Internal Clinical Guidelines Team

Full version

Gallstone disease

Diagnosis and management of cholelithiasis, cholecystitis and choledocholithiasis

Clinical Guideline 188

Methods, evidence and recommendations

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Final guideline

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Contents

1 Overview

Gallstone disease is the term used in this guideline to refer to the presence of stones in the gallbladder or common bile duct and the symptoms and complications they cause. The following aspects of gallstone disease are included in this guideline (full definitions of these terms are provided in the glossary):

- Asymptomatic gallbladder stones
- Symptomatic gallbladder stones, including biliary colic, acute cholecystitis, Mirrizi syndrome, and Xanthogranulomatous cholecystitis.
- Common bile duct stones, including biliary colic, cholangitis, obstructive jaundice and gallstone pancreatitis.

Other complications of gallstones (such as gastric outlet obstruction, or gallstone ileus) and other conditions related to the gallbladder (such as gallbladder cancer, or biliary dyskinesia) are not included in this guideline.

Most people with gallstone disease have asymptomatic gallbladder stones, meaning the stones are confined to the gallbladder and they do not have any symptoms. The disease is identified coincidentally as a result of investigations for other conditions. People with asymptomatic gallbladder stones may never go on to develop symptoms or complications, but there is variation within the NHS in how people are managed once asymptomatic gallbladder stones have been diagnosed. Some patients are offered treatments to prevent symptoms and complications developing, and others are offered a watch and wait approach so that active treatment only begins once the stones begin to cause symptoms.

The symptoms of gallstone disease range from mild, non-specific symptoms that can be difficult to diagnose, to severe pain and/or complications which are often easily recognised as gallstone disease by health professionals. People with mild, non-specific symptoms of gallstone disease may attribute their symptoms to other conditions, or may be misdiagnosed and undergo unnecessary investigations and treatment. This has a detrimental effect on quality of life and has an impact on the use of NHS resources. Thus, there is a need to identify whether there are any specific signs, symptoms or risk factors for gallstone disease and to identify the best method for diagnosing the condition so that patients can be managed appropriately.

There is uncertainty about the best way of treating gallstone disease. There are a range of endoscopic, surgical and medical treatments available, but it is unclear which treatments are the most appropriate for which patients. There is also uncertainty about the timing of cholecystectomy, and whether it should take place during the acute presentation of the disease, or if it should be delayed until after the acute symptoms have subsided.

This guideline addresses these uncertainties and provides recommendations on how to identify, diagnose and manage gallstone disease.

Patient-centred care

This guideline offers best practice advice on the care of adults with gallstone disease.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

2 Summary Section

Guideline development group (GDG) members

Name	Role
Gary McVeigh (GDG Chair)	Professor of Cardiovascular Medicine, Queen's University Belfast/Consultant Physician, Belfast Health and Social Care Trust
Elaine Dobinson Evans	Patient/ carer member
Simon Dwerryhouse	Consultant Upper Gastrointestinal and Bariatric Surgeon, Gloucestershire Royal Hospital
Rafik Filobbos (from Nov 2013)	Consultant Radiologist with specialist interest in Gastrointestinal/ Hepatobiliary imaging, North Manchester General Hospital
Imran Jawaid	Principal General Practitioner, Hadlow, Tonbridge
Angela Madden (co-opted expert)	Professional Lead for Nutrition and Dietetics, University of Hertfordshire
Peter Morgan	Consultant Anaesthetist, St James's University Hospital
Gerri Mortimore	Lead Hepatology Clinical Nurse Specialist, Derby Hospitals NHS Foundation Trust
Kofi Oppong	Consultant Gastroenterologist, Newcastle Hospitals NHS Trust
Charles Rendell	Patient/ carer member
Richard Sturgess	Consultant Hepatologist and Physician, University Hospital Aintree
Giles Toogood	Consultant Hepatobiliary and Liver Transplant Surgeon, St James' University Hospital
Luke Williams	Consultant Gastrointestinal Radiologist, Salford Royal NHS Foundation Trust

Internal clinical guidelines team

Name	Role
Emma Banks (until April 2013)	Project Manager
Susan Ellerby	Consultant Clinical Adviser
Nicole Elliott	Associate Director
Michael Heath	Programme Manager
Hugh McGuire (from March 2014)	Technical Adviser
Stephanie Mills (from April 2013)	Project Manager
Gabriel Rogers	Technical Adviser (Health Economics)
Toni Tan (until March 2014)	Technical Adviser
Steven Ward	Technical Analyst (Health Economics)
Sheryl Warttig (until May 2014)	Technical Analyst

Centre for Clinical Practice commissioning team

Name	Role
Mark Baker	Clinical Adviser
Joy Carvill	Guideline Coordinator
Ben Doak	Guideline Commissioning Manager
Jaimella Espley (until Feb 2014)	Senior Medical Editor
James Hall (from Feb 2014)	Senior Medical Editor
Bhash Naidoo	Senior Technical Adviser (Health Economics)
Judith Thornton	Technical Lead
Sarah Willett	Guideline Lead

2.1 Key priorities for implementation

Reassure people with asymptomatic gallbladder stones found in a normal gallbladder and normal biliary tree that they do not need treatment unless they develop symptoms.

Offer early laparoscopic cholecystectomy (to be carried out within 1 week of diagnosis) to people with acute cholecystitis.

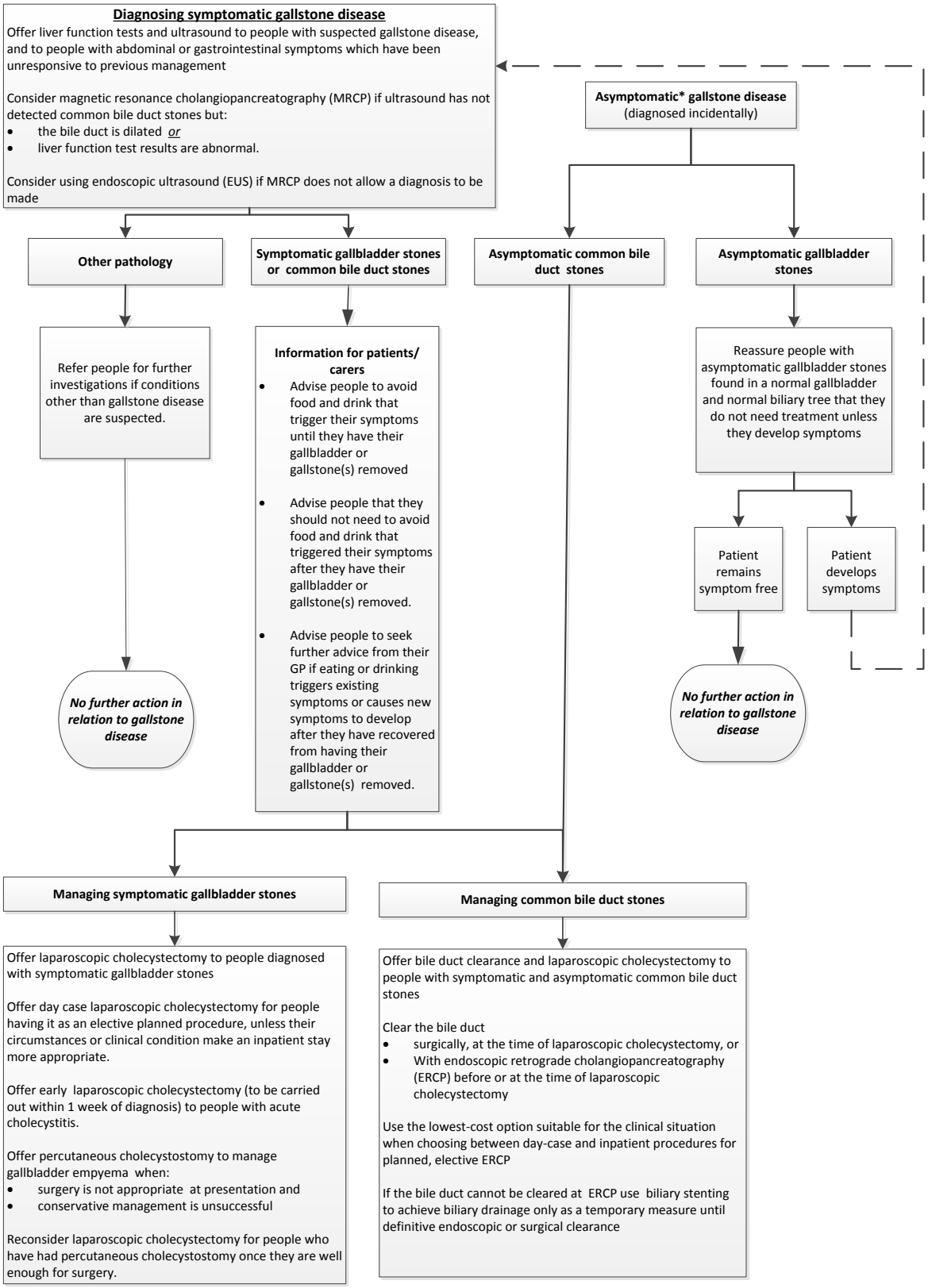
Reconsider laparoscopic cholecystectomy for people who have had percutaneous cholecystostomy once they are well enough for surgery.

