic sludge or microlithiasis, or recurrence of biliary symptoms after cholecystectomy [42], albeit the diverse spectrum of mutations makes the analysis laborious. The pathophysiological

Table 1
Updated inventory of potential human gallstone (*LITH*) genes

Gene	Gene symbol	Concordant mouse <i>Lith</i> locus	Function	Gene variants	Frequency			Population	Cases	Controls	OR (95% CI)	Potential mechanisms	References
					Rare monogenic	Families (oligogenic)	Common polygenic						
<i>Cholesterol stones</i>													
ATP-binding cassette transporter B4	<i>ABCB4</i> (<i>GBD1</i>)		Hepato-canalicular phosphatidylcholine (lecithin) floppase	Multiple		+		France, Germany, Netherlands, Spain			6.1	Biliary phospholipid secretion ↓	[42,43, 152,153]
ATP-binding cassette transporter B11	<i>ABCB11</i>	<i>Lith1</i>	Hepato-canalicular bile salt export pump	Multiple	+			Netherlands				Biliary bile salt secretion ↓	[154]
ATP-binding cassette transporter G5/G8	<i>ABCG5/G8</i> (<i>GBD4</i>)	<i>Lith9</i>	Hepato-canalicular cholesterol transporter	<i>ABCG8</i> p.D19H (<i>rs1188753</i>)			+	Germany, Sorbs, Chile, Romania, China	2280	1562	2.2 (1.8 – 2.6) for heterozygotes; 7.1 (0.9–158.6) for homozygotes	Biliary cholesterol secretion ↓	[35,36]
β ₃ adrenergic receptor	<i>ARDB3</i>			p.R64W (<i>rs4944</i>)			(+)*	Germany	143	143	9.0 (2.1–39.2)	Gallbladder hypomotility	[155]
Apolipoprotein A1	<i>APOA1</i>			–75G > A			(+)*	India	208	317	1.6 (1.1–2.2)	Biliary cholesterol secretion ↑ secondary to reverse cholesterol transport ↑	[156]
Apolipoprotein B	<i>APOB</i>			c.2488C > T c.4154G > A	+		(+)	China Poland	114 240	298 217	2.2 (1.2–4.0) 1.7 (1.2–2.4)	Biliary cholesterol secretion ↑ secondary to hepatic VLDL synthesis ↓	[157–160]
Apolipoprotein C1	<i>APOC1</i>			–317–321 insertion			(+)*	India	208	318	9.4 (1.1–78.8)	APOC1 ↑ → remnant-like particle cholesterol ↑	[161]
Cholecystokinin A receptor	<i>CCKAR</i>	<i>Lith13</i>		<i>rs1800857</i>	+		(+)*	India	165	190	2.3 (1.2–4.1)	Gallbladder and small intestinal hypomotility	[162–164]
Cholesteryl ester transfer protein	<i>CETP</i>			RFLP <i>Taq1B</i>			(+)*	Finland	91	92	1.5 (1.0–2.4)	HDL catabolism ↑	[165]
Cytochrome P450 7A1	<i>CYP7A1</i>		Cholesterol 7α-hydroxylase (rate-limiting enzyme of bile salt synthesis)	–204A > C	+		(+)*	United States, China	105	274	1.4 (1.0–2.0)	Bile salt synthesis ↓	[158,166]
Low-density lipoprotein receptor related protein associated protein 1	<i>LRPAP1</i>	<i>Lith13</i>		Intron 5 insertion/deletion (<i>rs11267919</i>)			(+)*	India	142	203	2.6 (1.1–5.8)	Hepatic uptake of cholesterol from chylomicron remnants via LRP ↑	[167]
Nuclear receptor 1H4	<i>NR1H4</i>	<i>Lith7</i>	Farnesoid X receptor (central bile salt sensor)	–20647T > G			(+)	Mexico	82	78	2.4 (1.0–5.7)	Bile salt synthesis ↓	[47]
				–1G > T IVS7–31A > T							3.8 (1.0–4.0) 2.0 (1.1–3.9)		
<i>Black pigment stones</i>													
Ankyrin 1	<i>ANK1</i>		Erythrocyte membrane protein	Multiple		+						Spherocytosis → hemolysis	[168]
Cystic fibrosis transmembrane regulator	<i>CFTR</i> (<i>ABCC7</i>)		Chloride channel	ΔF508	+							Enterohepatic bilirubin circulation ↓, bile pH ↓, faecal bile salt excretion↑	[51]
Glucose-6-phosphate dehydrogenase	<i>G6PD</i>		Erythrocyte enzymes	Multiple	+	+	+					Hemolysis	[169]
Glucose-6-phosphate isomerase	<i>GPI</i>			p.L339P									
Pyruvate kinase	<i>PKLR</i>			p.R510Q									
Hemoglobin	<i>HBA1/2</i> <i>HBB</i>			HbH p.E26K (HbE) p.E6V (HbS)		+	+					α-Thalassemia/ β-Thalassemia intermedia/minor/ Sickle cell anemia → hemolysis	[170–172]
UDP glucuronosyl transferase 1A1	<i>UGT1A1</i>		Bilirubin UDP glucuronosyl-transferase	Promoter A(TA) _n TAA			+					Hepatic bilirubin conjugation ↓	[52,53,171, 173–181]

