Clinical Practice Guidelines

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# EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones☆

European Association for the Study of the Liver (EASL)*



## Introduction

Gallstones or cholelithiasis are a major public health problem in Europe and other developed countries and affect up to 20% of the population. Gallstone disease is the most common gastrointestinal disorder for which patients are admitted to hospitals in European countries [1]. The interdisciplinary care for patients with gallstone disease has advanced considerably during recent decades thanks to a growing insight into the pathophysiological mechanisms and remarkable technical developments in endoscopic and surgical procedures. In contrast, primary prevention for this common disease is still in its infancy.

The EASL Clinical Practice Guidelines (CPG) on the prevention, diagnosis and therapy of gallstones aim to provide current recommendations on the following issues:

1. Prevention of gallstones
2. Diagnosis of gallbladder stones
3. Medical therapy of gallbladder stones
4. Surgical therapy of gallbladder stones
5. Diagnosis of bile duct stones
6. Endoscopic and surgical therapy of bile duct stones
7. Diagnosis and therapy of intrahepatic stones
8. Therapy of gallstones during pregnancy

The EASL CPG on gallstone disease define the use of preventive, diagnostic and therapeutic modalities, including medical, endoscopic and surgical procedures, in the management of patients with gallstones. They are intended to assist physicians and other professional healthcare workers as well as patients and interested individuals in the clinical decision making process by describing a range of generally accepted approaches for the prevention, diagnosis and treatment of gallstone disease.

These guidelines have been produced using evidence from PubMed and Cochrane database searches until September 2015. The evidence and recommendations in these guidelines have been graded on the strength of the supporting evidence according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) [2–5]. We considered within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. Each recommendation has been qualified by giving the grade of evidence underlying the recommendation. The evidence is graded as follows: (A) high quality evidence: further research is very unlikely to change our confidence in the estimate of effect (randomized trials or double-upgraded observational studies); (B) moderate quality evidence: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (downgraded randomized trials or upgraded observational studies); (C) low quality evidence: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate (observational studies or double-downgraded randomized trials); and (D) very low quality evidence: we are very uncertain about the estimate (case series/case reports, downgraded observational studies, triple-downgraded randomized trials). The strength of the recommendations is based on both the aggregate evidence quality and an assessment of the anticipated benefits and harms. A strong recommendation has been made when there is certainty about the various factors that determine the strength of a recommendation, and most or all of the individuals in the relevant population will benefit by following the recommendation; a weak recommendation has been given when there is uncertainty about the various factors that determine the strength of a recommendation.

## Prevention of gallstones

### *Primary prevention of gallstones*

Both cholesterol and pigment gallstone diseases originate from the complex interaction of genetic, environmental, local, systemic and metabolic abnormalities [6]. In Western populations cholesterol gallstones account for 90–95% of all gallstones. Black pigment stones are the major stone type in patients with chronic haemolytic disorders or cirrhosis, although most patients with black pigment stones have neither of these conditions. Cholesterol and black pigment stones are nearly always formed in the gallbladder, whereas brown pigment stones develop primarily in the main bile duct. In Western subjects brown pigment stones are usually found in the bile ducts following cholecystectomy and in patients with sclerosing cholangitis, whereas in Oriental patients they occur in association with chronic infectious

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cholangitis [7]. Sludge is not a cause of gallstone formation and arises with stasis and reduced enterohepatic bile circulation, although stasis itself will contribute to gallstone formation. Since gallstone disease is one of the most prevalent and costly digestive diseases in Western countries [8], primary non-pharmacological prevention would be desirable in the general population [9]. Several risk factors exist for cholesterol, pigment and mixed gallstones. For some non-genetic risk factors, general or specific primary preventive measures are conceivable.

*Lifestyle*

*Can gallstones be prevented?*

Healthy lifestyle and food, regular physical activity and maintenance of an ideal body weight might prevent cholesterol gallbladder stones and symptomatic gallstones (**low quality evidence; weak recommendation**)

Comment: Lifestyle affects the pathogenesis of cholesterol gallstones acting on one or more factors belonging to the metabolic syndrome, namely obesity, diabetes mellitus, and insulin resistance [10–16]. Obesity predisposes to gallstone formation [17] and increases the risk of cholecystectomy by increasing the risk of symptomatic gallstones [18–28]. Thus, increased body mass index (BMI) is a definitive risk factor for gallstone growth [6,20,26,29], and increased BMI *per se* is also a causal risk factor for symptomatic gallstone disease, particularly in women [30]. The risk of symptomatic gallstones has been reported to rise with increasing BMI and waist circumference as well as serum triglycerides [31].

Additional obesity-associated factors facilitating cholesterol gallstone formation include gallbladder stasis [32–35], insulin resistance, dyslipidemia (reduced high density lipoproteins, HDL [31] and hypertriglyceridemia), sedentary lifestyle [30,36], hormone replacement therapy [30], and fast food consumption [30]. Prospective cohort studies [31,37,38] rather than case-control [28,39,40] and cross-sectional studies [19,41–43] are of value when investigating serum lipids and their association with gallstone disease and obesity. Appropriate lifestyle interventions should therefore focus on ideal weight maintenance and weight reduction among overweight and obese individuals in the general population [30]. Insulin resistance and diabetes mellitus type 2 are also strongly associated with cholesterol gallstones independently of obesity [44]. Such conditions represent additional targets for the prevention of gallstones.

*Physical activity*

Questionnaire-based surveys found that physical activity appears to protect against gallstone formation [36,45–48] and to cut the risk of symptomatic stones by about 30% [36,45,49–51]. In a recent prospective cohort study (European prospective investigation into cancer (EPIC)-Norfolk) using a validated questionnaire against energy expenditure and cardio-respiratory fitness [52], a total of 25,639 volunteers, aged 40–74 years, were ranked into four groups of increasing physical activity and monitored over 14 years for symptomatic gallstones. After 5 and 14 years, 135 (uncomplicated) and 290 (complicated) incident cases of symptomatic gallstones were recorded, respectively (68% women). The highest level of physical activity (equivalent to exercising for 1 h a day in a sedentary job, or 30 min a day in a standing job, or heavy manual job without any additional activity) was associated with a 70% decreased risk of symptomatic gallstones in both sexes; a likely causal effect was particularly seen after 5 years. The potential beneficial effects of physical activity on gallstone formation and associated complications are supported by pathogenic mechanisms. Hyperinsulinemia promotes hepatic uptake of cholesterol [53] predisposing to increased secretion of biliary cholesterol [54] and decreased secretion of bile acids (both conditions predispose to cholesterol supersaturated lithogenic bile) [55]. By contrast, regular exercise reduces insulin levels [56], insulin resistance [57], triglyceridemia [58], and fatty acid-dependent hypersecretion of gallbladder mucin [59]. Also, during physical activity serum HDL-cholesterol levels increase [60,61] as marker of increasing reverse cholesterol transport to the liver [62]. Notably, HDL-cholesterol is the precursor of bile acids [63], which contribute to decreased biliary cholesterol saturation, and indeed HDL-cholesterol levels are inversely related to gallstone prevalence [41]. An additional effect of physical activity involves the prokinetic effect on the intestine [64] and cholecystokinin-dependent gallbladder contraction [65]. The importance of maintaining an ideal body weight and regular physical activity should therefore be reinforced in the general population [45], since the overall beneficial effects of physical activity on cardiovascular health extend beyond the protective effect on gallstone formation [29].

*Diet*

Large population-based, long-term, prospective epidemiological studies aiming to identify the protective value of dietary components are hampered by difficulties in estimating the precise quantity and ingestion pattern of nutrients. Nevertheless, high-fiber and high-calcium diets reduce biliary hydrophobic bile acids, whereas a regular eating pattern decreases gallbladder stasis by increasing regular gallbladder emptying [45]. Both aspects play a preventive role for cholesterol cholelithiasis. The likelihood of gallstone disease is increased by consumption of typical Westernized hypercaloric diets [66], including meat intake [48]. Reducing total caloric intake might therefore prove useful [67].

Fruit and vegetables [68] might be protective against gallstone disease, but data on the benefits of vegetarian diets remain controversial. Although protection might be conferred by a lower BMI [69], and regular use of vegetable oils and vitamin C [46,70], studies on different populations have shown either a protective effect [71–75] or a lack of a protective effect of vegetarian diets on gallstones [47,76].

Poly- and monounsaturated fats [77], and specifically nut consumption [77,78], might protect against gallstone disease, possibly as part of a healthy diet.

Data regarding coffee intake are controversial: caffeine intake (sources: coffee, black tea, and caffeinated soft drinks) and coffee in particular, are reportedly protective in some [79–84], but not all epidemiological studies [47]. Geographical, cultural and drinking patterns of coffee might explain discrepant results [47]. Besides the potential effect on hepatobiliary secretion of cholesterol and intestinal motility, additional mechanisms of action caffeine or coffee intake are still poorly understood.

Although prospective epidemiological studies reported protective effects of alcohol consumption on gallstone formation [31,78,79], and multifactorial analysis indicated that Danish patients with symptomatic gallstones consume less alcohol as compared to those with asymptomatic stones [30], the findings are controversial [72,81–83,85,86], and due to its negative effects on overall health, alcohol cannot be recommended for the prevention of gallstones.

Regular vitamin C supplementation or regular use of vitamin C-enriched diet might have a protective effect on gallstone formation. In fact, cholesterol conversion to bile acids requires 7α-hydroxylation and an appropriate content of vitamin C in the hepatocyte [87,88]. In humans, vitamin C deficiency might therefore increase the risk of cholesterol gallstone formation [70]. In gallstone patients, vitamin C supplementation (500 mg × 4 times a day) changed biliary bile acid composition, increased phospholipids, and proved to be protective by prolonging the crystallization time of biliary cholesterol [89]. Furthermore, observational studies have identified an association between low vitamin C consumption and risk of gallstones/gallbladder disease [48,70,90] or cholecystectomy [91]. In a German observational population-based study (n = 2129 subjects aged 18–65 years), gallstone prevalence by ultrasonography was 4.7% *vs.* 8.2% in patients reporting regular use of vitamin C (n = 232) or not using vitamin C (n = 1897), respectively [92].

*Prevention of gallstones in the general population*

*Is a pharmacological treatment advisable for the prevention of gallstones in the general population?*

Pharmacological prevention of gallstones is not advisable in the general population (**very low quality evidence; weak recommendation**)

Comment: There is no indication for administering ursodeoxycholic acid (UDCA) as a preventive drug for gallstone disease in the general population, apart from high risk groups (see section Primary prevention of gallstones in high risk groups). Similarly, there is not enough evidence to embark on gallstone/sludge prophylaxis with UDCA in pregnancy (because gallstone may be transient in this situation) or with omega-3 fatty acid supplementation [93].

Conflicting results are available on the protective effect of statins alone or with UDCA on gallstone disease. The use of statins was evaluated in two population-based case-control studies. A decreased risk of gallstone disease and cholecystectomy emerged with regular use of statins [94,95], a trend confirmed in the Nurses' Health Study evaluating the use of statins over a period of 10 years [96]. A case-controlled study confirmed the protective effect of statin use on the risk of cholecystectomy [97]. Although results appear promising, the protective effect of lovastatin [98–101], pravastatin alone [102–106] or with UDCA [107], simvastatin alone [103,108–112] or with UDCA [113,114] and fluvastatin [115] on biliary cholesterol saturation, biliary lipid composition, cholesterol crystallization, gallstone formation, and stone dissolution is weak and not always confirmed. In a recent meta-analysis involving a total of 622868 participants from six studies (four case-control studies, one cohort study and one cross-sectional study), current statin use was associated with a lower risk of cholecystectomy as compared with non-use. The effect was significantly more evident for moderate and high statin use than low statin use (i.e. 1–4 prescriptions) [116]. A Finnish case-control study matched 272 patients using statins with 272 patients not using statins by age and sex to investigate the influence of statin use on complicated gallstone disease at gallbladder surgery. While patients using statins did not have worse outcomes after cholecystectomy than non-users, statin treatment was associated with a shorter operation time for laparoscopic cholecystectomy [117]. So far, however, better controlled studies are required to confirm such findings, and statins cannot be proposed for the prevention of gallstones [118,119].

Ezetimibe is a selective cholesterol absorption inhibitor acting on the intestinal Niemann–Pick C1-like 1 (NPC1L1) protein. Murine studies based on lithogenic diets have shown beneficial effects of ezetimibe on biliary lipid composition, intestinal cholesterol absorption and biliary cholesterol secretion and saturation, crystal aggregation, gallstone formation, bile flow, gallbladder motility function, and cholecystosteatosis [120–123]. In the hamster model on a lithogenic diet, ezetimibe prevented the increase of biliary cholesterol and cholesterol accumulation in the liver [124]. The translational value of such effects of ezetimibe was confirmed in a pilot study in cholesterol gallstone patients: ezetimibe reduced biliary cholesterol saturation and retarded cholesterol crystallization [120]. However, in a small retrospective, case-control study ezetimibe did not appear to influence the prevalence of gallstones [125]. More recently, in a large Danish study involving 67,385 participants, it was shown that genetic variation in *NPC1L1*, mimicking the effect of ezetimibe monotherapy, was indeed associated with a dose-dependent reduction of serum low-density lipoprotein (LDL) cholesterol concentrations and the risk of ischemic vascular disease. However, the cumulative incidence of symptomatic gallstone disease increased (sample of 3,886 subjects) [126]. The possibility exists that in humans (who express NPC1L1 in intestine and liver) genetically reduced activity of NPC1L1 causes lower uptake rates of cholesterol from both the intestine into enterocytes and from bile into hepatocytes. The latter effect might increase the risk of gallstone disease. Gallbladder-related adverse effects, however, were not associated with ezetimibe treatment in the IMPROVE-IT trial with a minimum follow-up of 2.5 years (comparing patients treated with ezetimibe plus statin to patients treated with statin alone) [127]. Overall, these data indicate that the use of ezetimibe for the prevention of cholesterol gallstones warrants further investigation [118,119,128,129]. This therapeutic approach should be put in perspective when confronted with groups of patients displaying metabolic abnormalities and high cardiovascular risk, the use of combined lipid-lowering therapy (statins/ezetimibe), gender-specific gallstone risk (higher in women than in men), and the overall duration of ezetimibe treatment.