Clear the bile duct:

- surgically at the time of laparoscopic cholecystectomy **or**
- with endoscopic retrograde cholangiopancreatography (ERCP) before or at the time of laparoscopic cholecystectomy.

If the bile duct cannot be cleared with ERCP, use biliary stenting to achieve biliary drainage only as a temporary measure until definitive endoscopic or surgical clearance.

2.2 Algorithm



2.3 List of all recommendations

Offer liver function tests and ultrasound to people with suspected gallstone disease, and to people with abdominal or gastrointestinal symptoms that have been unresponsive to previous management. (Recommendation 1)

Consider magnetic resonance cholangiopancreatography (MRCP) if ultrasound has not detected common bile duct stones but the:

- **bile duct is dilated** and/or
- **liver function test results are abnormal. (Recommendation 2)**

Consider endoscopic ultrasound (EUS) if MRCP does not allow a diagnosis to be made. (Recommendation 3)

Refer people for further investigations if conditions other than gallstone disease are suspected. (Recommendation 4)

Reassure people with asymptomatic gallbladder stones found in a normal gallbladder and normal biliary tree that they do not need treatment unless they develop symptoms. (Recommendation 5)

Offer laparoscopic cholecystectomy to people diagnosed with symptomatic gallbladder stones. (Recommendation 6)

Offer day-case laparoscopic cholecystectomy for people having it as an elective planned procedure, unless their circumstances or clinical condition make an inpatient stay necessary. (Recommendation 7)

Offer early laparoscopic cholecystectomy (to be carried out within 1 week of diagnosis) to people with acute cholecystitis. (Recommendation 14)

Offer percutaneous cholecystostomy to manage gallbladder empyema when:

- **surgery is contraindicated at presentation** and
- **conservative management is unsuccessful. (Recommendation 8)**

Reconsider laparoscopic cholecystectomy for people who have had percutaneous cholecystostomy once they are well enough for surgery. (Recommendation 9)

Offer bile duct clearance and laparoscopic cholecystectomy to people with symptomatic or asymptomatic common bile duct stones. (Recommendation 10)

Clear the bile duct:

- **surgically at the time of laparoscopic cholecystectomy or**
- **with endoscopic retrograde cholangiopancreatography (ERCP) before or at the time of laparoscopic cholecystectomy. (Recommendation 11)**

If the bile duct cannot be cleared with ERCP, use biliary stenting to achieve biliary drainage only as a temporary measure until definitive endoscopic or surgical clearance. (Recommendation 12)

Use the lowest-cost option suitable for the clinical situation when choosing between day-case and inpatient procedures for elective ERCP. (Recommendation 13)

Advise people to avoid food and drink that triggers their symptoms until they have their gallbladder or gallstones removed. (Recommendation 15)

Advise people that they should not need to avoid food and drink that triggered their symptoms after they have their gallbladder or gallstones removed. (Recommendation 16)

Advise people to seek further advice from their GP if eating or drinking triggers existing symptoms or causes new symptoms to develop after they have recovered from having their gallbladder or gallstones removed. (Recommendation 17)

Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1. What are the long-term benefits and harms, and cost effectiveness of endoscopic ultrasound (EUS) compared with magnetic resonance cholangiopancreatography (MRCP) in adults with suspected common bile duct stones?

2. What are the benefits and harms, and cost effectiveness of routine intraoperative cholangiography in people with low to intermediate risk of common bile duct stones?

3. What models of service delivery enable intraoperative endoscopic retrograde cholangiopancreatography (ERCP) for bile duct clearance to be delivered within the NHS? What are the costs and benefits of different models of service delivery?

4. In adults with common bile duct stones, should laparoscopic cholecystectomy be performed early (within 2 weeks of bile duct clearance), or should it be delayed (until 6 weeks after bile duct clearance)?

5. What is the long-term effect of laparoscopic cholecystectomy on outcomes that are important to patients?

Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also ‘Patient-centred care’).

Interventions that must (or must not) be used

We usually use ‘must’ or ‘must not’ only if there is a legal duty to apply the recommendation. Occasionally we use ‘must’ (or ‘must not’) if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a ‘strong’ recommendation

We use ‘offer’ (and similar words such as ‘refer’ or ‘advise’) when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, ‘Do not offer…’) when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use ‘consider’ when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

3 Methods

This guideline was developed in accordance with the process set out in 'The guidelines manual (2012)'. There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available. In instances where the guidelines manual does not provide advice, additional methods are used and are described below.

3.1 Additional methods used in this guideline

3.1.1 Methods for combining diagnostic evidence:

Meta-analysis of diagnostic test accuracy data was conducted in accordance with the process set out in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

A hierarchical, bivariate model was performed in R using MADA code (R Code Team 2012) to generate pooled estimates of sensitivity and specificity.

3.1.2 Methods for combining direct and indirect evidence (network meta-analysis)

Conventional 'pairwise' meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from two or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally consistent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions.

The evidence in section 4.6 of this guideline was analysed using network meta-analysis, to inform decisions about managing common bile duct stones.

Synthesis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models.

Results were reported summarising 10,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values were used.

Prior distributions

Non-informative prior distributions were used in all models. Trial-specific baselines and treatment effects were assigned N(0, 1000) priors, and the between-trial standard deviations

used in random-effects models were given U(0, 5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Choice of reference option

To undertake an NMA, one option in the network must be specified as a common 'reference' option. The model will estimate the effects of all other options in comparison this. The choice of reference option is mathematically arbitrary; however, it may have implications for the computational efficiency of the network and/or the interpretability of outputs. For these reasons, the option that had been compared with the highest number of the other options was chosen as the reference.

Reported outputs

The NMA outputs shown in this guideline (see appendix H.7.5) are as follows:

- Network diagram, showing the availability of evidence. In these diagrams:
  - node size is proportional to the total number of participants across the evidence base that were randomised to receive the treatment in question
  - the width of connecting lines is proportional to the number of trial-level comparisons available.
- Table of input data, showing the evidence used in the model.
- Relative effect matrix, showing an estimate of effect for each intervention compared with each of its comparators. An estimate of effect based on direct evidence only (using pairwise frequentist meta-analysis with the same fixed or random-effects models as the NMA) is also presented for comparisons where data are available
- Plot of the relative effectiveness, including the results of the NMA of each intervention compared with the reference treatment (see E.2.4) and any direct estimate available for the same comparison.
- Tabulated rank probabilities, giving the probability of each treatment being best (that is, ranked #1) and its median rank with 95% credible interval (CrI). In these outputs, higher ranking always reflects what is best for the patient (for example, higher rates of disease eradication, lower rates of adverse events, higher IQ, lower blood pressure, and so on).
- Histograms demonstrating the probability of each treatment being at each possible rank ('rankograms')

Applying GRADE to network meta-analysis

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a network meta-analysis is still a developing methodology. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis.

Risk of bias

In addition to the usual criteria to assess the risk of bias or 'limitations' of studies for each pairwise analysis within a network, the risk of bias was assessed for each direct comparison and assessed to see how it would affect the indirect comparisons. In addition, there was an assessment of treatment effect modifiers to see if they differed between links in the network.