Abbreviations: GBD, gallbladder disease; OMIM; online mendelian inheritance in men, RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism.

* No replication.

basis of *ABCB4* deficiency is consistent with the spontaneous occurrence of cholecystolithiasis in *Abcb4* knock-out mice [43].

The expression of ABC transporters is under control of nuclear receptors, which are ligand-activated transcription factors [44–46]. The hepatic bile salt export pump *ABCB11* (Table 1) and *ABCB4* are induced by the farnesoid X receptor (FXR; official gene symbol *NR1H4*), which also represses bile salt synthesis,

whereas *ABCG5* and *ABCG8* are target genes of the liver X receptor, which represents an oxysterol (and glucose) sensor. Recently *NR1H4* variants, which might also modify gallbladder motility due to altered FGF-19 expression and bacterial growth in the intestine, have been linked to gallstone formation in a Mexican cohort [47] and Caucasian patients with intrahepatic cholestasis of pregnancy, a condition known to be associated with gallstones [48], but additional studies are needed to

establish nuclear receptors as “gallstone genes”. Table 1 summarizes studies on “gallstone genes” in humans; it should be noted, however, that – except for *ABCG8* and *ABCB4* – most studies have yet to be replicated in larger cohorts and other ethnic groups.

2.2. Black pigment stones

A very small proportion of gallbladder stones (2%) are black pigment stones [12]. They consist predominantly of polymerized calcium bilirubinate, which precipitates if the ion product of calcium and unconjugated bilirubin exceeds its solubility product and polymerizes slowly in biliary sludge. Hemolytic anemias (Table 1) are the most obvious sources of excess unconjugated bilirubin. Another potential pathway involves ileal disease or resection, causing spillage of bile salts into the colon, which promotes solubilization and absorption of unconjugated bilirubin and results in increased enterohepatic cycling and biliary secretion of bilirubin [49]. This mechanism might contribute to the high-gallstone prevalence rates in Crohn’s disease [50] and cystic fibrosis [51]. Both in patients with hemolytic anemias and cystic fibrosis, the Gilbert syndrome-associated *UGT1A1* promoter variant increases the susceptibility to pigment stone formation [52,53]. Accordingly, a recent regression analysis showed that serum bilirubin levels and the incidence of gallstones are strongly associated with the number of *UGT1A1* promoter [TA] repeats in subjects with sickle cell disease, with each additional repeat correlating with an increase in serum bilirubin levels of 21% and cholelithiasis risk of 87% [53].