Finally, aspirin is currently not accepted for the prevention of gallstones [6].

*Primary prevention of gallstones in high risk groups*

*Rapid weight loss*

*When can ursodeoxycholic acid be used to prevent gallstones in obese patients?*

In situations that are associated with rapid weight loss (e.g. very-low-calorie diet, bariatric surgery), temporary ursodeoxycholic acid (at least 500 mg per day until body weight has stabilized) may be recommended (**moderate quality evidence; weak recommendation**)

Comment: Increased BMI and female gender are definitive risk factors for gallstone growth [6,20,26,29]. Increased BMI is also a causal risk factor for symptomatic gallstone disease [30]. Obesity will influence most pathogenic mechanisms for gallstone formation, i.e. supersaturation of bile with cholesterol, increased propensity to cholesterol crystallization, stone aggregation, and defective gallbladder emptying [6,26,130–134]. However, the risk of gallstones also increases significantly during rapid weight loss (>1.5 kg/week) due to a weight reduction programme [131,135–137] and decreases at approximately 2 years when body weight stabilizes [138,139]. Weight cycling is also a modest independent risk factor for gallstone formation [48,82,132,140]. By contrast, progressive reduction of body weight at moderate speed (max. 1.5 kg/week) [136,141,142] in obese subjects decreases excessive *de novo* biosynthesis and biliary excretion of cholesterol, with decreased risk of gallstone formation. A recent study performing a multivariate analysis in 171 patients reported that factors associated with gallstone formation after bariatric surgery are higher rate of weight loss, progressive decrease in percentage of gallbladder emptying, prolonged overnight fasting, and reduced intake of calories and fibers [143].

Rapid weight loss can be achieved by very-low-calorie diets (i.e. diets containing less than 800 kcal per day [139,144–147] or bariatric surgery, such as Roux-en-Y gastric bypass (RYGB)) [81,131,137–139,148–152]. Although the majority of newly formed gallstones remains asymptomatic following rapid weight loss, the risk of both uncomplicated and complicated gallstone disease and cholecystectomy is still increased and is 3-fold greater in very-low-calorie than in low-calorie diets [139]. Appropriate fat content (at least 7 g/day) in very-low-calorie diets might improve gallbladder motility and decrease the risk of symptomatic gallstones, as shown in recent controlled studies [139,153,154]. Patients undergoing rapid weight loss are more likely to become symptomatic for gallstones, with incidence reaching 28% to 71% after gastric bypass [27,150,151,155,156]. Cholecystectomy is indicated in up to one-third of patients by 3 years after surgery [27,150]. After bariatric surgery, the risk of developing gallstone disease increases to 48% for weight loss greater than 25% of original weight, especially after gastric bypass or sleeve gastrectomy [157–162]. The same trend is observed in obese patients using hypocaloric diets postoperatively [137].

In obese patients undergoing rapid weight loss either with very-low-calorie diets or bariatric surgery without cholecystectomy, the litholytic hydrophilic UDCA prevents cholesterol gallstone formation following rapid weight reduction. However, the costs of chronic treatment and patient compliance have to be considered [137,138,148–151,163]. A meta-analysis of 13 randomised control trials (RCTs) on the protective effect of UDCA during weight loss (1,791 patients, 1,217 randomized to UDCA and 574 randomized to placebo) confirmed that UDCA (range 300–1,200 mg/day) can prevent gallbladder stone formation during dieting or after bariatric surgery [164]. Treatment with UDCA should last until body weight is stabilized at a dose (range 500–600 mg/day) that is lower than for litholysis [150]. Indeed, treatment efficacy is best during the period of weight loss, since the risk of developing stones decreases once the weight has stabilized [150]. A decision tree analysis shows that gallstone prevention with UDCA lowers costs [165]. UDCA has become the standard prophylactic treatment for cholesterol cholelithiasis in obese patients following very-low-calorie diets or after bariatric surgery. Patients undergoing either vertical banded gastroplasty or adjustable gastric banding were randomized to placebo or 500 mg UDCA/day. Incidence of gallstone formation at 12 and 24 months was 22% and 30% (placebo group) and 3% and 8% (UDCA), respectively. Cholecystectomy rate was 12% and 5% in placebo and UDCA groups, respectively [138]. In the study of Wudel *et al.* [151], gallstones developed in 71% of patients within 12 months of gastric bypass; 41% of these gallstone patients became symptomatic, and 67% of symptomatic, patients were cholecystectomized. UDCA was effective in preventing gallstone formation as compared to placebo, but a major concern was the poor therapeutic outcome due to lack of compliance. Further studies are required to confirm that a combined intervention (e.g. diet plus UDCA) has the potential to improve stone prevention during weight loss [143,166].

The beneficial effect of fish oil (n-3) polyunsaturated fatty acids on biliary crystallization was confirmed in a randomized double-blind placebo-controlled trial in obese women during rapid weight loss with a hypocaloric diet (1200 kcal/day), and compared with UDCA (1200 mg/day) [93].

No severe side effect can be expected with UDCA at the dosage employed in previous studies (i.e. 300–1200 mg/day) [137,138,147,148,151]. Sugerman *et al.* [150] noted that some patients on UDCA dropped out because of "vomiting or skin rashes", but similar rates were observed in the placebo group. Similar adverse events between UDCA and placebo, unrelated to the dose of UDCA, were reported by Shiffman *et al.* [147] (i.e. constipation, headache, diarrhea, dizziness, and upper respiratory infections, ranging from 16% to 30% of patients).

No indication exists for aspirin use to prevent gallstone recurrence [167].

*Should prophylactic cholecystectomy be performed during bariatric surgery in obese subjects undergoing rapid weight loss?*

Prophylactic cholecytectomy is not routinely indicated during bariatric surgery (**very low quality evidence; weak recommendation**)

Comment: Gallstone-related complications after bariatric surgery generally appear within 7–18 months [168–172]. During a median follow-up of 3 years, almost 20% of patients undergoing laparoscopic RYGB with an intact gallbladder became symptomatic and required cholecystectomy. The estimated 5-year gallbladder disease-free survival was low (77.4%) [173]. Another theoretical advantage of prophylactic cholecystectomy would be prevention of future bile duct stones, which can be difficult to remove endoscopically after RYGB, due to altered anatomy. Based on such estimates, concurrent prophylactic cholecystectomy during RYGB has previously been recommended, based on the rationale that the conversion rate to open surgery is not increased, neither is operative time nor hospital stay [173]. Further studies, however, have suggested that most patients remain asymptomatic [156,157,160,168,169,174–178] and never require further interventions following RYGB. Thus, concurrent (prophylactic) cholecystectomy during laparoscopic bypass surgery is no longer routinely performed [168,169,174–176,179].

Essentially, cholecystectomy is reserved for the subgroup of patients with symptomatic gallstones or abnormal gallbladder findings (e.g. chronic cholecystitis, tumor-like lesions) [152,171,173,180,181]. This assumption stands despite the fact that post-RYGB cholecystectomy in symptomatic gallstone patients becomes more difficult and endoscopic retrograde cholangiopancreatography (ERCP) may not be feasible for anatomical reasons [182].

With areas of uncertainties concerning the most cost-effective strategy for gallbladder management in patients undergoing RYGB, a recent decision model was developed on the US Health system background [183]. Three possible options were compared: prophylactic concurrent cholecystectomy, RYGB with preserved gallbladder (with or without postoperative UDCA therapy), and selective cholecystectomy only for patients with gallstones identified by ultrasonography. The most cost-effective strategy was RYGB without cholecystectomy, provided that the risk of post-surgical gallstone complications remains low [180] and UDCA is not used. UDCA treatment appears a too expensive option after RYGB, and in this case concurrent cholecystectomy becomes less costly. Another limitation with UDCA use is the variable compliance to daily prescription, ranging from 40% to 85% [150,151,158,168,172].

*Long-term therapy with somatostatin or analogues*

*Is primary prevention of gallstones with ursodeoxycholic acid of indicated in patients on somatostatin or analogue treatment?*

In patients on long-term therapy with somatostatin or analogues, concomitant treatment with ursodeoxycholic acid can be considered to prevent cholesterol gallstone formation (**low quality evidence; weak recommendation**)

Comment: Patients requiring long-term therapy with somatostatin or various analogues (e.g. patients with neuroendocrine neoplasms) exhibit prolongation of intestinal transit, severely impaired gallbladder emptying despite preserved postprandial cholecystokinin (CCK) release [184], and several lithogenic changes in bile [185–188]. Despite the frequent occurrence of gallstones, they infrequently become symptomatic or prompt acute surgery [189]. Careful follow-up of these patients with respect to cholelithogenic changes is recommended, and concomitant treatment with UDCA might be considered [186,187,190].

*Total parenteral nutrition*

*Is primary prevention of gallstones indicated during total parenteral nutrition?*

Patients on total parenteral nutrition are at increased risk of gallbladder sludge formation but no recommendation for prevention can be given (**very low quality evidence; weak recommendation**)

Comment: Biliary sludge is often found incidentally in conditions of increased gallbladder stasis and/or concurrent change of biliary composition, e.g. prolonged fasting (especially during total parenteral nutrition, TPN) [191]. Due to transient changes of gallbladder kinetics and biliary composition, both sludge and small gallstones might disappear after restoration of oral diet (e.g. three meals a day with sufficient fat to improve gallbladder emptying and sludge clearance) [192–196]. Patients on TPN should be shifted to enteral nutrition whenever possible. Controversial data exist concerning the stimulation of the gallbladder in TPN with CCK (either by daily exogenous CCK or by fast infusion of high doses of crystalline amino acids) [192,193,197–199]. In one study a mixed soybean/medium chain triglyceride/olive/fish oil emulsion used for long-term parenteral nutrition was associated with both disappearance and decreased size of gallstones after 3 and 2 months, respectively in two children continuing UDCA at 15 mg/kg/day [200]. The overall results of such studies, albeit convincing, are hampered by the low number of cases. Furthermore, there is no indication for prophylactic treatment with UDCA in patients with sludge after TPN has been interrupted [190]. Use of omega-3 fatty acid-enriched TPN likely increased omega-3 fatty acids content in biliary phosphatidylcholines and decreased biliary supersaturation in cholesterol [201] with a mechanism also involving biliary mucin suppression [202].

*Hormone therapy*

*Is there an indication for pharmacological or surgical prevention of gallstones during hormone replacement therapy?*

Physicians who prescribe hormone replacement therapy should be aware of the increased risk for gallstones. Currently there is no indication for pharmacological or surgical stone prevention during hormone replacement therapy (**very low quality evidence; weak recommendation**)

Comment: Hormone therapy is widely used for controlling menopausal symptoms and has also been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. A recent Cochrane meta-analysis [203] compared the effects of hormone therapy by oral, transdermal, subcutaneous or intranasal routes (oestrogen-only and combined continuous with or without progestogens) with placebo for 3 to 7 years. From 23 randomized double-blind studies (involving 42,830 women aged 26 to 91 years, mainly from the Heart and Estrogen-progestin Replacement Study (HERS) 1998 and the Women's Health Initiative (WHI) 1998 study) results showed a significantly increased risk of gallbladder disease with oestrogen-only (absolute risk increase from 26 to 45 per 1000, 95% confidence interval (CI = 36–57), with combined continuous treatment (absolute risk from 27 to 47 per 1000, 95% CI = 38–60), including postmenopausal women with cardiovascular disease [204,205]. The risk started to increase in the active group in the first year. Caution is therefore recommended in prescribing different types of continuous hormone therapy for controlling menopausal symptoms. While carefully evaluating potential severe health hazards, treatment should be reserved for groups

at low risk of cardiovascular disease, venous thrombo-embolism, or breast cancer. The risk of gallbladder disease is well established, but medical gallstone prophylaxis has not been addressed in randomized trials thus far.

*Prevention of recurrent bile duct stones*

*Are there effective strategies to prevent recurrent bile duct stones?*

No general recommendation can be given for the pharmacological prevention of recurrent bile duct stones (**very low quality evidence; weak recommendation**)

Comment: Recurrent bile duct stones are observed in 5–20% of patients after endoscopic sphincterotomy [206–211] and can usually be removed endoscopically. Currently, there are no validated prophylactic measures. No consistent benefit of pharmacological secondary prevention has been observed, and data on the potential effects of UDCA [212] have not been validated in randomized controlled trials [212,213].

Patients with mutations of the gene encoding the phosphatidylcholine floppase ABCB4 have a monogenic predisposition for low phospholipid-associated cholelithiasis (LPAC). Due to low biliary phospholipid concentrations, cholesterol gallstone disease develops before the age of 40 years with intrahepatic bile duct and gallbladder cholesterol stones and recurrent biliary symptoms after cholecystectomy [214–217]. The diagnosis is based on medical history, clinical findings, and imaging. Microscopic examination of duodenal bile or hepatic bile obtained during ERCP for crystals and microliths (and chemical analysis) can contribute to patient management in this setting. Whereas diagnostic clues are provided by the family history of cholelithiasis in first-degree relatives and recurrent bile duct stones [218], genetic testing via sequence analysis of the *ABCB4* gene may provide additional information but is not necessary to make the diagnosis of LPAC. The majority of LPAC patients benefit from prophylactic or long-term therapy with UDCA (15 mg/kg body weight per day) to be initiated in young adults to prevent the occurrence or the recurrence of stones as well as related complications [216].