For network meta-analyses with a large proportion of studies that were judged to be susceptible to bias, some downgrading decision rules were applied.

- If 50% or more studies in the network were inadequate or unclear for a particular parameter of quality, the outcome was downgraded by 1 level.

- As with pairwise meta-analyses, studies with differences in concomitant treatment between groups, or which did not report concomitant treatment between groups (where permitted), were treated with caution. Additionally, if there were differences in concomitant treatment among the studies included in different links across the network, the overall outcome was downgraded.

Inconsistency

Inconsistency was assessed for the heterogeneity of individual pairwise comparisons in the network, and also between direct and indirect comparisons where both were available (that is, where there were 'loops' in the network).

Heterogeneity across studies for each direct pairwise meta-analysis was assessed using I2. This allowed for the assessment of heterogeneity within the included studies using the following decision rules:

- If there was considerable heterogeneity for 1 link or more in a network, the outcome was downgraded 1 level.
- If there was more than 1 link in the network with considerable, substantial or moderate heterogeneity, consideration was given to downgrading 2 levels.

To assess for consistency in each pairwise comparison where both direct and indirect evidence are available, the values of the direct and indirect estimates were compared to see if they were similar.

The overall value of tau was also assessed to compare heterogeneity across the network.

Indirectness

As with pairwise meta-analyses, studies included in a network were assessed for how well they fit the PICO (population, intervention, comparator, outcome) specified in the review protocol.

Imprecision

Imprecision was assessed for a number of variables:

- Sufficient head-to-head trials in the network.
- Sufficient number of studies to form the network (if there was a high proportion of 'links' formed with only 1 trial, the outcome was downgraded).
- Overall certainty/uncertainty of the effect estimates (size of credible intervals, including for each drug compared with the reference option, and size of credible intervals for the overall rankings within the network).
- For networks, imprecision was considered around both the direct and indirect effect estimates.

When assessing imprecision for pairwise comparisons, or for networks with only 1 trial for all 'links' in the network, the confidence interval around the direct estimate was used (since the results were largely led by a non-informative prior).

3.1.3 References

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4 Evidence Review and Recommendations

4.1 Signs, symptoms and risk factors for gallstone disease

4.1.1 Review Question 1

What signs, symptoms, and risk factors should prompt a clinician to suspect symptomatic gallstone disease in adults presenting to healthcare services?

4.1.2 Evidence Review

The aim of this question was to identify the specific signs, symptoms, and risk factors that can predict gallstone disease in adults who present at healthcare services. This question did not aim to identify signs, symptoms and risk factors for gallstone disease in the general population. This is because the majority of people with gallstone disease in the general population are asymptomatic, and the potential signs, symptoms and risk factors identified at a population level may be different to the signs, symptoms and risk factors that cause people to seek medical attention.

A systematic search was conducted (see appendix D.1), which identified 7802 references. After removing duplicates the references were screened by their titles and abstracts. This led to 74 references being obtained and reviewed against the inclusion and exclusion criteria as described in the review protocol (appendix C.1).

Primary research of any study design was eligible for inclusion if it satisfied the following criteria:

- The included participants were adults presenting to healthcare services: studies were not eligible if they recruited a sample of the general population. This is because the use of evidence from populations in non-healthcare settings may misrepresent the type and severity of the signs, symptoms and risk factors that cause people to present at healthcare services.
- Results were analysed using a multivariate method, such as multiple regression: Multivariate analyses enable independent risk factors for gallstone disease to be identified, as this type of analysis can account for the effects of other risk factors. For example, a bivariate analysis may reveal that there are 4 risk factors for gallstone disease (being over the age of 40, smoking, being obese, and having more than 1 pregnancy). From this analysis it is impossible to tell if a person presenting with all 4 risk factors has a different risk of gallstone disease to a person with just 2 of the risk factors. It is not known if the risk factors are dependent or independent of each other. Multivariate analysis can take the interrelationships between risk factors into consideration and identify independent risk factors for gallstone disease. If a multivariate analysis shows that all 4 risk factors are independently related to gallstone disease, then someone presenting with all 4 risk factors has a different risk status to someone presenting with fewer risk factors.

Overall, 73 studies were excluded as they did not meet the eligibility criteria. A list of excluded studies and reasons for their exclusion is provided in appendix F.

One study met the eligibility criteria and was included. Data were extracted into detailed evidence tables (see appendix G.1) and are summarised in Table 1 below.

The GRADE framework was modified for this review. As prospective studies were considered to be the highest quality evidence, these were rated initially as high quality while

retrospective studies were downgraded to start as low quality. The evidence for the outcomes was then assessed in the normal GRADE framework by downgrading or upgrading on the basis of inconsistency, imprecision and indirectness. The modified GRADE profiles are in appendix I.1. After applying the modified GRADE framework the evidence was judged to be very low in quality. Full GRADE profiles are in appendix I.1

Table 1: Summary of included studies for review question 1

Study reference	Population	Prognostic factors	Results	Authors conclusions
(Wegge and Kjaergaard 1985) N=192 Denmark	Patients admitted to hospital with upper abdominal pain less than a week in duration and no previous diagnosis of gallstones	The results of a structured interview and physical examination were condensed into 37 prognostic factors.	Univariate analyses found that 6 prognostic factors predicted gallstone disease (Age 50 years+, previous attacks of similar pain, intolerance to fatty food, received analgesic injection at home, radiation of pain to back or shoulder, tenderness in the upper right quadrant), but these factors did not remain significant in subsequent multivariate analysis.	Classical signs and symptoms are relatively poor in establishing the diagnosis of gallstone disease, but their absence is a relatively good indicator for excluding the diagnosis.

4.1.3 Health economic evidence

A literature search was conducted jointly for review questions 1 and 2 by applying standard health economic filters to the clinical search strategies (see Appendix D). For review questions 1 and 2, 914 references were retrieved, of which 16 were retained after title and abstract screening. No health economic studies were found for question 1. Health economic modelling was not prioritised for this review question.

4.1.4 Evidence Statements

Very low quality evidence from 1 retrospective cohort study did not identify any factors that could predict gallstone disease in those presenting with upper abdominal pain lasting less than one week.

4.1.5 Evidence to Recommendations

Relative value of different outcomes	There was insufficient evidence relating to any outcome from this review question as the single included study only included people presenting with upper abdominal pain lasting less than one week.
Trade off between benefits and harms	Some people present to healthcare services with typical signs, symptoms and risk factors for gallstone disease (such as sudden severe abdominal pain, nausea, jaundice etc.) as in the included study. The GDG agreed that most medical professionals would suspect gallstone disease in people presenting with these typical symptoms, as these features are well recognised and medical students are routinely educated about them. There was insufficient

	evidence available to support or refute these typical signs, symptoms and risk factors as the single study identified only included people presenting with upper abdominal pain lasting less than a week. The GDG considered putting typical signs and symptoms in a recommendation based on their combined knowledge and experience but felt that that may become a barrier to people who present with atypical signs and symptoms. The GDG also acknowledged that some people with gallstone disease present with symptoms that can be vague and easily misattributed to other conditions (such as indigestion or general abdominal discomfort) by both the patient and their healthcare professional. This can mean that gallstone disease is not immediately considered, and patients may be investigated or treated for a condition that they do not have. This ultimately affects patient quality of life, and the use of NHS resources as patients will continue to have unresolved symptoms that may get worse, resulting in inappropriate treatments and investigations being offered to the patient. However, there was insufficient evidence available to enable this group of patients to be identified. Thus the GDG decided not to make a recommendation based on typical signs and symptoms or risk factors that should prompt a clinician to suspect symptomatic gallstone disease in adults presenting to healthcare services.
Consideration of Health Benefits and Resource Use	No health economic evidence was found.
Quality of evidence	The single study available for this review was of very low quality, and insufficient evidence was provided to support decision making.
Other considerations	The GDG acknowledged the lack of research that was available around identifying signs, symptoms and risk factors for gallstone disease, but felt that good quality research in this area would have limited value as the benefits would be small. The identification of specific signs, symptoms and risk factors would ultimately refine the number of people who were offered ultrasound and liver function tests (these tests were reviewed and recommended in section 4.2 of this guideline). Since these tests are relatively low cost and easy to perform, are low risk and minimally invasive to patients, and are widely used for a range of conditions, refining the number of these tests that are performed would not lead to major cost savings or improvements in the quality of NHS care. Therefore, the GDG did not feel that a research recommendation would be useful.