2.3. Brown pigment stones

Many bile duct stones are mixed stones (secondary bile duct stones, i.e. cholesterol stones originating from the gallbladder with a pigment shell) [54]. Brown pigment stones (primary bile duct stones) form as a result of stasis and infection within the bile ducts. Bacterial β -glucuronidase converts soluble conjugated bilirubin back to the insoluble unconjugated state, leading to the precipitation of bilirubin as calcium salts of long-chain fatty acids. Hence, this stone type is associated with the presence of duodenal diverticula, biliary strictures or parasites.

Intrahepatic stones are rare in the Western world and frequent in Asia. In comparison to cholesterol gallbladder stones, their prevalence is clearly declining. Most of these stones are brown pigment stones associated with strictures, congenital anomalies or parasites, but the frequency of cholesterol stones ranges from 6% to 13% [55]. The pathogenesis of primary intrahepatic cholesterol stones remains unclear, and *ABCB4* variants could predispose to their formation, as discussed above.

3. Clinical course

3.1. Gallbladder stones

In a prospective study of asymptomatic Caucasian stone carriers, the cumulative risk of being admitted to hospital and treated for symptoms or complications was 7.6% during the first 5 years of follow-up, and this risk appeared to continue in subsequent years [56]. Biliary colic is defined as pain localized in the mid-epigastrium or the right upper quadrant, which lasts longer than 15 min. Acute complications (cholecystitis, cholangitis, pancreatitis) develop in 0.1–0.3% of asymptomatic stone carriers per year [57,58]. Obviously, the risk of cholecystitis is higher in patients with large solitary stones, whereas the risk of pancreatitis is higher in patients with small multiple stones and preserved gallbladder motility [59]. Most patients with acute cholecystitis have an obstruction of the cystic duct, triggering the synthesis of prostaglandins I_2 and E_2 , which mediate the inflammatory response. In about 20% of the cases, a secondary bacterial infection (most commonly by *Escherichia coli*, *Klebsiella*, *Enterococcus faecalis*) occurs [60,61]. After an episode of biliary pain the majority of patients develop repeated biliary symptoms [62]. The incidence of complications in these symptomatic patients is as high as 1–3% per year [58,63]. However after 5 years without symptoms, the risk of biliary colic or complications is as low as in asymptomatic stone carriers [64].

Of note, the natural history of gallstone disease in at-risk populations in Native Americans and Hispanics has not been studied systematically and remains not well known. Epidemiological and small case-control studies suggested that it could differ from the more benign natural history of gallstone disease in Caucasians and that the conversion rate from asymptomatic to symptomatic stones or complications is increased compared to European patients [65]. In a population based longitudinal survey performed in a high-risk area, 65% of Hispanic gallstone patients were cholecystectomized or were symptomatic at the age of 45–50 years [4,11]. Also, follow-up studies performed in small cohorts of Chilean Hispanics suggested a more aggressive natural history gallstone disease [66–68]. Interestingly, multiple gallstones are more frequent (65–70%) than solitary stones in Hispanic and Native American populations [4]. Moreover, gallbladder cancer, the most serious complication of cholelithiasis, is the leading cause of death of cancer in Chilean women and highly prevalent in other South American populations [69].

3.2. Bile duct stones

The natural history of choledocholithiasis is not well defined. Although complications are more common and more severe compared to symptomatic cholecystolithiasis, it has been assumed that less than 50% of the

patients with bile duct stones develop symptoms and more than 20% of the stones pass spontaneously [70,71].