## Diagnosis of gallbladder stones

*Biliary colic*

*When should symptomatic gallbladder stones be suspected?*

The characteristic symptoms of gallbladder stones, i.e. episodic attacks of severe pain in the right upper abdominal quadrant or epigastrium for at least 15-30 minutes with radiation to the right back or shoulder and a positive reaction to analgesics, should be identified by medical history and physical examination (**very low quality evidence; weak recommendation**)

Comment: Gallbladder stones are present in 10–20% of Western populations but the incidence increases with age and is higher in women. In about 80% of carriers they are asymptomatic. The natural history of asymptomatic gallstones suggests that most remain asymptomatic throughout life. Symptoms develop with a rate of 1–4% per year, 20% becoming symptomatic within 20 years of diagnosis [219–222]. Complications occur with a rate of 1–3% per year after the first colic episode, and 0.1–0.3% in asymptomatic patients [219,223].

Only three symptoms are significantly associated with the presence of gallstones: biliary colic (Odds Ratio (OR) = 2.6; 95% CI = 2.4–2.9), radiating pain (OR = 2.8; 95% CI = 2.2–3.7) and the use of analgesics (OR = 2.0; 95% CI = 1.6–2.5) [224]. Although biliary pain has a positive likelihood ratio of 1.34, the positive predictive value of biliary symptoms is very low (0.25) [225]. Nausea and vomiting may be present. Pain is severe (intensity higher than 5 on a 0–10 pain visual analogue scale) and begins abruptly or increases progressively in intensity before stabilizing. This results from gallbladder distention after acute and usually transient obstruction of the cystic duct by a stone or sludge. Most attacks resolve spontaneously. Irregular periodicity of the pain, onset at approximately 1 h after meals, onset during the evening or at night, awakening the patient from sleep, and duration of more than 1 h are all highly suggestive of biliary pain [226,227]. Duration longer than 5 h indicates most often acute cholecystitis. Complications of gallstones are preceded by at least one "warning" episode of biliary colic in over half of the patients [228,229].

In about 50% of patients the pain episodes recur after a first biliary attack [219,223,230]. Symptoms such as dyspepsia, heartburn, bloating, flatulence are often present in these patients. They are not characteristic of gallstone disease, as they can also occur in individuals without stones and might indicate disorders such as functional dyspepsia, gastroesophageal reflux disease, irritable bowel syndrome, or cardiac disease. If present in patients with gallstones, they usually persist after cholecystectomy [226,231–233]. Alternative causes of upper abdominal pain should be considered in the differential diagnosis of biliary pain.

Laboratory tests do not contribute to the diagnosis of uncomplicated symptomatic gallbladder stones, since they show normal values in the large majority of patients.

*Imaging*

*Which imaging modality is most appropriate to diagnose gallstones?*

In a patient with a recent history of biliary pain, abdominal ultrasound should be performed (**high quality evidence; strong recommendation**)

In case of strong clinical suspicion of gallbladder stones and negative abdominal ultrasound, endoscopic ultrasound (or magnetic resonance imaging) may be performed (**low quality evidence; weak recommendation**)

Comment: Abdominal ultrasonography is the imaging of choice in patients with upper abdominal quadrant pain. Its accuracy for detecting gallbladder stones is in excess of 95% [234–236]. Older patients with atypical abdominal pain,

immunocompromised patients with unclear site of infection, or patients with bacteremia suspicious for an abdominal septic focus may also be evaluated by abdominal ultrasound for the presence of (complicated) gallstones.

In abdominal ultrasound, gallstones appear as echogenic foci with a hypoechoic distal shadow. Mobility differentiates stones from polyps and should be proven by examining the patient in different positions such as supine, left lateral decubitus or upright. Biliary sludge is also detected by ultrasound as sand-like small echogenic foci [237].

Endoscopic ultrasound (EUS) has a high sensitivity of 94–98% to detect cholecystolithiasis in patients with biliary pain but normal abdominal ultrasound [238]. The procedure might be particularly helpful in patients with unexplained acute and acute recurrent pancreatitis, which might be caused by biliary sludge [239–242]. Magnetic resonance imaging (MRI) has been recommended when ultrasound findings are inconclusive [243,244]. Computed tomography (CT) is less useful for diagnosis of gallbladder stones.

*Acute cholecystitis*

*What are the appropriate investigations to diagnose acute cholecystitis?*

Acute cholecystitis should be suspected in a patient with fever, severe pain located in the right upper abdominal quadrant lasting for several hours, and right upper abdominal pain and tenderness on palpation (Murphy's sign) (**moderate quality evidence; strong recommendation**)

In case of strong clinical suspicion of acute cholecystitis, a computerised tomography scan may be performed (**very low quality evidence; weak recommendation**)

Comment: Acute cholecystitis is the most common complication of gallstone disease, occurring in about 10% of the patients with symptomatic gallstones [245]. Acute inflammation of the gallbladder wall is usually due to obstruction of the cystic duct by a stone. Acute cholecystitis is present in 3–9% of all patients with acute abdominal symptoms who present in the emergency room, and about 45–80% of the patients report previous attacks of biliary pain [223,229]. Patients with acute cholecystitis have severe and worsening pain lasting for several (usually more than 5) hours, irradiating in the interscapular area or right shoulder, accompanied by fever and often by nausea and vomiting. Pain in the right (but not the left) upper abdominal quadrant associated with tenderness on palpation (Murphy's sign) is highly specific and sensitive for the diagnosis [246]. Fever and elevated inflammatory parameters (white blood count, C-reactive protein) are usually present. To assess the severity of acute cholecystitis, which guides further monitoring and treatment decisions, the evaluation of blood urea nitrogen, creatinine, albumin and arterial blood gas analysis may be required [247].

Abdominal ultrasound accurately detects gallstones, a distended gallbladder, thickened (>4 mm) gallbladder wall, pericholecystic fluid and a sonographic Murphy's sign (intensified pain upon probe pressure directly over the gallbladder). Ultrasound has lower sensitivity for detecting stones in the setting of acute cholecystitis [243], but the combination of gallbladder stones with either a sonographic Murphy's sign or a thickened gallbladder wall has a positive predictive value of 92% and 95%, respectively, for acute cholecystitis [248].

Although CT for acute cholecystitis is still underevaluated, it can accurately visualize gallbladder distention and wall thickening and identify complications of acute cholecystitis such as gallbladder wall emphysema, abscess formation, and perforation [249,250]. Thus, it is often used preoperatively in emergency room settings.

Radioisotope cholescintigraphy (Tc-HIDA scan) detects cystic duct obstruction by failure of the gallbladder to fill after intravenous injection of the tracer. It has very high sensitivity for the diagnosis of acute cholecystitis [250–252], but the lack of gallstone visualization and the ionizing radiation make ultrasound the preferred imaging modality in Europe [244]. Although in a recent meta-analysis there were no significant differences in specificity among abdominal ultrasound (83%; 95% CI = 74–89%), MR imaging (81%; 95% CI = 69–90%) and cholescintigraphy (90%; 95% CI = 86–93%) [250], the latter two modalities are less suitable for the acute settings.

## Medical therapy of gallstones

*Bile acid dissolution therapy*

*Should gallbladder stones be dissolved with bile acids taken orally?*

Litholysis using bile acids alone or in combination with extracorporeal shock wave lithotripsy is not recommended for gallbladder stones (**moderate quality evidence; strong recommendation**)

Comment: Although meta-analysis of studies on litholysis using UDCA [253] showed acceptable therapy success in patients with small non-calcified stones in a functioning gallbladder (63% of patients free from stones after >6 months), there is a lack of effectiveness in preventing symptoms and complications that subsequently occur as there is a high long-term recurrence rate (25–64% after 5 years and 49–80% after 10 years) [254–265]. Evidence from randomized controlled trials, systematic reviews and cohort studies show that extracorporeal shock wave lithotripsy (ESWL), similar to bile acid dissolution therapy with UDCA alone, has a low rate of cure, with only 55% of carefully selected patients remaining free of stones [266].

The majority of recurring stones are symptomatic, and a third of patients have to undergo cholecystectomy after an average of 3 years [267]. Over 3 months, only 26% of patients remained free of colic after treatment with UDCA compared with 33% after placebo, and about 2% of patients had gallstone complications after treatment with UDCA, which is similar to the annual rate of complications in those not taking the drug [253,264,265,268–272].

The results of a Japanese cohort analysis that showed a litholysis independent reduction of the risk of biliary pain or acute cholecystitis [273] were not confirmed in a subsequent Dutch study, in which UDCA did not reduce biliary symptoms in highly symptomatic patients on the cholecystectomy waiting list [268].

*Therapy of biliary colic*

*How is a patient with biliary colic treated?*

Biliary colic should be treated with nonsteroidal anti-inflammatory drugs (e.g. diclofenac, indomethacin) (**moderate quality evidence; weak recommendation**)

In addition, spasmolytics (e.g. butylscopolamine) and for severe symptoms, opioids (e.g. buprenorphine) may be indicated (**low quality evidence; strong recommendation**)

Comment: When treating acute biliary colic one must differentiate between immediate drug therapy against pain and causal therapy, i.e. cholecystectomy. Based on evidence from only one trial, early laparoscopic cholecystectomy within 24 h after the diagnosis of biliary colic provides causal therapy and decreases the morbidity on the cholecystectomy waiting list [274], but further RCTs are needed before this approach can be recommended in the setting of short waiting times [275].

For the analgesic treatment of biliary colic analgesics in combination with spasmolytics are commonly used. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (e.g. 50–75 mg I.M.), ketoprofen (e.g. 200 mg I.V.) or indomethacin (e.g. 50 mg I.V. or 2 × 75 mg suppositories) have analgesic effects on biliary colic [276–278]. Recent RCTs illustrate that their administration reduces the risk of developing acute cholecystitis during the course of biliary colic [278–280]. In comparison with other drugs NSAIDs are more efficacious in controlling pain than spasmolytic drugs [278]. Contraindications such as a history of hypersensitivity/severe allergic reactions to an NSAID as well as impairment of renal function and gastrointestinal complications have to be considered. Weaker analgesics such as metamizol [281] or paracetamol might be sufficient in individual cases. In addition, biliary colic caused by gallbladder stones has also been successfully treated with nitroglycerin [282].

For severe symptoms, stronger analgesically active opioids are administered, although there was no difference between NSAIDs and opioids in RCTs [278]. Best suited might be buprenorphine, because it appears to contract the sphincter Oddi less than morphine [283–285]. The efficacy of different drug combinations (e.g. NSAIDs + opioids) has not been sufficiently evaluated.

*Antibiotics*

*Are antibiotics generally indicated in acute cholecystitis?*

Antibiotics in mild acute cholecystitis, i.e. without cholangitis, bacteriemia/sepsis, abscess or perforation, are not recommended at all times (**very low quality evidence; weak recommendation**)

Comment: Initial therapy for acute cholecystitis is directed towards general support for the patient, including fluid and electrolyte replacement as well as the correction of metabolic imbalances. Antimicrobial therapy is usually empirical in patients with acute cholecystitis. However, no correlation between the severity of symptoms, gallbladder description, or positive gallbladder culture and the use of antibiotics postoperatively has been observed [286]. Recently a small randomized controlled trial could not demonstrate that intravenous antibiotic treatment with amoxicllin/clavulanate or a combination of ciprofloxacin and metronidazole improves early outcome of hospital course in patients with mild acute cholecystitis [287]. Immunocompromised patients with complicated cholecystitis (acute cholangitis, bacteremia/sepsis, perforation, abscess) commonly receive antibiotics. Initial therapy should cover the Enterobacteriaceae, in particular *Escherichia coli*. Coverage of anaerobes, in particular *Bacteroides* spp., is warranted in patients in serious clinical condition [288]. In prospective series, age ⩾70 years, diabetes as comorbidity and distended gallbladder at admission were associated with failure of conservative treatment; persistent leukocytosis and tachycardia were found to be predictors for the need of cholecystectomy at 24 and 48 h follow-up [289].

## Surgical therapy of gallbladder stones

*Patients with symptomatic gallstones*

*What is the treatment for symptomatic gallbladder stones?*

Cholecystectomy is the preferred option for treatment of symptomatic gallbladder stones (**moderate quality evidence; strong recommendation**)

Comment: Depending on the intensity and the number of symptomatic episodes, a cholecystectomy should be performed for symptomatic cholecystolithiasis because approximately half of the patients have recurring colic [268]. The risk of complications such as acute cholecystitis, biliary pancreatitis, obstructive jaundice, and cholangitis is 0.5–3% per year [219,221,230,290,291]. The alternatives for surgery include bile acid dissolution therapy with UDCA and ESWL but such treatments cannot be recommended because of the low rate of cure, high rate of recurrence of gallstones, and the lack of effectiveness in preventing symptoms and complications after medical treatment. The rate of cure is only 27% after UDCA and only 55% after ESWL in carefully selected patients and the rate of recurrent gallstones was >40% after complete dissolution of stones or ESWL within a period of 4 years. Furthermore, approximately 30% of patients had symptoms within 3 months irrespective of whether UDCA was used and the annual rate of complications after UDCA was approximately 2%, which is similar to the annual rate of complications in those not taking UDCA [190,253,264,265,268,292]. Cholecystectomy prevents gallstone complications but may not be necessary if biliary colic symptoms have not occurred within the last 5 years or after just one episode of biliary colic (with an approximately 50% chance of another colic within 1 year) [221]. While the recurrence of biliary colic does not increase the rate of complications associated with cholecystectomy, it is difficult to predict the patients that will develop complications such as acute cholecystitis, pancreatitis, obstructive jaundice, and cholangitis, all of which increase the risk of conversion to an open procedure and prolong hospital stay after cholecystectomy. Abdominal symptoms persist in every third to fourth

patient after cholecystectomy [231,232,293–297]; whereas symptoms are often not very specific, individualized decision making as towards cholecystectomy is mandatory to reduce redundant operations.