4.1.6 Recommendations

No recommendations were made in relation to this review question.

4.1.7 Research recommendations

No research recommendations were made in relation to this review question.

4.1.8 References

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4.2 Diagnosing gallstone disease

4.2.1 Review Question 2

What is the most accurate strategy for diagnosing gallstone disease in adults suspected of the condition?

4.2.2 Evidence Review

The aim of this question was to assess all available methods for diagnosing gallstone disease and establish which methods are the most accurate.

A systematic search was conducted (appendix D.2), which identified 6312 references. After removing duplicates and screening the references based on their titles and abstracts, 310 references were obtained. These were reviewed against the inclusion and exclusion criteria as detailed in the review protocols (appendix C.2).

Primary research utilising a randomised controlled trial, cohort, or cross sectional design was eligible for inclusion. Studies also had to have utilised a valid reference standard. Currently there is no accepted reference standard for confirming the presence or absence of gallstone disease, so studies were only included if they met the following criteria:

- Surgery as the reference standard for evaluating the gallbladder: this is the best available method for diagnosing gallstones in the gallbladder and cholecystitis.
- Endoscopic retrograde cholangiopancreatography (ERCP) as the reference standard for evaluating the biliary tract: this is the best available method for diagnosing common bile duct stones.

These procedures can accurately confirm the presence of gallstone disease by extracting the gallstone(s). Other tests such as endoscopic ultrasound, magnetic resonance cholangiopancreatographydo do not extract gallstones, so were considered unsuitable as reference standards.

It is much more difficult to confirm the absence of gallstone disease. Gallstones or common bile duct stones may be missed during endoscopic or surgical investigations. Patients can be followed up to establish if signs and symptoms persist, which can indicate that gallstone disease is present but was missed during previous investigations. However, this can be misleading, as the patient's signs and symptoms can be caused by other conditions, or new gallstone disease could have developed since the original investigations. As there is no alternative method for definitively confirming the absence of gallstone disease, surgery and ERCP were accepted as the best available reference standards, and their potential inaccuracies are acknowledged.

During the review, a date restriction was also imposed on all studies that utilised endoscopic, surgical, or radiological methodologies. This was because technological advances have made older studies of limited relevance to clinical practice today. An arbitrary publication of date of 1993 or later was used as it coincides with the approximate introduction of laparoscopic cholecystectomy into clinical practice in the UK. The only exceptions to this date restriction were studies that focused on predicting the presence of gallstone disease using clinical history taking, physical examination and simple blood tests, as these factors are not as dependent on technology, and studies conducted over 20 years ago are likely to still be relevant to clinical practice today.

Overall, 23 studies met the eligibility criteria and were included in the review. Evidence was extracted into detailed evidence tables (see appendix G.2). Diagnostic test accuracy data were provided by 20 studies, and where possible these data were pooled in relevant meta-

analyses. Some of these studies compared to see whether diagnostic test accuracy differed depending on who interpreted the test results (for example, radiologist compared with ultrasonographer, or experienced radiologist compared with inexperienced radiologist). This produced different results for the same sets of patients. It would be inappropriate to use both results in the meta-analysis as this would be double counting. Instead the results reported by the interpreter most similar to those intended to use the test in clinical practice were included in the analysis. If both interpreters were intended to use the test, their test results were averaged and this was taken into the meta-analysis.

Data about predictive factors for gallstone disease were provided by 3 studies. It was not possible to pool the data from these studies, as each study investigated different predictive factors.

Data from the included studies were extracted into detailed evidence Table 2 and Table 3 below, and the GRADE framework for diagnostic evidence was used to quality assess the evidence. However, for this review, the GDG took a liberal approach to set the threshold for accuracy of 0.50 for both sensitivity and specificity on the basis that they wanted to identify the test(s) that were better than chance. Any test that did not meet this threshold was not considered clinically useful. Full GRADE profiles are presented in Appendix I.2.

Table 2: Summary of included studies reporting diagnostic test accuracy

Study	Population	Reference standard	Index tests/prognostic factors	Results	
				Sensitivity	Specificity
(Ahmed and Diggory 2011) UK	1869 patients undergoing laparoscopic cholecystectomy for symptoms related to gallstone disease	Surgery	Ultrasound performed by radiologist or ultrasonographer	100% (CI=100 to 100)	14.4% (CI=10.4 to 18.4)
			Ultrasound performed by radiologist	100% (CI=99.9 to 100)	13.9% (CI= 7.2 to 20.7)
			Ultrasound performed by ultrasonographer	100% (CI= 99.9 to 100)	12.4% (CI= 8.0 to 16.8)
(Altun et al. 2007) USA/Brazil	32 patients with histopathologically proven cholecystitis	Surgery	1.5T MR	94.7% (CI=82.1 to 100)	69.2% (CI=40.3 to 98.2)
(Chan et al. 1996) Hong Kong	45 hospital inpatients referred for endoscopy for suspected CBDS	ERCP	1.5T MRCP	94.7% (CI=82.1 to 100)	84.6% (CI= 68.8 to 100)
(De Vargas et al. 2006) Italy	12 patients with acute cholecystitis	Surgery	CT with injection of contrast agent	100% (CI=94.4 to 1.00)	100% (CI= 83.3 to 100)
			Ultrasound	37.5% (CI= 10.7 to 64.3%)	100% (CI= 96.4 to 100)
(Griffin et al. 2003) UK	115 patients with gallstones referred for ERCP prior to cholecystectomy	ERCP	MRCP	83.8% (CI=70.6 to 97.0)	96.2% (CI=91.2 to 100)
			MRCP (stones ≤5mm)	28.6% (CI=0 to 69.2)	100% (CI= 99.3 to 100)
			MRCP (stones	96.7%	96.2%

Study	Population	Reference standard	Index tests/prognostic factors	Results	
				Sensitivity	Specificity
			>5mm)	(CI=88.6 to 100)	(CI=91.2 to 100)
(Hakansson et al. 2000) Sweden	35 patients with suspected cholecystitis	Surgery	Ultrasound	65.4% (CI=45.2 to 85.6)	88.9% (62.8 to 100)
			MRCP	88.5% (CI=74.3 to 100)	88.9% (CI=62.8 to 100)
(Holzknecht et al. 1998) Germany	61 patients with a planned ERCP	ERCP	MRCP (consensus of 2 radiologists)	92.3% (CI=74.0 to 100)	95.8% (CI=89.1 to 100)
			MRCP (one radiologist)	84.6% (CI=61.2 to 100)	93.8% (CI=85.9 to 100)
(Jovanovic et al. 2011) Boznia and Herzegovina	203 patients undergoing ERCP for suspected CBDS	ERCP	Ultrasound (dilated CBD or stones)	90.8% (CI=84.6 to 97.0)	34.3% (CI=24.7 to 43.8)
			Ultrasound (dilated CBD and stones)	82.0% (CI=76.1 to 87.9)	52.0% (CI=30.4 to 73.6)
(Karki 2013) India	88 patients with suspected obstructive jaundice (immediate post ERCP cases were excluded)	ERCP	Ultrasound (for detecting CBDS)	100% (no confidence intervals reported)	89% (no confidence intervals reported)
(Kondo et al. 2005) Japan	28 patients suspected of CBDS	ERCP	MRCP	87.5% (CI=72.2 to 100)	75.0% (CI=20.1 to 100)
			CT cholangiography with contrast agent (iotroxic acid)	87.5% (CI+=72.2 to 100)	75.0% (CI=20.1 to 100)
			EUS	100% (CI=97.9 to 100)	50% (CI=0 to 100)
(Park et al. 1998) South Korea	35 patients suspected of cholecystitis	Surgery	Ultrasound (gallbladder wall thickening)	96.6% (CI=88.2 to 100)	83.3% (CI=96.4 to 100)
			Ultrasound (cystic duct obstruction)	61.9% (CI=38.8 to 85.1)	100% (CI=96.4 to 100)
			MRCP (gallbladder wall thickening)	69.0% (CI=50.4 to 87.5%)	83.3% (CI=45.2 to 100)
			MRCP (cystic duct obstruction)	100% (CI=97.6 to 100)	92.9% (CI=75.8 to 100)
(Polkowski	50 patients	ERCP	CT	90.6%	87.5%

