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