*Indications in patients with asymptomatic gallbladder stones*

*Should patients with asymptomatic gallstones be treated?*

Routine treatment is not recommended for patients with asymptomatic gallbladder stones (**very low quality evidence; weak recommendation**)

Comment: There have been no RCTs assessing the benefit of cholecystectomy in asymptomatic patients. Neither comprehensive clinical observations nor detailed analyses of prospective studies on the clinical course of asymptomatic cholecystolithiasis prove the efficacy of cholecystectomy in asymptomatic patients with stones. Approximately, 0.7–2.5% of patients with asymptomatic gallstones develop symptoms related to gallstones every year. The annual incidence of complications such as acute cholecystitis, acute pancreatitis, obstructive jaundice, or cholangitis is 0.1–0.3% [219,221]. The treatment (open or laparoscopic cholecystectomy) of asymptomatic patients with gallbladder stones does not increase their life expectancy, because the risk of surgery (mortality and morbidity) outweighs the probability of complications [223,298]. Furthermore, costs are lower for patients with asymptomatic gallstones if one waits until symptoms or complications occur rather than prophylactic cholecystectomy or litholysis (see recommendation: Should gallbladder stones be dissolved with bile acids taken orally?) [299]. In Western countries with a low gallbladder carcinoma prevalence [300], the slight but still very low risk of gallbladder cancer in asymptomatic cholecystolithiasis does not justify its treatment [301,302]. Diabetics also do not need prophylactic therapy [303,304].

*Exceptions*

*Is cholecystectomy indicated in patients with porcelain gallbladder?*

Asymptomatic patients with porcelain gallbladder may undergo cholecystectomy (**very low quality evidence; weak recommendation**)

Comment: A relatively high percentage of patients develop gallbladder carcinoma without prophylactic cholecystectomy. According to earlier studies with porcelain gallbladder mainly diagnosed on abdominal X-ray, carcinomas are found in up to 20% of all calcified gallbladders [305]. This connection was not confirmed in all series [306] and a causative relationship between porcelain gallbladder and gallbladder cancer has not been established [307]. Differentiation between homogeneous wall calcification (carcinoma rate very low) and spotty calcification (carcinoma rate 7%) should also be made [308]. A cholecystectomy may be avoided in patients with homogeneous wall calcifications [304]. A porcelain gallbladder is currently mainly diagnosed with ultrasound, with selection of a different population compared to earlier studies. A confirmation using CT is recommended before surgery.

An association between gallbladder carcinoma and gallstones has been noted in several studies [309–312]. However, given the complications related to cholecystectomy including the risk of bile duct injury (see section Bile duct injuries), there is considerable uncertainty in benefits of prophylactic cholecystectomy in this patient group. Depending on additional risk factors between 67 and 769 cholecystectomies have to be performed to prevent a gallbladder tumor [313].

*Is surgery indicated for gallbladder polyps?*

Cholecystectomy should be performed in patients with gallbladder polyps ≥1 cm without or with gallstones regardless of their symptoms (**moderate quality evidence; strong recommendation**). Cholecystectomy should also be considered in patients with asymptomatic gallbladder stones and gallbladder polyps 6-10 mm and in case of growing polyps (**very low quality evidence; weak recommendation**)

Cholecystectomy may be recommended for asymptomatic patients with primary sclerosing cholangitis and gallbladder polyps irrespective of size (**low quality evidence; weak recommendation**)

Cholecystectomy is not indicated in patients with asymptomatic gallbladder stones and gallbladder polyps ≤5 mm (**moderate quality evidence; strong recommendation**)

Comment: The prevalence of gallbladder polyps in the general population is between 1% and 7% [314–318]. The prevalence of adenomas (which are considered to be premalignant) in people with gallbladder polyps is under 5% [315,319]. In several large studies polyps that were $\geqslant$1 cm in diameter had a clearly increased probability of adenomas. Since up to 50% of polyps $\geqslant$1 cm in diameter carry carcinoma [315,316,320–323], patients should undergo cholecystectomy.

Given the complications associated with cholecystectomy (see section Bile duct injuries), there is considerable uncertainty in benefits of prophylactic cholecystectomy in patients with asymptomatic gallbladder stones and gallbladder polyps with a size of 6–10 mm. A systematic review based on 10 observational studies noted that the rate of growth of polyp may not be a good predictor of a neoplastic polyp [324]. However, the same review noted that some malignant neoplastic polyps were less than 1 cm (but $\geqslant$5 mm), although the vast majority of intermediate polyps (6–10 mm) show a benign natural course [325]. Gallbladder polyps can be demonstrated more precisely with endosonography than with transcutaneous sonography (87–97% *vs.* 52–76%) [326,327]. Therefore, endosonography may be helpful to differentiate gallbladder polyps of 6–10 mm in size that are suspicious of gallbladder cancer on transcutaneous sonography.

In patients with primary sclerosing cholangitis (PSC), gallbladder mass lesions are frequently malignant and the incidence of intraepithelial neoplasia is high [328–330], therefore it

is reasonable to offer cholecystectomy to PSC patients with gallbladder polyps or other mass lesions, even if these are <1 cm in diameter.

For polyps >18–20 mm an open cholecystectomy should primarily be considered because of the significant malignancy risk [319,323,331,332]. Although there is no high quality evidence, polyps 6–10 mm in size not being removed could be followed-up by ultrasound (in non-obese patients) or endosonography performed initially every 3 to 6 months and later annually, if polyp size does not increase [316,323]. It seems reasonable not to follow-up asymptomatic polyps ⩽5 mm, generally detected as incidental finding. During ultrasound, gallbladder polyps may be differentiated from gallbladder stones by changing the patient's position. The presence of more than one polyp favours a diagnosis of cholesterol polyps rather than adenomas. The depiction of vessels in the polyp base that are typical for adenomas is occasionally successful using color duplex sonography [333].

*Is cholecystectomy recommended to patients undergoing other surgery?*

Cholecystectomy is not routinely recommended for patients with asymptomatic stones during abdominal surgery including bariatric surgery and in those undergoing kidney, lung or pancreas transplantation (**very low quality evidence; weak recommendation**)

In patients in the early phase after heart or lung transplantation with symptomatic gallbladder stones, cholecystectomy should be deferred whenever possible (**very low quality evidence; weak recommendation**)

Comment: The risk of gallbladder stones becoming symptomatic and of complications developing after malabsorptive/restrictive obesity surgery is 10–15% [157,172]. Considering that patients will subsequently require a major operation if they develop symptoms related to gallstones and the fact that no evidence of increased complications because of concomitant cholecystectomy during major abdominal operations exists [171], prophylactic cholecystectomy may be offered to patients with asymptomatic gallstones undergoing major abdominal operations, although not generally recommended.

The incidence of asymptomatic cholecystolithiasis rises in the first 2 years after heart, pulmonary, kidney and pancreas transplantation, with an increased incidence of complications. Prophylactic cholecystectomy reduces mortality and was calculated to be cost-effective in asymptomatic patients with gallbladder stones after heart transplantation [334,335], but is not cost-effective in patients undergoing kidney or lung transplantation [334]. Because the mortality of cholecystectomy before and immediately after heart or lung transplantation is markedly increased, it is preferable to delay the surgery after transplantation whenever possible [336–339]. In contrast, the risk of treatment of gallbladder stones in patients who had solid transplantation is comparable to the general population [340].

*Should prophylactic cholecystectomy be offered to patients with hereditary spherocytosis or sickle cell disease?*

Cholecystectomy should be considered in patients with hereditary spherocytosis and sickle cell disease and concomitant asymptomatic gallstones at the time of splenectomy. In patients with sickle cell disease and asymptomatic gallstones, an additional reason for prophylactic cholecystectomy during other abdominal surgery is to avoid diagnostic uncertainty in case of sickle cell crises (**very low quality evidence; weak recommendation**)

Comment: Hereditary spherocytosis belongs to a group of heterogeneous inherited anemias characterized by spherical-shaped erythrocytes (spherocytes) on the peripheral blood smear. Common complications include haemolytic episodes, aplastic crises and (as the most common outcome) formation of pigment (bilirubinate) cholelithiasis [341,342]. Gallstone prevalence increases from 5% to 40–50% by 10 and >50 years of age respectively, with a 4 to 5-fold increased risk in the presence of Gilbert's syndrome. Splenectomy is an important therapeutic option, cures the majority of patients with hereditary spherocytosis, and prevents hemolytic-dependent cholelithiasis. Indeed, preventive measures are required in this special group of patients to avoid gallstone-related complications before splenectomy is performed. Prophylactic (laparoscopic) cholecystectomy is advisable in asymptomatic gallstone patients [157,343] at the time of splenectomy [342].

Patients with sickle cell disease have high risk of pigment stone formation. Haemolysis and infections can be prevented by early recognition of sickle cell disease, taking appropriate measures for the prevention of sickling crises. Prophylactic cholecystectomy during abdominal surgery for other reasons is advised in patients with sickle cell disease and asymptomatic gallstones as to avoid diagnostic uncertainty in case of sickle cell crises [157,343].

*Preoperative investigations*

*What additional investigations are necessary before elective cholecystectomy?*

In addition to abdominal ultrasound for confirming the presence of gallstones (**moderate quality evidence; strong recommendation**), no routine tests are necessary. Liver biochemical tests may be performed in individually selected cases (**very low quality evidence; weak recommendation**)

Comment: The preoperative work up in patients scheduled for cholecystectomy includes physical examination, abdominal ultrasound, laboratory tests, and other radiologic examinations. Before elective cholecystectomy, at least one abdominal ultrasound should confirm the presence of gallbladder stones; however it does not need to be repeated immediately preoperatively if already performed. Routine esophago-gastroduodenoscopy (EGD) in patients referred for cholecystectomy is

not recommended. Despite the diagnostic sensitivity of endoscopic yield, a meta-analysis of 12 cohort studies comprising 6,317 patients reported that its value as a tool to prevent surgery is limited, hence preoperative EGD should only be considered selectively [344].

Although a routine electrocardiogram (ECG) is often performed preoperatively, only 2% of the anaesthesiologists reported that they changed preoperative management of patients in light of ECG findings [345]. Preoperative ECG should be considered in patients who have cardiac risk factors, but should not be recommended routinely for patients who have no risk factors and are scheduled for low risk surgery such as cholecystectomy [346].

Two randomized studies and one review compared asymptomatic patients receiving or not receiving chest X-ray and they did not find any difference in delays or cancellation of surgery [347–349]. It can be concluded that in young patients both ECG and chest X-ray may not be required; they can be ordered in the elderly patients or in selected cases with high risk of postoperative complications [350,351].

Laboratory tests include white blood count which may be useful in evaluating the postoperative outcome, in particular in patients with complications such as infections, or to check the evolution of leukocytosis when surgery is performed for acute cholecystitis [352]. Since the risk of transfusions is 0.7% for laparoscopic cholecystectomy (slightly higher in case of "open procedure"), even the routine preoperative evaluation of haemoglobin and haematocrit is not considered mandatory [352,353]. Platelets count, international normalized ratio and partial thromboplastin time are often screened and requested to evaluate coagulation factors in patients scheduled for surgery. However, coagulation tests are not recommended (unless there are specific risk factors for bleeding in the patient's history) [350], but in all patients bleeding history has to be taken adequately.

Liver biochemical tests such as bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GT) and alkaline phosphatase (AP) can be useful for predicting the presence of bile duct obstruction or other hepatic disease [353–356] but there is currently no evidence that these tests are mandatory. The absence of common bile duct (CBD) dilation and lack of biochemical alterations makes the diagnosis of choledocholithiasis highly unlikely [355,357]. In this group of patients, preoperative EUS or magnetic resonance cholangiopancreatography (MRCP), or intraoperative cholangiography are not required.

*Type of cholecystectomy*

*Should cholecystectomy be performed by open or laparoscopic access routinely?*

Laparoscopic cholecystectomy is the standard method of cholecystectomy for symptomatic gallbladder stones including acute calculous cholecystitis
(**high quality evidence; strong recommendation**)

Comment: Worldwide the laparoscopic cholecystectomy has become a standard intervention. Today more than 93% of all cholecystectomies are started laparoscopically. The conversion rate to an open cholecystectomy is 4–8% [358–361]. The current meta-analysis [362] of RCTs that compared both procedures [363,364–397] shows an identical complication rate for the laparoscopic cholecystectomy with an average hospital stay of 3 days shorter and a 3 weeks shorter convalescence period. This reflects the cost analyses that demonstrate an 18% cost reduction for the inpatient treatment using the laparoscopic procedure compared to the open cholecystectomy [398]. Even in historic comparisons, the current complication rates (bile leak 0.4–1.5%, wound infection 1.3–1.8%, pancreatitis 0.3%, bleeding 0.2–1.4%) are also lower than for the open cholecystectomy [358,361]. A large meta-analysis in 1996 [399] still suggested a trend towards more bile duct injuries. Today the major bile duct injury rate after cholecystectomy is low (0.2–0.4%) and independent of whether the procedure is carried out by open or laparoscopic access [361,362,400,401]. Also at meta-analysis level, the 'small-incision cholecystectomy' has proved to be equivalent to laparoscopic cholecystectomy and may serve as a valuable alternative [362].