Study	Population	Reference standard	Index tests/prognostic factors	Results	
				Sensitivity	Specificity
et al. 1999) Poland	referred for ERCP for suspected CBDS		Cholangiography with contrast infusion	(CI=79 to 100)	(CI=68.2 to 100)
			EUS	91.2% (CI=80.2 to 100)	100% (CI=96.9 to 100)
(Regan et al. 1996)	23 patients with suspected CBDS	ERCP	MR cholangiography (no contrast agent)	93.3% (CI=77.4 to 100)	87.5% (CI=53.8 to 100)
			Ultrasound	60% (CI=31.9 to 88.1)	100% (CI=93.8 to 100)
(Rickes et al. 2006) Germany	124 Patients suspected of CBDS	ERCP	Ultrasound (experienced investigator)	81.5% (CI=65 to 98)	87.5% (CI=58.3 to 100)
			Ultrasound (inexperienced investigator)	46.3% (CI=32.1 to 60.5)	91.4% (CI=80.7 to 100)
(Soto et al. 2000) Colombia	51 patients referred for ERCP for suspected CBDS	ERCP	CT	65.4% (CI=45.2 to 85.6)	84% (CI=67.6 to 100)
			CT Cholangiography with oral contrast (iopodic acid)	92.3% (CI=80.1 to 100)	92% (CI=79.4 to 100)
			MRCP	96.2% (CI=86.8 to 100)	100% (CI= 98 to 100)
(Soto et al. 1999) Colombia	29 patients referred for ERCP for suspected CBDS	ERCP	CT Cholangiography with oral contrast (iopanoic acid) (radiologist 1)	92.9% (CI=75.8 to 100)	100% (CI=96.7 to 100)
			CT Cholangiography with oral contrast (iopanoic acid) (radiologist 2)	85.7% (CI=63.8 to 100)	100% (CI=96.7 to 100)
(Stiris 2000) Norway	50 patients suspected of CBDS	ERCP	MRCP	87.5% (CI=74.5 to 100)	94.4% (CI=81.1 to 100)
(Sugiyama and Atomi 1997) Japan	142 patients referred for ERCP for suspected CBDS	ERCP	EUS	96.1% (CI=89.8 to 100)	100% (CI=99.5 to 100)
			Ultrasound	62.7% (CI=48.5 to 77.0)	94.5% (CI=89.3 to 99.7)
			CT	70.6% (CI=57.1 to 84.1)	96.7% (CI=92.5 to 100)

Study	Population	Reference standard	Index tests/prognostic factors	Results	
				Sensitivity	Specificity
(Sugiyama et al. 1998) Japan	97 patients referred for ERCP for suspected CBDS	ERCP	MRCP	91.2% (CI=80.2 to 100)	100% (CI= 99.2 to 100)
			Ultrasound	70.6% (CI=53.8 to 87.4)	95.2% (CI=89.2 to 100)
(Tseng et al. 2008) Taiwan	266 patients referred for ERCP for suspected CBDS	ERCP	CT	77.3% (CI=70.6 to 84.0)	72.8% (CI=63.7 to 81.9)

CT= computed tomography
ERCP= endoscopic retrograde cholangiopancreatography
EUS= endoscopic ultrasound
MR= Magnetic resonance
MRCP= magnetic resonance cholangiopancreatography

Table 3: Studies reporting prognostic data

Study	Population	Reference standard	Prognostic factors	Significant predictors
(Alponat et al. 1997) Singapore	Patients undergoing laparoscopic cholecystectomy who were indicated for ERCP	ERCP	age, sex, history of right hypochondrial pain, indication for procedure-previous or present elevated serum liver enzymes, clinical findings of cholangitis, jaundice, pancreatitis, dilated CBD over 6mm with or without stone on ultrasound, serum level of each liver enzyme (AST,ALT, ALP, GGT,LDH) bilirubin and ultrasonographic findings	Cholangitis, CBD>6mm with stone on ultrasound AST Bilirubin
(Barr et al. 1999) USA	Patients who had undergone ERCP prior to laparoscopic cholecystectomy	ERCP	age, sex, admission temperature, weight, AST, ALT, ALP, GGT, bilirubin, amylase, lipase, current or recent medications, common bile duct diameter as measured by ultrasonography, ERC findings of the presence or absence of common bile duct stones	AMY GGT CBD diameter ALP
(Shiozawa et al. 2005) Japan	Patients who had undergone ERCP prior to laparoscopic cholecystectomy	ERCP	age, gender, abdominal pain, fever elevation, jaundice, pancreatitis, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), gamma glutamyl	ALP Bilirubin AMY CBD diameter

Study	Population	Reference standard	Prognostic factors	Significant predictors
			transpeptidase (GGT), alkaline phosphatase (ALP), amylase (AMY), and ultrasound findings.	

AST= Aspartate aminotransferase; ALP= Alkaline phosphatase; AMY= Amylase; CBD= Common bile duct; ERCP= endoscopic retrograde cholangiopancreatography; GGT= Gamma glutamyl transferase

4.2.3 Health economic evidence

A literature search was conducted jointly for review questions 1 and 2 by applying standard health economic filters to the clinical search strategies (see Appendix D). Searches for review questions 1 and 2 retrieved 914 studies, of which 16 were retained after title and abstract screening. For review question 2, 2 health economic studies were found (Howard et al. 2006; Kaltenthaler et al. 2004). An assessment of the quality of the economic evidence is given in Table 4. This review question was not prioritised for original health economic modelling.

Howard et al (2006) used a decision tree analysis to compare MRCP with ERCP for diagnosing post-cholecystectomy CBDS in patients with abdominal pain and/or abnormal liver function tests. Kaltenhaler et al. (2004) used a decision tree analysis to compare MRCP with diagnostic ERCP for patients with suspected CBDS. The GDG felt that, as it was based on UK data and covered a wider patient population, Kaltenhaler et al (2004) provided slightly higher quality evidence. However, both studies were felt to be of use. Both studies found that MRCP dominated ERCP, but this depended on the prior probability of CBDS. In probabilistic sensitivity analysis, Howard et al. (2006) was found to be 83% cost effective (at Australian $50,000/QALY threshold) and Kaltenhaler et al. (2004) was found to be 100% cost effective (at UK £20,000/QALY threshold). Indeed, Kaltenhaler et al. (2004) was found to be 97% cost saving.

MRCP appeared to be cost effective compared with ERCP for diagnosing CBDS under the majority of assumptions. The GDG considered that the results from the 2 studies reflected what they would expect to occur in standard clinical practice.