4. Prevention of gallstone formation and symptoms

Cholesterol gallstone formation may be prevented by lifestyle changes, in particular by reducing total caloric intake [72], but randomised controlled trials (RCT) have yet to be performed. In specific settings that are associated with an increased gallstone risk such as rapid weight loss (>1.5 kg/week) [73] or total parenteral nutrition, gallstone formation can be prevented efficiently by UDCA (at least 500 mg per day) [1,10,74,75] or early enteral nutrition, respectively. Administration of cholecystikinin (50 ng/kg/day i.v.) [76] or motilin agonists such as erythromycin or clarithromycin (500–600 mg) [77] might also have protective effects in the latter setting. An exciting new concept in the prevention of gallstone formation is the stimulation of nuclear receptors that regulate metabolism and secretion of biliary lipids [14,78], as shown by the efficient prevention with synthetic agonists of the central bile salt sensor FXR in mouse models [45].

Large sets of epidemiological data indicate that the rate of cholecystectomy or the incidence of symptomatic gallstone disease may be reduced by changes in lifestyle and/or dietary modifications. Sedentary lifestyle correlates with higher risk of cholecystectomy, and recreational physical activity is associated with a decreased risk of cholecystectomy [29,30]. Coffee and frequent nut consumption as well as moderate quantities of alcohol consumption have been proposed to reduce the risk of symptomatic gallstone disease [79–84]. Based on these observations, it is reasonable to motivate asymptomatic gallstone carriers to follow at least some of these recommendations to reduce the conversion rate from the asymptomatic to the symptomatic state.

With respect to pigment stones, attempts to decrease the enterohepatic circulation of bilirubin include the administration of agents that trap unconjugated bilirubin in the intestine by absorption to non-absorbable solids, or by forming insoluble salts with calcium or zinc. Recently the lipase inhibitor orlistat has been demonstrated to enhance faecal bilirubin excretion and to decrease serum bilirubin levels [85], but its stone protective effects have yet to be studied.

In contrast to gallbladder stones, no evidence-based agents for the prevention of bile duct stone recurrence are available.

5. Diagnosis

5.1. Gallbladder stones

Transabdominal ultrasound is the most common and accurate method for detecting gallbladder stones

≥ 5 mm, having a sensitivity of 97% and a specificity of 95% [86]. Furthermore, ultrasound is a very useful diagnostic tool for acute cholecystitis [87] and can also be employed to determine gallbladder volume and motility (normal ejection fraction $>60\%$) [59]. However, transabdominal ultrasound has lower sensitivity for microlithiasis (stone size 1–5 mm), which is a potential cause of recurrent biliary colic and complications such as recurrent pancreatitis or “acalculous” cholecystitis [88–90,92–94]. Endoscopic ultrasound and/or microscopic examination of bile can detect microlithiasis with higher sensitivity and specificity in 70–90% of cases [91–93].

5.2. Bile duct stones

Endoscopic retrograde cholangiography (ERC) is the preferred diagnostic method in patients with a high suspicion for bile duct stones (Fig. 1), since the procedure offers therapeutic options. The probability for bile duct stones is high if the bile duct is dilated (>7 mm) and bilirubin, γ -glutamyl transferase (GT) and/or alanine aminotransferase (ALT) are elevated, or if bile duct dilatation, gallbladder stones and biliary colic are present simultaneously [10,94]. Of note, ALT might be elevated in patients with symptomatic bile duct stones in whom γ -GT and alkaline phosphatase are not yet induced but acute (bile acid-mediated) hepatocellular damage predominates, including patients who lack dilated ducts in transabdominal ultrasound. Since ERC bears a risk of severe complications, endoscopic ultrasound and magnetic resonance cholangiography (MRC) should be performed in patients with intermediate probability of gallstones (Fig. 1). As summarized in a recent meta-analysis of 5 RCT including 301 patients [95], endoscopic ultrasound and MRC have sim-