As shown by RCTs, patients with acute cholecystitis can also be operated laparoscopically [402–404]. However, the operating time, the risks, and the conversion rates are higher for laparoscopic cholecystectomy in the acute-phase than for elective cholecystectomy after resolution of acute cholecystitis.

If there is strong suspicion of (advanced) gallbladder carcinoma, an open cholecystectomy should be performed instead of laparoscopic cholecystectomy. If Mirizzi's syndrome is present (if it was diagnosed preoperatively), it is not a contraindication for the laparoscopic method *per se*. However, particularly for Mirizzi II (fistula between gallbladder and hepatic duct), the physician should be prepared for conversion [405,406].

*Should an open or a laparoscopic cholecystectomy be performed in patients with cirrhosis?*

Laparoscopic cholecystectomy is the preferred method of cholecystectomy for symptomatic gallbladder stones in patients with Child-Pugh A or Child-Pugh B liver cirrhosis
(**moderate quality evidence; strong recommendation**)

Comment: For patients with Child-Pugh A or Child-Pugh B liver cirrhosis, laparoscopic cholecystectomy is associated with fewer complications than open cholecystectomy and hence is the preferred option [407]. However, the complication rates of cholecystectomy are high regardless of the laparoscopic or open access for Child-Pugh C patients [408], and most series report higher morbidity and conversion rates in patients with preoperative Model for End-Stage Liver Disease (MELD) scores >13 [409,410]. Where strong contraindications for cholecystectomy exist, as in end-stage liver disease, and severe symptomatic gallbladder stones, endoscopic cholecystoduodenal stenting has been reported in small retrospective series [411].

*Is there an alternative to laparoscopic cholecystectomy for the treatment of patients with symptomatic gallstones?*

Mini-laparotomy-cholecystectomy (laparotomy <8 cm) is the alternative to laparoscopic cholecystectomy
(**high quality evidence; strong recommendation**)

Comment: RCTs that compared the laparoscopic cholecystectomy to the mini-laparotomy-cholecystectomy (laparotomy <8 cm) found no difference between both procedures with respect to complication rates, duration of hospital stay, and convalescence periods [362,366,412–422] and hence the mini-laparotomy-cholecystectomy is a suitable alternative to laparoscopic cholecystectomy.

*Method of laparoscopic cholecystectomy*

*Number and size of ports*

*What is the number and size of ports that should be used for performing laparoscopic cholecystectomy?*

Currently laparoscopic cholecystectomy should be performed using 4 ports with 2 ports of at least 10 mm in size and 2 ports of at least 5 mm in size (**very low quality evidence; weak recommendation**)

Comment: There is considerable uncertainty regarding the clinical benefits of mini-laparoscopic cholecystectomy or single port laparoscopic cholecystectomy *vs.* standard laparoscopic cholecystectomy [423,424]. Their safety has yet to be established and they cannot be routinely recommended [423–425].

*Prophylactic antibiotic use*

*Is routine antibiotic prophylaxis necessary prior to elective laparoscopic cholecystectomy?*

Routine antibiotic prophylaxis is not necessary prior to elective laparoscopic cholecystectomy (**very low quality evidence; weak recommendation**)

Comment: A systematic review of RCTs showed that there were no significant differences in the proportion of people who developed surgical site infections (approximately 3% with or without prophylactic antibiotic use) or extra-abdominal infections (approximately 1.4% with or without prophylactic antibiotic use) [426]. An RCT demonstrated that there is no need for routine antibiotic prophylaxis even in patients in whom gallbladder is perforated during surgery [427].

*Intraoperative cholangiography*

*Is routine or selective intraoperative cholangiography necessary during cholecystectomy in patients at low risk of common bile duct stones?*

Routine or selective intraoperative cholangiography is not necessary during cholecystectomy in patients at low risk of common bile duct stones (**low quality evidence; weak recommendation**)

Comment: A systematic review of RCTs comparing routine or selective intraoperative cholangiography *vs.* no cholangiography showed that there were no significant differences in the proportion of people who had bile duct injury (no bile duct injury in cholangiography group *vs.* approximately 0.2% bile duct injury in the no cholangiography group), in the proportion of people with retained common bile duct stones, or in mortality risk [428]. The complications in patients receiving routine cholangiography were higher as compared to no cholangiography during the open cholecystectomy era [428]. The operating time was also longer in the routine cholangiography group than no cholangiography group [428] (which is expected because of additional procedure). Because of the lack of significant benefit after routine cholangiography and increased operating time after routine cholangiography, there is currently no evidence to recommend routine cholangiography during cholecystectomy. However, a retrospective database review showed that the incidence of bile duct injury was lower in patients undergoing intraoperative cholangiography compared to those not undergoing intraoperative cholangiography [429]. So, considerable uncertainty surrounds the issue of routine intraoperative cholangiography. In a recently published RCT, symptomatic gallstone patients with intermediate risk for choledocholithiasis were randomized to either immediate cholecystectomy with intraoperative cholangiography or to preoperative EUS, followed, if required, by ERCP and thereafter, laparoscopic cholecystectomy with intraoperative cholangiography. Patients who had immediate cholecystectomy as first step exhibited shorter hospital stay and fewer CBD investigations, without differences in morbidity or quality of life between both groups [430]. Nevertheless, the percentage of patients with detected common bile duct stones was approximately 20% in both groups only, possibly related to the relatively low specificity for bile duct stones of the inclusion criteria that were used to define intermediate risk (i.e. aminotransferase activities twice the upper limit of normal in the presence of at least one other modified liver biochemical test). Also, the experience of many surgeons with intraoperative cholangiography could be limited nowadays.

*Intraoperative loss of gallstones*

*Is conversion to open cholecystectomy indicated in patients in whom gallbladder stones have spilled into the intraperitoneal cavity and have not been retrieved?*

Intraoperative loss of gallbladder stones is not a reason for conversion to open surgery (**very low quality evidence; weak recommendation**)

Comment: Gallbladder perforations resulting in spillage of gallstones into the peritoneal cavity can occur in 4–19% of laparoscopic cholecystectomies [431–433]. If these stones are not retrieved, the patients may develop sequels such as pain, port-site abscess, intra-abdominal abscess, internal fistula such as colonic fistula, external fistula (intra-abdominal abscesses which drain spontaneously to the exterior) or wound sinus in 0–15% of patients [431–433]. Therefore, every attempt should be made to retrieve these stones by washing out the peritoneal cavity.

However, if the stones cannot be retrieved, conversion to open surgery is not necessary solely for the purpose of retrieving these stones.

*Day-surgery laparoscopic cholecystectomy*

*Is day-surgery safe in laparoscopic cholecystectomy?*

Day-surgery may be as safe as overnight stay laparoscopic cholecystectomy in patients without systemic disease (**moderate quality evidence; weak recommendation**)

Comment: A systematic review of RCTs reported that day-surgery appears just as safe as overnight stay surgery in laparoscopic cholecystectomy [434]. However, day-surgery does not seem to result in improvement in any patient-oriented outcomes such as return to normal activity or earlier return to work, although significant savings in terms of costs support better utilization of the limited health care resources.

*Timing of cholecystectomy*

*Patients with uncomplicated biliary colic*

*When should laparoscopic cholecystectomy be performed in patients with uncomplicated biliary colic?*

Cholecystectomy should be performed as early as possible for patients with uncomplicated biliary colic (**low quality evidence; weak recommendation**)

Comment: The major reason for delaying surgery in patients with uncomplicated biliary colic is the delay on the waiting list, i.e., there are no medical reasons for delaying surgery in an anaesthetically fit patient with uncomplicated biliary colic. Delaying surgery, on the other hand, exposes the patient to the risk of gallstone complications. Based on evidence from a single trial with a high risk of bias [274], early laparoscopic cholecystectomy (less than 24 h after diagnosis of biliary colic) decreases morbidity during the waiting period for elective laparoscopic cholecystectomy (mean waiting time 4 months), the hospital stay, and operating time. Therefore, early laparoscopic cholecystectomy is preferable.

*Patients with acute cholecystitis*

*How should patients with acute cholecystitis be treated?*

Early laparoscopic cholecystectomy (preferably within 72 h of admission) should be performed by surgeons with adequate expertise in patients with acute cholecystitis (**high quality evidence; strong recommendation**)

Comment: Acute cholecystitis is the most common complication of gallstone disease. A systematic review of RCTs comparing early laparoscopic cholecystectomy performed within 1 week of onset of symptoms *vs.* delayed laparoscopic cholecystectomy performed after at least 6 weeks of resolution of symptoms showed that early laparoscopic cholecystectomy shortens the total length of hospital stay by about 4 days [435]. Early laparoscopic cholecystectomy does not increase the rate of serious complications, as compared to late cholecystectomy (6.5% *vs.* 5.0%, respectively) [435]. The conversion rate for acute cholecystitis is approximately 20% in both the early and delayed groups [435] and is, thus, much higher than for the elective operation after uncomplicated biliary colic. The operation should be performed as soon as any anaesthetic or surgical issues are resolved. The reason is that the conversion rate is lower and the duration of hospital stay is shorter the earlier the operation takes place [436]. Conservative treatment of acute cholecystitis without routine cholecystectomy is possible. However, if treatment is merely conservative without routine cholecystectomy, over one-third of the patients have complications or are admitted as emergencies because of biliary pain. For 30% of the patients, a cholecystectomy is eventually necessary [437,438]. If the patient cannot have early elective surgery within 1 week because of late diagnosis or other medical reasons (high risk of surgery) [439], cholecystectomy should not be performed within the following 6 weeks since evidence from an RCT showed that morbidity after laparoscopic cholecystectomy between 7 and 45 days was approximately 2–3 times that of surgery performed early or after the 6 weeks interval [440].

In 10–30% of patients with acute cholecystitis severe complications such as gallbladder gangrene, empyema, or perforation develop [403,441,442]. A preoperative CT scan may provide helpful information in these situations. Fistulas between the gallbladder and the gastrointestinal tract develop in less than 1% of all gallstone patients. Clinically a bilioenteric fistula manifests by ascending cholangitis or bile acid loss syndrome. Approximately 60% of cholecystoduodenal fistulas are asymptomatic. If larger stones pass through the fistula, gallstone ileus can result [443]. Aerobilia in the absence of previous surgery or endoscopic procedures can indicate the presence of fistula and further investigations with MRI, with MRCP and ERCP may confirm the diagnosis.

*Patients with simultaneous gallbladder and bile duct stones*

*When should cholecystectomy be performed in patients with gallbladder stones after endoscopic removal of bile duct stones?*

In patients with simultaneous gallbladder and bile duct stones, early laparoscopic cholecystectomy should be performed within 72 h after preoperative ERCP for choledocholithiasis (**moderate quality evidence; strong recommendation**)

Comment: In a randomized trial to evaluate timing of laparoscopic cholecystectomy after endoscopic sphincterotomy, laparoscopic cholecystectomy within 72 h after ERCP leads to significantly less recurrent biliary events as compared to delayed laparoscopic cholecystectomy (after 6–8 weeks); there are no differences in conversion rate, operation time or surgical complications [444]. Same-day but separate ERCP and cholecystectomy

are not recommended, since this may impede complication management. No studies have compared intervals of 2–4 weeks with 6–8 weeks.

*Cholecystectomy in the elderly and in patients with high anaesthetic risk*

*Should cholecystectomy be performed in elderly patients and in patients with high anaesthetic risk?*

Cholecystectomy should be performed in the elderly and in patients with high anaesthetic risk with gallstone complications (such as acute cholecystitis, gallstone pancreatitis, or obstructive jaundice) as soon as the general status allows surgery (**low quality evidence; weak recommendation**). Laparoscopic cholecystectomy should not be withheld on the basis of chronological age alone (**very low quality evidence; weak recommendation**)

Comment: In elderly patients with symptomatic gallstones, cholecystectomy should be performed if possible. Although deferral of cholecystectomy after endoscopic sphincterotomy is an option in patients with biliary pancreatitis, evidence from a systematic review of RCTs showed that deferral of cholecystectomy was associated with higher mortality, recurrent biliary pain, jaundice or cholangitis, and further investigations were required [445]. However, most trials on elderly patients in this systematic review excluded those unfit for surgery. The trial that included only high risk patients (based on one or more of the following criteria: age over 70; high cardiac risk index (Goldman cardiac risk index >13); chronic pulmonary disease; liver cirrhosis Child-Pugh stages B or C; neurologic deficit or joint disease associated with severely impaired mobility; BMI >30 kg/m$^2$) found that the benefits following routine cholecystectomy compared to cholecystectomy deferral were similar to low risk patients [445].

In patients with severe acute cholecystitis or difficult anatomy of the biliary system, subtotal cholecystectomy (laparoscopic or open) or percutaneous cholecystostomy followed by cholecystectomy later are possible options [446,447]. In particular, percutaneous cholecystostomy represents a treatment alternative in high risk patients with acute cholecystitis [448,449]. Chang *et al.* [450] who removed the drain after a median time of 23 ± 16 days experienced recurrence of cholecystitis or cholangitis in 12% of their patients, but higher rates have been reported in other studies [451]. The issue of whether definitive treatment by cholecystectomy is needed in high risk surgical patients with acute cholecystitis after a percutaneous cholecystostomy is unsolved as there have been no RCTs addressing this issue. However, cholecystectomy should be considered, since patients whose medical condition improves after percutaneous cholecystostomy might worsen during follow-up without definitive surgical treatment [437].