Table 4: Economic Evidence – MRCP versus ERCP for detection of CBDS

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Howard et al (2006) Post-cholecystectomy patients with suspected biliary pathologic state Australia **Partially applicable**[a,b,f] **Potentially serious limitations**[c,d,e]	Effects: systematic review, literature, some estimates Costs: DRG data and other standard sources ($Aus, unspecified) Utilities: Literature and some assumptions	Decision tree with Monte Carlo simulation (length unspecified) MRCP followed by ERCP (if MRCP positive) for CBDS or benign strictures versus ERCP only Discounting not applied due to short horizon	−$1043	0.047 QALYs	MRCP dominates	MRCP first is both more effective and less expensive compared with ERCP as an initial diagnostic test	ICERs sensitive to prior probability of CBDS, MRCP is least costly when prior probability is less than 60% In PSA, MRCP has 59% chance of being cost saving, 83% chance of being cost effective at $Aus50,000/QALY threshold
Kaltenhaler et al (2004) Patients with suspected biliary obstruction UK **Partially applicable**[f] **Minor limitations**[c]	Effects: systematic review, literature, some assumptions Costs: UK reference costs (£UK, 2002) Utilities: literature, including some from health professionals	Decision tree with Monte Carlo simulation (1 year analysis) MRCP followed by ERCP (if MRCP positive) for suspected biliary obstruction versus diagnostic ERCP only Discounting not applied due to short horizon	−£163	0.012 QALYs	MRCP dominates	MRCP is both cost saving and result in improved quality of life	ICERs appear robust to the input values, but uncertainties in model structure and assumptions remain MRCP is least costly when prior probability of CBDS is less than 60% In PSA, MRCP has 97% chance of being cost saving, 99% chance of being cost effective at £20,000/ QALY threshold

Abbreviations
Aus; Australia
CBDS: Common bile duct stones
DRG: Diagnosis-Related Group
ERCP: Endoscopic retrograde cholangiopancreatography
ICER: Incremental cost effectiveness ratio

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
MRCP: Magnetic retrograde cholangiopancreatography PSA: Probabilistic sensitivity analysis UK: United Kingdom							
a Specific population, may not be generalisable to all gallstone patients b not UK based c Effect parameters not taken from best available sources d Diagnostic accuracy estimates based on all patients, not just post cholecystectomy patients e Costing year not given f Utilities not derived from patients							

4.2.4 Evidence Statements

While most of the diagnostic tests had sensitivities and specificities above 50%, some had confidence intervals below 50% for either sensitivity or specificity. This means that there is uncertainty in the evidence as some of the tests may actually perform worse than chance alone. The quality of this evidence was mainly moderate to low in quality.

Two partially applicable health economic studies with minor limitations found that, under a variety of assumptions, MRCP appeared cost effective compared with ERCP for diagnosing CBDS.

4.2.5 Evidence to Recommendations

Relative value of different outcomes	The various metrics for estimating diagnostic test accuracy were discussed by the GDG, and they agreed to base decisions on sensitivity and specificity. This is because other diagnostic test accuracy measures are less reliable (for example, positive and negative predictive values), or cannot be meta-analysed (for example, likelihood ratios, as robust methods for doing this have not yet been developed). The GDG discussed patient benefits, patient harms, and clinical utilities associated with diagnostic testing, and the minimum sensitivity and specificity values that it would tolerate. It agreed that sensitivity and specificity estimates at or below 0.50 (or with confidence intervals below 0.50) were not clinically useful as these results indicate that the test could perform the same or worse than chance alone. The GDG agreed that sensitivity and specificity were equally as important in all diagnostic tests, except for ultrasound and liver function tests where the GDG would accept lower sensitivity values. The GDG recognised that patients with false negative results at this early stage of the clinical pathway would be offered subsequent investigations as part of their differential diagnosis. Therefore they could tolerate lower levels of sensitivity, and so a higher number of false negative results, as patients would present to health services with recurrent symptoms at a later time point. The GDG felt that morbidity and mortality related to false negatives was lower at this early stage of investigations, than for people with false positives who would undergo unnecessary treatment. The GDG agreed that in practice other tests are only offered after ultrasound and liver function tests have been performed. Because of this, the GDG felt that for other tests sensitivity and specificity were equally as important, as false positive and false negative results are associated with similar levels of subsequent morbidity and mortality at this stage of the pathway.
Trade off between benefits and harms	**Abdominal ultrasound** <u>For gallbladder stones</u>: A single study provided very low quality evidence about ultrasound for diagnosing gallbladder stones. The

study showed that ultrasound was extremely useful for identifying the presence of gallstones (high sensitivity) but was not at all useful for ruling out gallstones in people who don't have them (low specificity). The GDG felt that these results did not match their own experiences of using the test to diagnose gallstones, and they felt that the test is both sensitive and specific. Since the evidence was based on a single study and contradicted clinical experience, the GDG agreed that the results were not reliable.

For cholecystitis: Three studies provided very low quality evidence about ultrasound for diagnosing cholecystitis. Point estimates for sensitivity and specificity were satisfactorily high, but confidence intervals fell below 0.50 for sensitivity. The GDG felt that it could accept lower sensitivity values for this test, as it is very low risk and is used routinely in the NHS for a range of conditions. In addition, the GDG noted that the studies included in this meta-analysis had very small populations, so the wide confidence intervals may be because of a lack of statistical power rather than a lack of sensitivity.

For common bile duct stones: Five studies provided low quality evidence about ultrasound for diagnosing common bile duct stones. Sensitivity and specificity values were satisfactorily high and supported the GDG's own knowledge and experience of the test. The GDG were confident that ultrasound was clinically useful in diagnosing common bile duct stones.

Overall: the GDG felt there was sufficient evidence to recommend ultrasound for diagnosing gallstone disease since it is accurate, widely available throughout the NHS and is of very low risk to the patient.

Cholescintigraphy (HIDA scan)

No evidence was available. The GDG agreed that this test is not routinely used for diagnosing gallstone disease, and that it is usually used for people for whom other tests are unsuitable. The GDG agreed not to make a recommendation based on the knowledge and experience of the group. The test exposes patients to ionising radiation and the associated risks, and other tests considered in this review have evidence supporting their use for diagnosing gallbladder stones.

Computer Tomography (CT)

For cholecystitis: A single, small study provided low quality evidence about CT for diagnosing cholecystitis. The study had unreliable estimates of specificity, as the confidence interval was below 0.50. The GDG agreed that there was insufficient evidence and decided not to make a recommendation based on the knowledge and experience of the group. They felt that other tests considered in this review are better at diagnosing cholecystitis.

For common bile duct stones: Three studies provided moderate quality evidence about CT for diagnosing common bile duct stones. The meta-analysis demonstrated that CT had satisfactory sensitivity and specificity estimates.

Overall: CT uses ionising radiation, and the sensitivity and specificity were found to be inferior to other tests, such as MRCP. Because of

this, the GDG felt that CT should not be recommended for diagnosing gallstone disease, as other tests are more sensitive, specific, and safer.

CT cholangiography (CTC)

For common bile duct stones: Evidence about CTC for common bile duct stones was provided by 4 studies. These showed that sensitivity and specificity were satisfactorily high, with reliable confidence intervals. However, the GDG decided not to recommend this test because the contrast agent needed to perform CTC (iotroxic acid) is not available in the UK. This test also exposes patients to ionising radiation, and the GDG felt that there were more accurate and safer tests for diagnosing common bile duct stones.

Endoscopic Ultrasound (EUS)

For common bile duct stones: Three studies provided low quality evidence about endoscopic ultrasound for diagnosing common bile duct stones. The meta-analysis demonstrated that endoscopic ultrasound had very high sensitivity and specificity estimates. However, the confidence intervals for specificity fell below 0.50, indicating that there is uncertainty about whether the test is clinically useful.

The GDG felt that these results did not reflect clinical reality, as EUS is becoming widely accepted as being an accurate test for diagnosing common bile duct stones. However, when ERCP is used as a reference standard against which to judge the accuracy of EUS, cases that are classified as false positives on EUS might actually be revealed as false negatives on ERCP, were a perfect reference standard with which to judge both tests available. Therefore, the GDG believed that such analyses may underestimate the accuracy of EUS.
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Liver function tests

For common bile duct stones: Three studies that could not be pooled examined predictors of common bile duct stones and included liver function tests among the variables that were examined. These studies examined different combinations of risk factors and so their results could not be meta-analysed. One study provided moderate quality evidence, and the other 2 provided very low quality evidence. All 3 studies found that liver function tests were clinically useful in predicting common bile duct stones. The GDG agreed that there was sufficient evidence to recommend the use of liver function tests for identifying common bile duct stones, as supportive evidence was provided by all 3 studies. The GDG based its decisions on the results of Shiozawa (2005), based on the moderate quality rating, large sample size, narrow confidence intervals and clinically useful sensitivity and specificity estimates. Like ultrasound, the GDG felt that liver function tests could be recommended because the test is widely available throughout the NHS and is of very low risk to the patient.