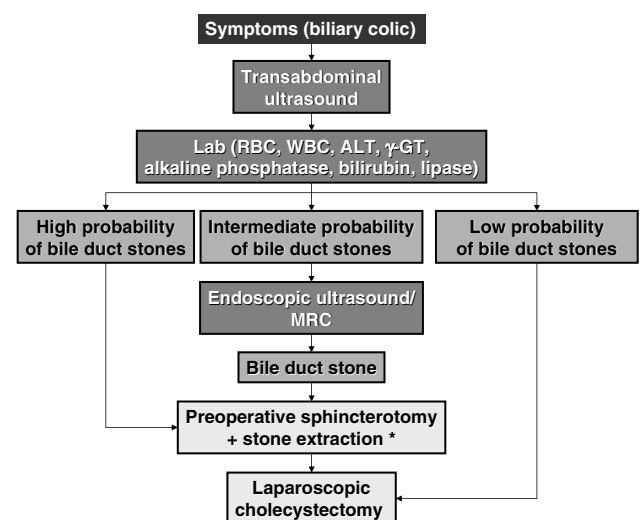


Fig. 1. Algorithm for symptomatic diagnosis and treatment of symptomatic gallstone disease (modified from [151]). *In centers with specific surgical expertise, laparoscopic bile duct revision can be performed [102]. Abbreviations: ALT, alanine aminotransferase; γ -GT, γ -glutamyltransferase; RBC, red blood count; WBC, white blood count.

ilar sensitivity (93 vs. 85%) and specificity (96 vs. 93%) for the detection of bile duct stones. Intraoperative cholangiography might be performed in patients who undergo cholecystectomy to visualize the anatomy and/or bile duct stones, but its non-selective use is not recommended in current guidelines [10], since less than 4% of the patients harbor unidentified stones [96]. For intrahepatic stones, abdominal ultrasound and MRC represent the first-line diagnostic tools.

6. Evidence-based therapy

6.1. Symptomatic gallbladder stones

Recently several meta-analyses and Cochrane reports have summarized the evidence for current therapeutic strategies of gallstone disease [97–105]. Today, the treatment of choice of symptomatic gallbladder stones is laparoscopic cholecystectomy (Fig. 1) [98]. Mortality rates following laparoscopic cholecystectomy range from less than 0.1% in clinical studies [106] to 0.7%, as documented for 171,611 cholecystectomies in Germany in 2005 [10]. Complication rates including bile duct injuries do not differ between laparoscopic and open cholecystectomy [10,98]. Laparoscopic cholecystectomy is associated with shorter hospital stays (–3 days), faster convalescence (–23 days) and lower costs (–18%) compared to open cholecystectomy [98]. Small incision cholecystectomy may serve as a surgical alternative for laparoscopic cholecystectomy [100].

6.2. Acute cholecystitis

Based on data from five RCT with 451 patients [101], early laparoscopic cholecystectomy is also recommended for mild and moderate acute cholecystitis [107]. Postponing cholecystectomy leads to longer hospital stays and most importantly, a substantial number of patients on the waiting list (18%) have to undergo emergency cholecystectomy [101]. The optimal timing and approach to the surgical therapy of acute cholecystitis is still a matter of controversy [107], but the best time to operate seems to be within the first 48–96 h [108]. A recent study from the Netherlands demonstrated that UDCA exerts no beneficial effect in patients with symptomatic gallstones awaiting cholecystectomy [62], but non-steroidal anti-inflammatory drugs may decrease the rate of progression from acute biliary colic to cholecystitis [109,110].

6.3. Non-surgical therapy of gallbladder stones

Due to the advantages of laparoscopic cholecystectomy, non-surgical therapy of gallbladder stones has been widely abandoned. UDCA, which comprises <10% of the

physiological bile acid pool, decreases biliary cholesterol secretion, increases solubility of cholesterol by formation of liquid crystals, and reduces intestinal cholesterol absorption [1,111]. UDCA (at least 10 mg/kg/day) might be used in a very small group of patients with non-calcified stones <5 mm, who present with mild and/or rare colic and refuse surgery [10,112]. UDCA has also been used successfully in patients with microlithiasis and recurrent “idiopathic” pancreatitis [88]. Due to the unsatisfactory long-term results with recurrence rates >40% after 5 years [113], extracorporeal shock-wave lithotripsy (ESWL) of gallbladder stones, which was pioneered in the 1980s at the University of Munich [114], has been replaced by laparoscopic cholecystectomy.