Endoscopic gallbladder drainage may have a potential as an alternative drainage method in acute cholecystitis. In a systematic review, the technical and clinical success rates as well as the frequency of adverse events in endoscopic nasogallbladder drainage or gallbladder drainage by transpapillary stent were 81% and 96%, 75% and 88%, and 3.6% and 6.3%, respectively [452].

Age limitations for performing laparoscopic cholecystectomy have not been defined. Some studies have shown that laparoscopic cholecystectomy can be performed safely even in those over the age of 75–80 years [453,454] while other studies have shown that the rate of conversion to open cholecystectomy, the rate of complications, and the length of hospital stay were higher in patients older than 65–70 years [455,456].

Finally, in a small randomized trial, ERCP with sphincterotomy was superior to conservative therapy in elderly patients with acute cholecystitis, considered at high risk for cholecystectomy [457].

*Bile duct injuries*

*Diagnosis of bile duct injuries*

*How are bile duct injuries diagnosed after surgery?*

Suspected bile duct injury after surgery warrants urgent investigation including laboratory tests (white blood count, bilirubin, liver enzymes) and imaging (abdominal ultrasound, contrast-enhanced CT, magnetic resonance cholangiopancreatography) to detect bile leak and/or intra-abdominal fluid while the patient is kept in hospital under close observation (**low quality evidence; weak recommendation**)

Comment: Bile duct injury is defined as any damage including leakage of the bile duct system with negative impact on the patient. Risk factors include impacted cystic duct stones, Mirizzi syndrome, impacted Hartmann's gallbladder pouch stone, inflammatory alterations, or anatomical anomalies of the intrahepatic ducts [458]. Bile duct injury is a complication with potentially major consequences for the patients, since they have a significantly higher 1 and 2-year mortality compared with those without such an injury [429,459]. Both, for diagnosing and classifying of bile duct injuries MRCP, contrast-enhanced CT, ERCP and/or percutaneous transhepatic cholangiography may be used [460–464]. In hospitals with little experience in bile duct injuries, MRCP is the diagnostic tool of choice, if available. MRCP with gadoxetic acid disodium identifies a bile leak with a sensitivity of 76–100% and specificity of up to 100% [465–468] and may be used as a non-invasive test to detect bile leak. Subsequent ERCP establishes the nature of bile duct injury in at least 90% [469,470].

Only around 40% of the lesions are recognized during primary cholecystectomy. Intraoperative cholangiography allows the early identification of bile duct injury in 70% of patients [469,470]. Since the introduction of laparoscopic cholecystectomy, the literature points to an increased number of bile duct injuries, as compared to the era of open cholecystectomy [471]. A study of more than 50,000 unselected patients from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks) revealed that 1.5% of patients undergoing cholecystectomy between 2005 and 2010 developed bile duct injury, but only a fifth of these injuries (0.3%) involved partial or complete transection of the bile duct [429]. The reported incidence of bile duct injuries in laparoscopic cholecystectomy varies between 0.04–1.5% [362,472–481]. The incidence in open cholecystectomy ranges from 0–0.5% [459,473,480,482,483]. However, a systematic review of RCTs comparing laparoscopic cholecystectomy *vs.*

open cholecystectomy did not find any significant difference in the incidence of bile duct injuries between the two groups (0.2% in each group) [480]. Therefore the true incidence of bile duct injuries is not known, probably due to underreporting bias [480]. Factors that could play a role include learning curve effect, inadequate critical view of safety and anatomical variations [458,475,477,478,481,484].

At present no adequate data are available yet on the incidence of bile duct injuries during new laparoscopic techniques (single port, mini-laparoscopic, NOTES) as compared to the conventional laparoscopic cholecystectomy.

*Treatment of bile duct injuries*

*What is the recommended treatment for intraoperatively recognized bile duct injuries?*

Primary surgical repair of intraoperatively recognized bile duct lesions A, B or C (see Table 1) can be carried out, if surgical expertise is available. For type D lesions intraoperative consultation of an expert center is mandatory; merely subhepatic drainage is advised and the patient is referred to an expert center. Late reconstruction (after 6-8 weeks) is advised, often with hepatico-jejunostomy (**low quality evidence; weak recommendation**)

*What is the recommended treatment for postoperatively established bile duct injuries?*

Bile duct lesions types A, B or C should be treated endoscopically; late surgical treatment is the recommended treatment for type D injury (**low quality evidence; weak recommendation**)

Comment: The proper diagnosis and classification of bile duct injury is of great importance for the choice of treatment. A comparison of the literature data is complicated due to the use of various classification systems for bile duct injuries [458,484–488]. The Amsterdam classification [486] is often used (Table 1), since in this scheme classification can be directly linked to the treatment. After classification of the injury, the patient should be referred to a specialized center with a multidisciplinary expertise team.

In case of intraoperatively recognized bile duct lesion, reclosure of type A lesion, or primary repair of type B, C, or D can be carried out, if surgical expertise is available. Otherwise merely subhepatic drainage and referral to expertise center is mandatory.

Postoperatively, established bile duct injuries are referred to expertise centers. Primary treatment consists of treatment of sepsis and subhepatic drainage. Early (diagnostic) laparoscopy or laparotomy are not advised. Type A, B or C lesions are treated endoscopically with transpapillary stenting and dilatation (type C). For type D lesions surgical reconstruction is advised at 6–8 weeks after injury.

Otherwise, the timing of surgical repair of bile duct injury is controversial. The options include primary repair at the time of cholecystectomy, early repair (after cholecystectomy but within approximately 6 weeks), and delayed repair (later than 6 weeks). One retrospective study in France found that mortality, morbidity and surgical failure rates requiring interventions (mostly further surgical interventions) were higher in primary repair (3%, 39% and 64%, respectively) than early (within 6 weeks) (2%, 29% and 43%, respectively) or delayed repair (after 6 weeks) (1%, 14% and 8% respectively) [489]. It should be noted that in this study, 40% of the primary repair group, 50% of the early repair group and 100% of the delayed repair group were managed in tertiary referral centers, which probably contributes to the significant differences. Direct repair (choledochodochal repair) is the usual method of repair in primary and early repairs, whereas Roux-en-Y hepaticojejunostomy is the usual surgical treatment for delayed repair [489]. Another cost-effectiveness study concluded that early bile duct repair by specialist surgeons was more cost-effective than delayed bile duct repair, whereas primary repair by the non-specialist was the least cost-effective option based on observational series [490].

The long-term results of hepaticojejunal anastomoses are successful in 70% [491,492]. Local infection or sepsis is an independent risk factor for a poor result of the early surgical reconstruction [493]. Mortality in patients with bile duct injury during cholecystectomy is higher than in those undergoing cholecystectomy without bile duct injury after 1 year (4% *vs.* 1%) with an overall hazard ratio of 1.92 (95% CI = 1.24–2.97) [429].

Health-related quality of life after bile duct repair is variable with some studies reporting similar quality of life in patients who had undergone surgical reconstruction, whereas others reporting poorer quality of life in those who had bile duct injury several years after corrective surgery as compared to those who did not have bile duct injury [494].

*Persistent biliary symptoms after cholecystectomy*

*How are persistent symptoms after cholecystectomy handled?*

Endoscopic ultrasound or magnetic resonance cholangiopancreatography should be considered in the diagnostic evaluation of post cholecystectomy patients with biliary symptoms (**low quality evidence; weak recommendation**)

Endoscopic sphincterotomy is not supported for patients with abdominal pain after cholecystectomy and no significant abnormalities on imaging or laboratory studies (**moderate quality evidence; strong recommendation**)

**Table 1. Classification of bile duct injuries.**

| |
|---|
| A: cystic duct or aberrant bile duct leakage |
| B: CBD leakage, with or without stricture |
| C: CBD stricture without leakage |
| D: complete CBD transection with or without tissue loss |

CBD, common bile duct.

Comment: Symptoms may persist or return in some patients after cholecystectomy. In fact, 10–40% of patients have persistent complaints after cholecystectomy, sometimes after a brief interval without symptoms [495,496]. "Post cholecystectomy syndrome" is an old term that is nowadays replaced by more specific causes. Importantly, presence of bile duct stones should be excluded. In the rare subgroup of patients with LPAC syndrome caused by *ABCB4* gene mutations, symptoms recur after cholecystectomy due to the presence of intrahepatic sludge and microliths, or recurrent bile duct stones (see section Prevention of recurrent bile duct stones) [216].

In an RCT [497], 118 patients with post cholecystectomy pain were screened, and crystals were detected microscopically in duodenal bile from 12 patients. When using UDCA for a few months, the biliary-type abdominal pain significantly improved or resolved. This study provides evidence that microlithiasis may be a cause for post cholecystectomy pain. Microlithiasis can be confirmed by the microscopic examination of duodenal bile or hepatic bile obtained during ERCP [498].

More probable, since gallstone symptoms are relatively unspecific, alternative preexisting causes should be considered, such as functional dyspepsia, irritable bowel syndrome, (duodeno-) gastro-oesophageal reflux, and (rarely) sphincter of Oddi dysfunction [496]. As demonstrated in a large RCT in patients with abdominal pain after cholecystectomy undergoing ERCP with manometry, sphincterotomy did not reduce disability due to pain in comparison to a sham procedure [499]. These findings do not support endoscopic sphincterotomy for these patients.

## Diagnosis of bile duct stones

*Medical history and physical examination*

*When should common bile duct stones be looked for?*

Common bile duct stones should be searched for in patients with jaundice, acute cholangitis or acute pancreatitis (**high quality evidence; strong recommendation**)

Comment: CBD stones are present in 3–16% (depending on age) of patients with stones in the gallbladder [500–507]. They either occur by migration from the gallbladder (secondary stones), or less often develop *de novo* in the bile duct, for example in case of CBD dilation with stasis (primary stones). In contrast to gallbladder stones, CBD stones are asymptomatic in only 5–12% of cases [508]. The natural history of asymptomatic CBD stones is not well known, but it seems to be more benign than that of symptomatic CBD stones. In a small series of patients, CBD stones remained asymptomatic during a 5-year follow-up [509].

The common presentation of symptomatic CBD stones is acute biliary pain, caused by distention of the CBD following its partial or complete obstruction. The pain is located in the right upper abdominal quadrant or the epigastrium, lasts more than 30 min and up to several hours, and does not depend on the body position. It might be challenging to differentiate the pain from that caused by gallbladder stones. Spontaneous passage of the stones into the duodenum, in case of small stones [510], or backwards into the distended duct may relieve the pain. Especially small stones impacted in the sphincter of Oddi may cause distal obstruction and trigger acute pancreatitis. Larger stones cause more often proximal obstruction. Bile duct obstruction is often followed by complications, such as jaundice and cholangitis.

*Laboratory diagnosis and imaging*

*Are laboratory tests included in the diagnostic work up of common bile duct stones?*

The evaluation of patients with suspected common bile duct stones commonly includes serum liver biochemical tests (**low quality evidence; weak recommendation**)

Comment: Patients with symptomatic CBD stones often have altered liver biochemical tests. The initial evaluation of suspected CBD stones includes serum bilirubin concentrations as well ALT, AST, γ-GT and AP activities [511,512]. In particular in the first 72 h of biliary obstruction, serum aminotransferase activities are markedly elevated, followed by a more gradual rise in the AP and bilirubin levels if the obstruction persists [513]. If liver biochemical tests show normal values in the first 24 h following onset of pain, and if CBD dilation is absent on ultrasound, the probability of a CBD stone is very low [355,357]. In contrast, the positive predictive values for abnormal bilirubin, AP or γ-GT range from 25–50% only [357,512,514,515]. These latter cholestatic liver biochemical tests progressively increase with the duration and severity of biliary obstruction. For example in one study, a serum bilirubin concentration of at least 1.7 mg/dL (29 μmol/L) portended a specificity of 60% for CBD stones, whereas the specificity increased to 75% at a cutoff of 4 mg/dl (68 μmol/L); however, only one-third or less of patients with choledocholithiasis display such marked hyperbilirubinemia [512,514].

*What imaging modality should be used to detect CBD stones?*

Abdominal ultrasound should be the first imaging method when CBD stones are suspected (**low quality evidence; weak recommendation**). Stones in the gallbladder, a dilated CBD, acute cholangitis and hyperbilirubinemia are strong predictors for CBD stones (**high quality evidence; strong recommendation**)

Patients with an intermediate probability of CBD stones should undergo further evaluation with endoscopic ultrasound (or magnetic resonance cholangiopancreatography) (**moderate quality evidence; strong recommendation**)

Comment: Abdominal ultrasound detects CBD dilation with high sensitivity, which is an indirect sign for the presence of CBD stones. In fact, stones may be directly visualized in the dilated CBD. The ultrasound sensitivity for CBD stones is considerably lower than that for gallbladder stones [516,517], but can be as high as 80% for experienced operators [518]. Ultrasonographic evidence of bile duct stone, CBD dilation, signs of acute cholangitis and jaundice are the best predictors for CBD stones [516]. A negative ultrasound result does not eliminate the diagnosis of CBD stones, if suspected; however, when liver biochemical tests are also normal, the probability is very low.

In patients with intermediate probability of CBD stones and inconclusive abdominal ultrasound, EUS is a valuable alternative. EUS and MRCP detect CBD stones >5 mm with similar accuracy, but EUS is more cost-effective than MRCP [519–527]. According to a recent systematic review [528], the sensitivity of EUS is 95% with a specificity of 97%, whereas the sensitivity of MRCP is 93% with a specificity of 96%.