Magnetic Resonance Cholangiopancreatography (MRCP)

For cholecystitis: Two studies provided low quality evidence about

MRCP for diagnosing cholecystitis and demonstrated satisfactorily high estimates of sensitivity and specificity. Only one of these studies considered the presence of gallstones when diagnosing cholecystitis. The GDG felt that healthcare professionals would consider the presence of gallstones when making their diagnosis, and if this had been done in both studies included in the evidence, then diagnostic test accuracy would be more certain. The GDG felt that they could explain some of the uncertainty in the sensitivity and specificity estimates for MRCP, and so could be confident that this test is clinically useful.

For common bile duct stones**:** Eight studies provided moderate quality evidence about MRCP for diagnosing common bile duct stones. The meta-analysis demonstrated sufficiently robust sensitivity and specificity values, so the GDG was confident that MRCP was also clinically useful and should be recommended.

Magnetic Resonance Imaging- contrast enhanced (MRI- contrast enhanced)

For cholecystitis: The GDG agreed there was insufficient evidence to recommend MRI for cholecystitis, as evidence came from a single small study using contrast enhancement, which is not normally done in clinical practice today. Point estimates were satisfactorily high, but confidence intervals for specificity fell below 0.50, so the GDG were unsure if the test was useful. The GDG agreed not to make a recommendation about MRI based on the knowledge and experience of the group, as it felt that other tests considered in this review are better tests for diagnosing cholecystitis and conditions associated with gallstone disease.

Summary of all diagnostic methods

After reviewing and discussing the evidence, the GDG agreed that ultrasound, liver function tests, EUS and MRCP could be recommended for diagnosing gallstone disease. The GDG then discussed the sequencing of diagnostic tests and based these discussions on the group's knowledge and experience.

The evidence review in section 4.1 of this guideline discussed the 2 main ways that patients with gallstone disease present to health care services: either with typical signs, symptoms, and risk factors for gallstone disease, or with vague abdominal or gastrointestinal symptoms that can easily be misattributed to other conditions. Because of this, the group felt that ultrasound and liver function tests should be recommended as first line investigations for patients with suspected gallstone disease. In addition, these tests were recommended for patients with abdominal or gastrointestinal symptoms that are not responding to treatment as expected, since this group of patients may have 'unsuspected' gallstone disease. This was felt to be of benefit to both patients and the NHS as these tests are clinically useful, relatively cheap and widely available. Improving the identification of gallstone disease in people without typical symptoms would ultimately enable patients to progress to more appropriate investigations or treatment pathways.

The group then discussed if MRCP and EUS should both be offered as second line investigations.

	MRCP is widely available throughout the NHS, is relatively quick to perform on an outpatient basis, and requires no sedation. It is less effective at diagnosing common bile duct stones than EUS and is not an appropriate test for patients with metal implants or claustrophobia. The GDG agreed that EUS is a more accurate test than MRCP, but EUS is an invasive test and procedural errors could result in adverse effects for the patient (such as perforation and even death). The test is normally performed with the patient under sedation, which carries its own risks to the patient, and requires the patient to be accompanied by a responsible adult for 24 hours after sedation. People who do not have a responsible adult to escort them will need to be admitted to hospital. Furthermore, EUS is not as widely available throughout the NHS as other tests (such as MRCP) are. Although the GDG agreed that EUS was probably superior at diagnosing gallstone disease than MRCP when performed by highly skilled operators, there was acknowledgement that not all operators would be highly skilled. Although skilled operators should also perform MRCP, the GDG felt that there is less potential for harm if less skilled operators performed the test. This is because MRCP is non-invasive, and the entire diagnostic process is recorded. This means that poor quality or equivocal tests can be reviewed by another operator, who may be able to offer a diagnosis without having to investigate the patient again. EUS only records key images from the test, so a second reviewer would not be able to check unclear or poor quality tests and in these cases patients would need to have another test performed. The GDG agreed that in most cases MRCP would be safer and more acceptable to patients than EUS and recommended MRCP as a second line investigation and EUS as a third line investigation. However, the GDG wanted to stress that this should not preclude appropriately trained and experienced operators using EUS instead of MRCP if appropriate.
Consideration of Health Benefits and Resource Use	Limited published health economic evidence suggested that MRCP appears cost effective compared with ERCP for diagnosing CBDS. In most situations MRCP appeared more effective and less costly than ERCP. Despite the limitations of the evidence presented, the GDG felt that it supported the primary use of MRCP for diagnosing CBDS. The GDG noted that there was no health economic comparison available for many of the other diagnostic interventions under consideration.
Quality of evidence	Overall, the evidence was moderate to very low in quality. For gallbladder stones, only low quality evidence on ultrasound was found. For cholecystitis, low quality evidence on MRCP and CT and very low quality evidence on ultrasound and MRI was found. For common bile duct stones, moderate quality evidence was found on MRCP, CT, CT cholangiography, and for a model predicting

	common bile duct stones using liver function tests and other predictors. Low quality evidence was found for ultrasound and endoscopic ultrasound, and very low quality evidence was found for 2 models predicting common bile duct stones using liver function tests and other predictors.
Other considerations	None

4.2.6 Recommendations

1. **Offer liver function tests and ultrasound to people with suspected gallstone disease, and to people with abdominal or gastrointestinal symptoms that have been unresponsive to previous management**

2. **Consider magnetic resonance cholangiopancreatography (MRCP) if ultrasound has not detected common bile duct stones but the:**
   - **bile duct is dilated and/or**
   - **liver function test results are abnormal.**

3. **Consider endoscopic ultrasound (EUS) if MRCP does not allow a diagnosis to be made.**

4. **Refer people for further investigations if conditions other than gallstone disease are suspected.**

4.2.7 Research recommendations

1. **What are the long-term benefits and harms, and cost effectiveness of endoscopic ultrasound (EUS) compared with magnetic resonance cholangiopancreatography (MRCP) in adults with suspected common bile duct stones?**

Why this is important

MRCP and EUS have both been found to be sufficiently accurate for diagnosing common bile duct stones, with EUS regarded as the most accurate test. MRCP is non-invasive and so carries negligible risks to the patient. However, EUS carries a small but significant risk of patient harms, including death. There is insufficient evidence available to determine whether the benefits of improved diagnosis associated with EUS outweigh its procedural risks. Therefore, research is needed to compare MRCP with EUS to evaluate the subsequent management of common bile duct stones.

4.2.8 References

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4.3 Asymptomatic gallbladder stones

4.3.1 Review Question 3

What factors predict which patients with asymptomatic gallbladder stones will develop acute complications?

4.3.2 Evidence Review

The aim of this review question was to establish whether some people with asymptomatic gallbladder stones are at a higher risk of developing complications than others.

A systematic search (appendix D.3) retrieved 12,256 references. After removing duplicates and screening the references based on their titles and abstracts, 56 references were obtained and reviewed against the inclusion and exclusion criteria as described in the review protocol (appendix C.3).

Primary research using a randomised controlled trial, cohort or cross sectional design was eligible for inclusion. Two main types of study were expected to be found by the search: prospective studies recruiting a sample of the general population to identify and follow up people with asymptomatic gallbladder stones, and retrospective reviews of people presenting with symptomatic gallstone disease whose prior medical history was examined to identify whether asymptomatic gallbladder stones had previously been diagnosed. Both types of study were eligible for inclusion.

From the review, 55 studies were excluded, mainly because they provided prevalence and/or incidence data only. A list of the excluded studies and reasons for their exclusion is provided in appendix F.

One prospective cohort study met the eligibility criteria and was included. Data were extracted into detailed evidence tables (see appendix G.3) and are summarised in Table 5 below.

Appropriate methodology checklists were used to appraise the methodological quality of individual studies, and a modified version of the GRADE framework was applied to summarise the overall quality of the evidence (see appendix I.3). In this approach the prospective cohort study was started with a ‘high’ quality rating and was further downgraded as appropriate, according to standard GRADE framework. Overall this evidence was rated as very low in quality.