6.4. Asymptomatic gallbladder stones

Asymptomatic cholecystolithiasis is not a general indication for cholecystectomy, since the risk of complications from surgery outweighs the advantage of preventing possible complications from asymptomatic gallbladder stones [63]. However, these cost-benefit analyses are based on data from open cholecystectomy, and there are no RCT comparing laparoscopic cholecystectomy vs. no cholecystectomy in patients with silent gallstones. The prevention of gallbladder cancer is an established indication for cholecystectomy in patients with gallbladder polyps >10 mm (cancer risk up to 50%) [10,115] or calcified gallbladders (cancer risk 7% in gallbladders with selective mucosal calcifications) [116]. Prophylactic cholecystectomy can also be considered for patients with stones larger than 3 cm [117,118], patients whose gallbladder lumen is not visualized in trans-abdominal ultrasound (“wall echo shadow” or WES sign due to the wall of the contracted gallbladder, echoes from gallstones located immediately beneath the wall, and prominent posterior shadowing) [119], or patients with recurrent “idiopathic” pancreatitis due to occult gallstones or microlithiasis [120]. Bariatric surgery for morbid obesity, extended intestinal resection in Crohn’s disease or total gastrectomy with lymphadenectomy, all of which increase the gallstone risk substantially, can be combined with simultaneous cholecystectomy [10,121]. Expectant management is currently recommended for kidney and/or pancreas transplant recipients [122], whereas a recent decision analysis [123] indicated that prophylactic posttransplantation cholecystectomy might be preferred after heart transplantation, in particular for diabetic patients [124].

A rationale for prophylactic cholecystectomy might also exist in populations with very high incidence of gallbladder cancer such as some North and South Native American and Hispanic populations with Amerindian heritage [69,125,126]. It has been suggested that the risk of gallbladder cancer is greater than would be expected simply on the basis of stone prevalence and approxi-

mates 3–5% of patients with asymptomatic gallstones [125]. Further observational studies, which measure additional outcomes such as obstructive jaundice, biliary pancreatitis and gallbladder cancer, are necessary to design RCT evaluating whether no cholecystectomy or cholecystectomy is better for asymptomatic gallstones and to develop evidence-based guidelines for prophylactic cholecystectomy in high-risk populations [104,127].

6.5. Bile duct stones

In many patients, gallbladder and bile duct stones coexist and different options are available: (i) “therapeutic splitting” with endoscopic removal of bile duct stones followed by cholecystectomy, which is standard of care in the large majority of hospitals [128]; (ii) surgical treatment with (laparoscopic) cholecystectomy and bile duct exploration [102,129]; or (iii) flexible splitting, e.g. intraoperative or postoperative splitting (Fig. 1). Whereas the combined surgical approach has the advantages of subjecting the patient to just one procedure with similar success and complications rates compared to therapeutic splitting [102,129], it is technically demanding and not widely available. On the other hand, sphincterotomy and endoscopic bile duct clearance with standard equipment (Dormia basket, balloon) are successful in over 90% of the patients, but the complication rates of ERC including sphincterotomy and other therapeutic procedures exceed 10% in prospective studies [130,131]. Endoscopic balloon dilation is less successful for stone removal, requires higher rates of mechanical lithotripsy, and carries a higher risk of pancreatitis, but has lower rates of bleeding and infection [103]. Factors that predict failure of mechanical lithotripsy are not absolute stone diameter but stone impaction in the bile duct [132] and stone size in relation to bile duct diameter. Treatment options for difficult stones include mechanical lithotripsy, laser lithotripsy, electrohydraulic lithotripsy, and ESWL. All transpapillary approaches can also be performed via a percutaneous access with similar success rates. The question as to which method should be employed depends on local expertise. In small RCT, ESWL was somewhat less efficient than laser lithotripsy [133,134], but it is technically less demanding and shows low complication rates. Two RCT compared postoperative ERC and laparoscopic bile duct revision: The combined surgical approach showed shorter hospital stays and lower costs, but the technical challenge is reflected by a high rate of bile leaks [102,135]. It remains to be determined whether simultaneous laparoscopic cholecystectomy and intraoperative ERC offer advantages.