CT imaging has a high sensitivity for CBD dilation [529,530]. It also evaluates other possible causes of upper abdominal pain and gallstone complications but is associated with a significant radiation dose. ERCP detects CBD stones with a very high sensitivity [520,530,531]. However, it is a procedure with radiation exposure and only recommended as first diagnostic step for patients with high probability of CBD stones, in whom concomitant endoscopic therapy is envisaged.

*Diagnosis of acute cholangitis*

*How is acute cholangitis diagnosed?*

In patients with fever and a history of chills, with abdominal pain and/or jaundice, white blood cells, C-reactive protein and liver biochemical tests should be determined and abdominal ultrasound should be performed as the initial investigations (**moderate quality evidence; strong recommendation**)

Comment: Acute cholangitis can be diagnosed by the presence of the Charcot's triad, i.e. pain and tenderness in the right upper quadrant, high spiking fever, often with rigors, and jaundice. Charcot's triad has high specificity but low sensitivity [532]. Pain may be the single symptom in a minority of patients, and can be absent, especially in elderly patients. Jaundice is present in 60–70% and fever in 90% of the patients with acute cholangitis [532–536].

The biochemical signs of acute cholangitis are leucocytosis with a left shift and increased serum C-reactive protein (CRP) concentrations. Aminotransferase activities and cholestatic parameters often increase within the first hours following the pain attack. Abdominal ultrasound often demonstrates CBD dilation, though it is less sensitive for CBD stones, and the examination of the distal bile duct is even more difficult in the setting of acute inflammation. There is currently sufficient evidence that EUS is superior to MRCP in this setting [522,524] and to CT [524] in detecting CBD stones in patients with obstructive jaundice.

*Diagnosis of acute biliary pancreatitis*

*How is acute biliary pancreatitis diagnosed?*

The diagnosis of acute biliary pancreatitis is based on the presence of upper abdominal pain and altered pancreatic and liver biochemical tests in patients with gallbladder and/or common bile duct stones (**moderate quality evidence; strong recommendation**)

The exclusion of bile duct stones by endoscopic ultrasound (or magnetic resonance cholangiopancreatography) may prevent the potential risks of endoscopic retrograde cholangiopancreatography in patients with acute biliary pancreatitis and suspected bile duct stones (**low quality evidence; weak recommendation**)

Comment: In 4–8% of the patients with gallbladder stones, stones migrate into the main bile duct causing acute pancreatitis as they pass into the duodenum or impact in the sphincter of Oddi [537,538]. It is outside the scope of this guideline to discuss acute pancreatitis in detail, and for further information we refer to the current acute pancreatitis guideline of the International Association of Pancreatology [539].

Gallstone migration, even of small stones, is often preceded by a period of biliary obstruction [540]. A warning pain is absent in 50% of cases [228,229]. Biochemical tests indicate hyperlipasemia or hyperamylasemia (>3 times the upper limit of normal), elevated aminotransferase activities and cholestatic parameters, leucocytosis and increased CRP concentrations. In the absence of alcohol abuse or known pre-existent abnormal liver biochemistry, ALT activities >150 U/ml indicate the biliary cause of pancreatitis with a positive predictive value exceeding 85% [541–544]. Biliary crystals can be detected microscopically in duodenal or hepatic bile obtained during ERCP in patients with idiopathic acute pancreatitis, indicating the biliary cause [241,242,498,545].

Ultrasound is the first investigation usually performed. Patients with pancreatitis or obstructive jaundice have more and smaller gallbladder stones than those with acute cholecystitis or uncomplicated gallstone disease [240]. Ultrasound frequently visualizes CBD dilation but is less accurate in detecting gallstones in acute pancreatitis. EUS or MRCP can be performed in this situation, when the biliary aetiology is not clear or when ERCP is considered [356].

MRCP is reasonably accurate to detect bile duct stones in patients with biliary pancreatitis [546,547] but might miss small stones. EUS is superior to all other methods in detecting stones <5 mm, i.e. those that often cause acute pancreatitis. Its sensitivity reaches 100% and specificity is 95%, resulting in an accuracy of 97% for the diagnosis of CBD stones [548]. In patients with mild disease in whom laparoscopic cholecystectomy is ultimately planned ERCP and sphincterotomy is not indicated unless there are bile duct stones present, which should first be confirmed by MRCP or EUS [521].

## Endoscopic and surgical therapy of bile duct stones

*Treatment of bile duct stones without complications*

*What is the recommended treatment for bile duct stones?*

Endoscopic sphincterotomy and stone extraction is a recommended treatment of bile duct stones (**moderate quality evidence; weak recommendation**). Intraoperative endoscopic retrograde cholangiopancreatography or laparoscopic bile duct exploration in combination with cholecystectomy are alternatives when adequate expertise is available (**moderate quality evidence; strong recommendation**)

In case of failed standard stone extraction, extracorporeal shock wave, electrohydraulic or laser lithotripsy may be performed (**low quality evidence; weak recommendation**). In the case of altered anatomy (e.g. previous Roux-en-Y anastomosis, bariatric surgery) percutaneous or endoscopic (balloon endoscopy-assisted) treatment of bile duct stones can be considered (**low quality evidence; weak recommendation**). In the case of failed endoscopic therapy, cholecystectomy combined with bile duct exploration or intraoperative endoscopic retrograde cholangiopancreatography should be performed (**low quality evidence; weak recommendation**)

Comment: Choledocholithiasis is a relative frequent phenomenon in patients with symptomatic gallbladder stones (prevalence 3–16% of cases). Although there may be spontaneous passage to the small bowel in many cases, there is a significant risk of biliary pain and complications such as jaundice, cholangitis and pancreatitis. Therefore, the general consensus is that symptomatic choledocholithiasis should be treated. The natural history of asymptomatic choledocholithiasis appears more benign. Nevertheless, more than 25% of patients appear to develop (often serious) complications during follow-up [509,504,549]. The choice of therapy depends on time of diagnosis (before, during or after cholecystectomy) and local expertise [550,551]. In the last decades, there has been an expanding role for the endoscopic treatment (sphincterotomy and stone extraction) of bile duct stones. Nevertheless, ERCP is associated with a risk of complications (especially pancreatitis) and in recent years, experience and volume of the endoscopist has been a topic of considerable debate. Performance of at least 100 procedures annually is associated with better outcome, whereas patient age is not related to complication risk [552].

Endoscopic papillary balloon dilatation with a large diameter balloon (12–20 mm) represents an option to facilitate the extraction of large stones [553,554]. A meta-analysis including 6 RCTs with 835 patients [555] reported fewer overall complication rates and lower risk of perforation with no difference in post-ERC pancreatitis, infection, or bleeding.

Currently preoperative ERCP and laparoscopic cholecystectomy is the preferred option in the management of patients with simultaneous gallbladder and CBD stones, although there is evidence that intraoperative ERCP results in lower incidence of ERCP-related pancreatitis and shorter hospital stay, and is cost-effective in comparison to the splitting of procedures [549,556–558]. According to recent meta-analyses, in cases of failed endoscopic therapy, laparoscopic or open cholecystectomy combined with transcystic stone extraction or CBD exploration or intraoperative ERCP are alternatives, with comparable stone clearance rates, morbidity and mortality as primary endoscopic approach [559,560]. In high risk cases (see recommendation: Is primary closure preferred over T-tube drainage during surgical bile duct exploration?), T-tube insertion remains the safest option [561,562].

Surgical experience with open CBD exploration has decreased dramatically in the last decades, and the number of surgeons experienced in laparoscopic common bile duct exploration is limited. Therefore, endoscopic stone removal is currently the preferred approach in most countries. The timing of sphincterotomy, however, remains controversial. Two trials (one in patients with gallstone pancreatitis) indicate fewer endoscopic procedures and shorter hospital stay without increased morbidity with initial cholecystectomy (and postoperative ERCP) *vs.* initial endoscopic assessment of the CBD and subsequent cholecystectomy [430,563].

*What are the best forms of treatment for bile duct stones when detected intraoperatively or postoperatively?*

In case of intraoperative detection of bile duct stones, bile duct exploration, transcystic stone extraction or endoscopic clearance represent alternative treatment options (**moderate quality evidence; weak recommendation**). Upon postoperative diagnosis of bile duct stones, endoscopic sphincterotomy and stone extraction are recommended (**low quality evidence; weak recommendation**)

Comment: When bile duct stones are detected during the operation, transcystic stone extraction can be attempted, if the surgeon is experienced in this procedure. Transcystic stone extraction is safe, and success rate is approximately 75%. Laparoscopic stone extraction can have a high success rate, but has a relatively high complication rate and should not be performed except in centers of expertise [564–566]. Upon postoperative diagnosis of bile duct stones, endoscopic sphincterotomy and stone extraction are the common measures.

*Is primary closure preferred over T-tube drainage during surgical bile duct exploration?*

In case of surgical bile duct exploration, primary closure may be preferred over T-tube drainage in low risk cases (**low quality evidence; weak recommendation**)

Comment: Systematic reviews and meta-analysis on randomized controlled trials on primary closure *vs.* T-tube drainage demonstrated that T-tube drainage prolongs operating time and hospital stay compared to primary closure without any evidence of benefit after open or laparoscopic common bile duct exploration in low risk cases [561,567]. In high risk cases involving

patients with recurrent bile duct stones, acute cholangitis or multiple bile duct stones where ERCP has failed, T-tube insertion or alternative procedures such as choledochoduodenostomy represent safe options [561,562].

*When should cholecystectomy be performed in patients with gallbladder stones after endoscopic removal of bile duct stones?*

In patients with simultaneous gallbladder and bile duct stones, early laparoscopic cholecystectomy should be performed within 72 h after preoperative ERCP for choledocholithiasis (**moderate quality evidence; strong recommendation**)

Comment: See section: Patients with simultaneous gallbladder and bile duct stones

*Treatment of acute cholangitis*

*How should patients with acute cholangitis be treated?*

Treatment of cholangitis should include immediate broad spectrum antibiotics and biliary decompression (**moderate quality evidence; strong recommendation**)

Timing of biliary decompression depends on severity of the cholangitis and effects of medical therapy including antibiotics and may preferably be performed within 24 h; urgent decompression should be considered in case of severe cholangitis not responding to fluid resuscitation and intravenous antibiotics (**low quality evidence; weak recommendation**)

Endoscopic treatment with sphincterotomy is the preferred mode of biliary decompression; in the presence of contraindications for sphincterotomy, biliary stenting with stone removal at a later stage should be performed (**low quality evidence; weak recommendation**)

In case of failed endoscopic decompression or contraindications to endoscopic therapy, percutaneous bile duct drainage is the procedure of choice (**low quality evidence; weak recommendation**)

Comment: Cholangitis is a serious complication of gallstones, with significant morbidity and mortality, especially in the elderly [568]. First line treatment should include general supportive measures including adequate intravenous hydration and antibiotics, which are required in the first hour after hospital admission in case of sepsis [569]. Considering the polymicrobial content of infected bile, broad spectrum antibiotics should be applied. The choice of antibiotic coverage depends on cholangitis severity and local antimicrobial resistance patterns. Enteric gram-negative bacteria are usually cultured from bile of patients with acute cholangitis, especially *E. coli* and *Klebsiella* species. Nevertheless, the microbiological profile has changed in the last decades, due to increased instrumentation of the bile ducts and frequent use of antibiotics in the population. Polymicrobial bile cultures are often found. Anaerobic bacteria are usually isolated in conjunction with aerobic bacteria, rather than a sole isolate from bile, and often in the setting of previous bile duct instrumentation and a more severe clinical condition. There is a clear difference between results of bile cultures compared to associated blood cultures [570]. Bile cultures are positive in 80–100%, and blood cultures in 20–60% of patients with cholangitis. *Streptococcus* and *Enterococcus* species are infrequently and anaerobic bacteria are rarely cultured from blood. One of the main goals of antibiotics is to control bacteremia and sepsis. Most antibiotics (with the exception of quinolones) are not or are less well excreted into bile in case of biliary obstruction. Empirical antibiotic therapy that includes coverage of the aerobic gram-negative bacteria and anaerobic bacteria should be considered until the results of bile cultures and blood cultures are available. The duration of antibiotic therapy will depend on severity of the clinical condition at presentation, whether blood cultures were positive and recovery after biliary drainage.

Most cholangitis patients will respond satisfactorily to initial conservative therapy with broad spectrum antibiotics. Although these patients could get elective biliary decompression and stone removal, it appears wise to achieve biliary decompression in all cholangitis patients at the earliest time point possible, preferably within 24 h, since up to 20% of patients will run a progressive course with severe deterioration [571]. Urgent decompression should be considered in case of severe cholangitis not responding to fluid resuscitation and intravenous antibiotics. Consensus criteria for defining severity of cholangitis have been published [572].

Biliary decompression can be achieved by ERCP, percutaneous drainage or surgery. Results of endoscopic therapy for acute gallstone cholangitis were superior to surgical treatment, both in retrospective and prospective randomized trials [269,573]. Also, in a non-randomized study comparing percutaneous transhepatic biliary drainage with ERCP in elderly cholangitis patients, endoscopic drainage yielded significantly lower morbidity and mortality [574]. Therefore, ERCP is now considered the treatment of choice for acute cholangitis due to gallstones. Percutaneous transhepatic drainage should be considered when ERCP is impossible or has failed in expert hands, whereas surgery should be avoided. It is wise to aspirate bile after bile duct cannulation before contrast injection, in order to avoid increased bile duct pressure and bacteremias. Aspirated bile should be sent for culture. In stable patients, sphincterotomy with stone extraction can be performed during the initial procedure. Even if bile duct stones are not detected, sphincterotomy performed during endoscopic decompression leads to faster reconvalescence and shorter hospital stay [575]. In case of significant coagulation disturbances, large and multiple stones, or unstable patients, nasobiliary drain placement or biliary endoprostheses are preferred as initial treatment. Nasobiliary and endoprosthesis are equally effective under these circumstances [576]. Nevertheless, endoprosthesis should be preferred since this is less uncomfortable for the patient and is associated with less dislocation [576,577]. Definite stone removal can then be performed at a later stage, after recovery from the acute episode.