After endoscopic treatment of choledocholithiasis, a “wait-and-see policy” cannot be recommended to patients whose gallbladders remain in situ, since the risk of cholecystitis, jaundice or other complications exceeds

15% [105,136]; instead, elective cholecystectomy should be performed within 6 weeks [10].

In contrast to the evidence-based treatment algorithms for bile duct stones, the complicated nature of intrahepatic stones necessitates individual interdisciplinary approaches, including percutaneous cholangioscopy and surgical resection [55].

6.6. Acute cholangitis

Acute cholangitis is usually due to bile duct obstruction with subsequent bacterial infection (e.g., *E. coli*, *Klebsiella*, *Enterobacter*, *E. faecalis*) [137]. It is a potentially life-threatening complication, typically presenting with fever, jaundice and pain in the right upper quadrant (Charcot’s triad). Acute cholangitis necessitates antibiotics as first-line therapy and early or even urgent biliary drainage, preferably by endoscopic stone extraction, nasobiliary drainage or stent [138,139].

6.7. Biliary pancreatitis

An excellent review of the RCTs on biliary stones and pancreatitis [140] concluded that urgent ERC \pm sphincterotomy (within 24–72 h of presentation) should be performed in patients with severe pancreatitis or with evidence of bile duct obstruction and/or cholangitis [141–144]. In contrast, the effects of early ERC are non-significant in predicted mild disease and for reduction of mortality in either predicted mild or severe disease [97].

With gallbladder in situ, cholecystectomy should be performed early (during the same hospital stay) in patients with mild pancreatitis [145]. However to reduce the risk of sepsis and complications of cholecystectomy, surgery should be delayed in patients with moderate to severe acute pancreatitis who present with peripancreatic fluid collections or pseudocysts until these resolve or persist beyond 6 weeks [146].

7. Future perspectives

In the future, individual risk profiling might allow to distinguish between moderate- and high-risk groups of patients. These risk profiles are likely to include both genetic factors (e.g., *ABCG8* and *ABCB4* variants) and environmental factors. Primary preventive measures for individuals at moderate risk for symptoms or complications will include weight reduction and the modifications of lifestyle and diet. In contrast, patients with a very high lithogenic risk could be offered specific drugs for prevention or even prophylactic cholecystectomy [59,147]. If recurrence of gallstones could be prevented by targeted drug therapy or improved patient selection, non-surgical therapies including ESWL may be revived as acceptable therapeutic options [148,149]. The selec-

tion of patients for non-surgical therapy of gallbladder stones may involve the exclusion of patients with a strong genetic susceptibility to gallstone formation and hence, a high-risk of recurrence; in contrast, patients who carry gallbladder stones that were driven predominantly by environmental factors, such as high-caloric diet or rapid weight loss, may have a low-risk for the recurrence of gallstones once the triggering factors are controlled. One example in support of prophylactic therapy of cholelithiasis is asymptomatic family members of patients with ABCB4 deficiency who may benefit from preventative treatment with UDCA [42]. An example for avenues to improved patient selection for non-surgical therapy of gallbladder stones is the notion that carriers of the *APOE4* allele might possess an increased risk for the recurrence of gallstones following ESWL [150], albeit an overall risk of *APOE4* and gallstones could not be confirmed in a recent larger study [34]. Hence, to date these novel strategies for the prevention and treatment of gallstones are speculative and require extensive basic research and additional genetic studies.

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