*Treatment of acute biliary pancreatitis*

*Which patients with acute biliary pancreatitis should undergo endoscopic retrograde cholangiopancreatography?*

For biliary pancreatitis with suspected coexistent acute cholangitis antibiotics should be initiated, and endoscopic retrograde cholangiopancreatography with sphincterotomy and stone extraction should be performed, with timing depending on the severity of cholangitis but preferably within 24 h (**high quality evidence; strong recommendation**)

An endoscopic retrograde cholangiopancreatography is probably indicated in patients with biliary pancreatitis and obstructed bile duct (**low quality evidence; weak recommendation**)

An early endoscopic retrograde cholangiopancreatography is probably not indicated in patients with predicted severe biliary pancreatitis in the absence of cholangitis or obstructed bile duct (**low quality evidence; weak recommendation**)

An early endoscopic retrograde cholangiopancreatography is not indicated in patients with predicted mild biliary pancreatitis in the absence of cholangitis or obstructed bile duct (**moderate quality evidence; strong recommendation**)

In patients with suspected biliary pancreatitis without cholangitis, endoscopic ultrasound (or magnetic resonance cholangiopancreatography) may prevent potential endoscopic retrograde cholangiopancreatography and prevent its risks if no stones are detected (**low quality evidence; weak recommendation**)

Comment: It is outside the scope of this guideline to discuss acute pancreatitis in detail, but some aspects of endoscopic treatment are mentioned. For further information we refer to the guideline Acute Pancreatitis 2013 of the International Association of Pancreatology [539]. The advice in the current guideline is in line with the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guideline.

If concomitant cholangitis is suspected, an endoscopic intervention is recommended, preferably within 24 h [538,578–580]. Urgent ERCP should be considered in case of severe cholangitis not responding to fluid resuscitation and intravenous antibiotics. The role of ERCP in predicting severe pancreatitis without cholestasis/cholangitis is controversial. A meta-analysis of seven RCTs with 757 patients in total did not support ERCP in patients with biliary pancreatitis without cholangitis or biliary obstruction, regardless of the predicted severity of the pancreatitis [581]. However, in case of predicted severe pancreatitis, the number of included patients in the meta-analysis was too small to draw definite conclusions. The meta-analysis supported ERCP in patients with biliary obstruction without cholangitis. It should be realised that in the early stage of biliary pancreatitis, the prediction of bile duct stones based on liver biochemistry, abdominal ultrasound or CT scan is highly unreliable. The explanation is that not only bile duct stones, but also the peripancreatic edema can cause biliary obstruction [356]. Nevertheless, the course of laboratory parameters during the first 48 h after admission can predict to some extent clinical course and persistent bile duct stones, which are associated with the severity of acute pancreatitis and worse outcome [582,583]. Of note, MRCP or EUS can prevent a proportion of (negative) ERCP procedures that may be considered because of suspected bile duct obstruction in the absence of cholangitis. Although MRCP is non-invasive and less operator-dependent, the disadvantage in comparison to EUS is the lower sensitivity for small (<5 mm) CBD stones [519,522–524,531,547,584–614]. In fact, patients with biliary pancreatitis often exhibit such small stones [241,615].

The best timing for EUS, MRCP and ERCP in patients with biliary pancreatitis and biliary obstruction in absence of cholangitis is not clear (IAP pancreatitis guideline 2013). In a post-hoc analysis, the meta-analysis [581] found no significant effect of ERCP timing on mortality. ERCP is not necessary for mild biliary pancreatitis in absence of cholangitis or biliary obstruction [538,578,581,616,617]. A preoperative ERCP before cholecystectomy does not have to be carried out routinely, since small bile duct stones generally pass spontaneously with normalization of the laboratory parameters [618,619].

*What is the best time to perform cholecystectomy after acute biliary pancreatitis?*

Cholecystectomy during the same hospital admission is the preferred option in patients with mild acute biliary pancreatitis (**high quality evidence; strong recommendation**)

Comment: In patients with mild acute biliary pancreatitis, early laparoscopic cholecystectomy is preferable to laparoscopic cholecystectomy performed on the routine waiting list to avoid recurrent gallstone-related complications [620,621]. While laparoscopic cholecystectomy has generally been performed after the acute symptoms resolve and the serum amylase activities return to near normal levels, recent RCTs confirm that performing laparoscopic cholecystectomy during the same hospital admission results not only in shorter hospital stay [622] but also reduces the rate of recurrent gallstone-related complications (recurrent pancreatitis, cholecystitis, choledocholithiasis needing ERCP, gallstone colic) from 17% to 5% [621]. There have been concerns about performing the surgery very early because of the risk of predicted severe pancreatitis [623]. Waiting up to 72 h allows the pancreatitis to be confirmed to be mild and perform any additional investigations and treatments such as MRCP, EUS or ERCP if indicated [624] and hence may overcome the issue of predicted severe pancreatitis.

Considerable uncertainty exists regarding the timing of cholecystectomy in patients with severe acute biliary pancreatitis and no definite recommendations can be made regarding the timing of cholecystectomy in patients with acute severe pancreatitis, since there are no RCTs on this issue [624]. With open cholecystectomy, early cholecystectomy (within 6 weeks of index admission) resulted in increased complication rates (including increased risk of infected peripancreatic collections) and length of hospital stay in observational studies [625,626]. Delayed laparoscopic cholecystectomy may decrease the conversion to open cholecystectomy since the inflammation and fluid

collections associated with severe pancreatitis are likely to settle down or become well-defined pseudocysts during the waiting time. Disadvantages of delayed laparoscopic cholecystectomy are potential recurrence of biliary symptoms and prolonged hospital stay [627]. Nevertheless, it appears wise to postpone cholecystectomy in patients with severe biliary pancreatitis with peripancreatic collections until these collections are dissolved or in case of persistent collections, until at least 6 weeks after pancreatitis onset.

### Diagnosis and therapy of intrahepatic bile duct stones

*What is the preferred diagnostic method for intrahepatic bile duct stones?*

If intrahepatic bile duct stones are suspected, abdominal ultrasound is the first method of choice and magnetic resonance cholangiopancreatography the second (**very low quality evidence; weak recommendation**)

Comment: Intrahepatic bile duct stones (hepatolithiasis) typically occur in the setting of bile duct strictures and are seen after bile duct injury, in patients with primary or secondary sclerosing cholangitis, or recurrent pyogenic cholangitis ("oriental cholangitis") [628–631]. Ascending cholangitis is a frequent acute complication associated with hepatolithiasis, and chronic complications include secondary biliary cirrhosis, segmental or lobar atrophy, liver abscess, and cholangiocarcinoma.

Abdominal ultrasound has an advantage over diagnostic ERCP, because it is non-invasive and can identify bile ducts that are obstructed by non-calcified intrahepatic bile duct stones. MRCP is also to be preferred over ERCP for the diagnosis of hepatolithiasis (sensitivity 97% *vs.* 59%, respectively) and can reliably detect bile duct strictures (specificity 97%, sensitivity 93%) as well as lesions proximal of the obstruction and outside of the bile ducts [606,632–634]. Although stones are often not directly visible using CT, dilated ducts and strictures as well as liver abscesses can be demonstrated [632].

*Should asymptomatic intrahepatic bile duct stones be treated?*

Asymptomatic intrahepatic bile duct stones do not always have to be treated. The treatment decision should be made individually for each patient and interdisciplinarily for symptomatic intrahepatic bile duct stones (**very low quality evidence; weak recommendation**)

Comment: During the course of 15 years, asymptomatic intrahepatic bile duct stones became symptomatic only in 11.5% of patients after a mean of 3.4 years [633]. The most common symptoms are colic, jaundice and fever due to cholangitis or liver abscesses, and rarely cholangiocarcinoma [633]. Therefore, it is justified to use a wait-and-see approach. An interdisciplinary treatment plan is useful for symptomatic stones. For planning the subsequent treatment, both ERCP and percutaneous transhepatic cholangiography are primarily important. Surgical resection should be considered for patients with unilateral stone disease, particularly if biliary strictures and/or lobar atrophy are also present [635,636]. Partial hepatectomy is associated with stone clearance rates higher than 80% and fewer recurrences than endoscopic modalities [637–639].

The other treatment options for hepatolithiasis include peroral cholangioscopic lithotripsy (POCSL) or percutaneous transhepatic cholangioscopic lithotripsy (PTCSL), which may be useful for diffusely distributed intrahepatic bile duct stones [632,636,640–643]. In a series of POCSL for hepatolithiasis, the rate of complete stone removal was 64% [644]. For PTCSL, higher rates of complete stone clearance have been reported (80–85%) [645–647]. However, both POCSL and PTCSL are limited by high rates of recurrent stones on long-term follow-up (22–50%).

Patients with LPAC syndrome caused by *ABCB4* mutations (see section Prevention of recurrent bile duct stones) are prone to develop intrahepatic bile duct stones (alone or in combination with bile duct and gallbladder stones) [216]. Cholecystectomy is indicated in the case of symptomatic gallbladder stones or sludge [216]. Biliary drainage or partial hepatectomy may be indicated in the case of symptomatic intrahepatic bile duct dilation filled with stones. LPAC patients with end-stage liver disease may be candidates for liver transplantation.

### Therapy of gallstones during pregnancy

*Therapy of gallbladder stones during pregnancy*

*How are symptomatic gallbladder stones treated in pregnancy?*

Laparoscopic cholecystectomy can be performed during pregnancy if the indication is urgent, regardless of trimester (**low quality evidence; weak recommendation**)

Patients with gallbladder and bile duct stones who are asymptomatic after bile duct clearance should undergo cholecystectomy post partum (**very low quality evidence; weak recommendation**)

Comment: Gallbladder sludge or gallstones develop in 5% of pregnant women each, but only 1.2% of the women with sludge or stones presented with biliary pain in a large prospective study in 3,254 pregnancies [648]. Of note, a randomized intervention to increase physical activity (from 15.7 to 18.6 in the first and 10.2 to 12.1 MET-hours per week in the third trimester) did not decrease the incidence of gallbladder sludge or stones during pregnancy [649]. Sludge is associated with gallbladder hypomotility during pregnancy and is not an indication for intervention. There is no indication for treating pregnant women with sludge or stones with UDCA. Asymptomatic pregnant patients with stones are not treated. However, in many of these patients a cholecystectomy becomes necessary in the first year after pregnancy [650].

Pregnancy is not a general contraindication for cholecystectomy [651–653]. In fact, cholecystectomy is the second most common nonobstetric antenatal surgical procedure [654].

Surgical management of pregnant patients with symptomatic stones is supported by studies showing recurrent symptoms in 92%, 64% and 44% of patients in the first, second and third trimester, respectively [655,656], and 23–39% of patients develop pancreaticobiliary complications [657,658]. However comparing conservative and surgical treatment of symptomatic cholelithiasis, no significant differences with respect to the frequency of preterm delivery or fetal mortality were detected in 6 studies with a total of 310 patients [655]. The second trimester is the safest trimester for cholecystectomy. The current data and experience show that safe laparoscopic cholecystectomy is also possible for urgent indications in the first trimester [658–660]. In the third trimester the indication is more restrictive because of the crowded abdomen and the danger of inducing labour. The intra-abdominal pressure should be kept below 12–15 mmHg, and the fetus should be monitored during the operation [661,662].

*Treatment of bile duct stones during pregnancy*

*How are symptomatic bile duct stones treated in pregnancy?*

During pregnancy symptomatic bile duct stones should be treated by endoscopic sphincterotomy and stone extraction by an experienced endoscopist (**low quality evidence; weak recommendation**). The use of x-rays is not contraindicated provided care is taken to minimize radiation exposure (**very low quality evidence; weak recommendation**)

Comment: Several studies have confirmed the safety of ERCP during pregnancy [663–666]. The examination should be performed by an experienced endoscopist, since pregnancy is an independent risk factor for post-ERCP pancreatitis [666,667]. Radiation exposure during cholangiography has been estimated to be 2–10 rads with variable conceptus doses [656,668]. The fluoroscopy times and doses should be limited as much as possible and no hardcopy X-ray films with additional radiation exposure should be taken. Image guidance by ultrasound or bile aspiration can be applied to confirm successful biliary cannulation and reduce radiation [669,670]. The pregnant patient generally lies on her left side during ERCP to minimize compression of aorta and vena cava. During endoscopic sphincterotomy, the uterus should not be placed between the sphincterotome and the grounding pad.

## Future perspectives

According to the CPG panel members, the following future areas of research should be supported to further improve the prevention and treatment of gallstones:

- Research into strategies for primary prevention of gallstones
- Research on the pathogenesis of gallstones in patients with fatty liver disease
- Implementation of genetic and exogenous lithogenic risk factors in novel prevention strategies
- Cost-effectiveness analyses of the course of silent or mildly symptomatic gallbladder stones with respect to laparoscopic cholecystectomy
- Care research on long-term results of cholecystectomy and regionally different frequencies of operations
- Research into alternative treatments of gallstones, particularly for patients at high risk of surgery
- Studies on the risk for biliary colic and complications (in particular gallbladder cancer) in carriers of asymptomatic gallstones or gallbladder sludge
- Pathogenesis and prevention of recurrent common and intrahepatic bile duct stones
- Studies on the bile microbiome and inflammation of the bile ducts

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