Table 5: Summary of included studies for question 3

Study reference	Population	Prognostic factors investigated	Results	Authors conclusions
(Attili et al. 1995) N=118 Italy	Patients with asymptomatic gallstones, followed up for 10 years	Age, sex, body mass index, awareness of having gallstones before diagnosis, gallbladder opacification, number of stones, diameter of stones, radiopacity of stones, occurrence of biliary colic.	• Biliary colic No significant predictors • Complications The low number of events meant that analysis was not possible • Cholecystectomy Occurrence of biliary colic predicted cholecystectomy • Death No associations between potential predictive factors and death were reported.	The natural history of gallstones is less benign than is generally considered

4.3.3 Health economic evidence

A literature search was conducted for review question 3 by applying standard health economic filters to the clinical search strategies (see Appendix D). From the search, 1004 references were retrieved, of which 9 were retained after title and abstract screening. No health economic studies were found for question 3. Health economic modelling was not prioritised for this review question.

4.3.4 Evidence Statements

Very low quality evidence from a single study examined predictors of symptomatic gallstone disease in patients who were asymptomatic at the time the trial was conducted. Insufficient data were reported in the study to validate the author's findings that the following variables are not significant predictors of the development of biliary colic, other complications, or death:

- age
- sex
- body mass index
- awareness of having gallstones before diagnosis
- gallbladder opacification
- number of stones
- diameter of stones

- radiopacity of stones.

Occurrence of biliary colic was not found to be a predictor of additional complications or death.

4.3.5 Evidence to Recommendations

Relative value of different outcomes	The evidence was based on the results of a single study. Only descriptive data and significance levels were provided, so secondary analysis for the purposes of this review could not be performed. As no meaningful results were provided by the evidence, the GDG based its decisions on the knowledge and experience of the group, and alongside evidence presented in section 4.4 of this guideline.
Trade off between benefits and harms	For people with asymptomatic gallbladder stones in a normal biliary tree, the GDG agreed that there is currently no way of predicting which people will go on to develop complications. Based on their experience, the GDG agreed that most people with asymptomatic gallbladder stones will not develop complications. However, once a patient has been informed that they have asymptomatic gallbladder stones, they may worry about their risk of developing complications in future, and may ask about having treatment prophylactically. Because of this, the discussions are linked to the evidence about managing asymptomatic gallbladder stones, which is reviewed and has recommendations on asymptomatic gallbladder stones made in section 4.4. After considering the evidence (see 'Evidence to recommendations', section 4.4.5), the GDG felt that the prophylactic treatment of asymptomatic gallstones is likely to have a higher risk than leaving them untreated as all of the treatment options carry risks of adverse effects (such as side effects of medication and surgery risks,). Therefore the GDG recommended that healthcare professionals should reassure patients that asymptomatic gallstones do not need treatment unless they develop symptoms (see section 4.4.6 of this guideline). The GDG felt that some people with asymptomatic gallbladder stones will have other abnormalities detected, either in their biliary tree (such as calcification of the gallbladder) or elsewhere in their body at the time of gallbladder stone detection. For this group of people, the GDG agreed that there is a need to perform further tests and investigations to rule in or rule out other diseases and conditions, such as cancer. It is not within the scope of this guideline to describe or review the evidence for the range of other conditions that should be investigated, so the GDG felt that they could not make recommendations about what a healthcare professional should do when other abnormalities coexist with asymptomatic gallstones.
Consideration of Health Benefits and Resource Use	No health economic evidence was found.
Quality of evidence	A single study providing very low quality evidence was not adequately powered to predict acute complications.

Other considerations	The GDG acknowledged that definitions of asymptomatic gallbladder stones may vary and so the following definitions were developed: • Asymptomatic gallbladder stones: – stones in the gallbladder that are found incidentally, as a result of imaging investigations unrelated to gallstone disease, in people who have been completely symptom-free for at least 12 months before diagnosis. • Symptomatic gallbladder stones: – gallbladder stones found on imaging of the gallbladder (the GDG felt that a person undergoing gallbladder imaging must be experiencing symptoms to prompt the investigation) – people with diagnosed gallbladder stones who have experienced any symptoms in the past 12 months.

4.3.6 Recommendations & Research Recommendations

No specific recommendations were made in relation to this question.

4.3.7 References

Attili AF, De SA, Capri R et al. (1995) The natural history of gallstones: the GREPCO experience. The GREPCO Group. Hepatology 21: 655-60

4.4 Managing asymptomatic gallbladder stones

4.4.1 Review Question 4a

Which strategies should be used for managing asymptomatic gallbladder stones?

4.4.2 Evidence Review

This question aimed to establish if prophylactic treatment should be offered to people with asymptomatic gallbladder stones, to prevent them from developing symptoms in the future.

A single search was performed for questions 4a, 4b, 4c and 5, which identified 10,976 references. After removing duplicates and screening the references based on their titles and abstracts, 210 references were obtained and reviewed against the inclusion and exclusion criteria for this review question (appendix C)., and 47 references met the overall inclusion criteria. Details of excluded studies and reasons for their exclusion are in appendix F.4.

None of the 47 included references met the criteria for this specific review question (see study flow chart, appendix E.4).

4.4.3 Health economic evidence

A literature search was conducted jointly for questions 4 and 5 by applying standard health economic filters to the clinical search strategies (see Appendix D). From the literature search, 1,396 references were retrieved for questions 4 and 5, of which none were retained for question 4a. Health economic modelling was not prioritised for this review question.

4.4.4 Evidence Statements

No evidence that met the inclusion and exclusion criteria for this question was found.

4.4.5 Evidence to Recommendations

Relative value of different outcomes	No evidence was available for this review question. The GDG based its decisions on the knowledge and experience of the group.
Trade-off between benefits and harms	The GDG discussed the potential benefits and harms of the various treatment options that were considered, using its knowledge and experience as no evidence was available: • Dissolution therapy is used to painlessly dissolve gallbladder stones using oral tablets. This is safe, relatively cheap and patients may express a preference for this type of treatment. However, patients have to take dissolution drugs over a long time period, and possibly for the rest of their life. Some people may find this inconvenient, particularly as they will not be experiencing any symptoms. These drugs often have side effects such as diarrhoea, and adherence to the drugs over the long term may be affected by this. Furthermore, the GDG highlighted that dissolution therapies only work for certain types of gallbladder stones. Since there are several types of gallbladder stones and no way of knowing which type the patient has without extracting and examining the stones,

there is no way of knowing for which people dissolution therapies will be effective.

- Lithotripsy for gallbladder stones uses ultrasound waves to break up gallstones into smaller pieces, with the idea that smaller pieces can pass naturally through the biliary system without causing any symptoms for the patient. This treatment requires an ultrasound probe to be placed over the abdomen, and is painless and non-invasive. However, the GDG highlighted that lithotripsy is less effective for large or multiple stones, and like dissolution therapy is less effective on certain types of stones. In addition, lithotripsy carries a small but significant risk of pancreatitis, which can be life threatening.
- Cholecystectomy is a radical treatment where the gallbladder is removed during a surgical procedure. Although this treatment is safe and effective, there is a risk of harms (as with any surgery) such as infection, bleeding, bile leaks and injuries to the bile duct, and general risks associated with undergoing anaesthesia, all of which are rare but can be life threatening.
- Watch and wait/conservative management is when there is no active treatment until the gallbladder stones begin to show symptoms. In this case there is no risk to the patient until they develop symptoms and begin active treatment.

After discussing the various treatment options, the GDG agreed that most people with asymptomatic gallbladder stones will not go on to develop complications, and so the risks of intervention outweigh the risks of leaving asymptomatic stones untreated. Furthermore, the GDG felt that the resource implications of treating asymptomatic gallbladder stones should be considered, since the GDG felt a large proportion of the general population have asymptomatic gallbladder stones. Offering unnecessary treatment to a large number of people would not be the best use of NHS resources.

The GDG also felt that it was important to discuss asymptomatic common bile duct stones, which were reviewed as part of question 4c (see section 4.6). No evidence about asymptomatic common bile duct stones was found, but the GDG felt that they were able to make recommendations based on their knowledge and experience.

Asymptomatic common bile duct stones are different to asymptomatic gallbladder stones.

- Asymptomatic gallbladder stones are confined to the gallbladder, as are complications such as acute cholecystitis. The complications of gallbladder stones can be life threatening but are rarely so. Deaths caused by gallbladder stone complications usually occur in people with other comorbidities.
- Asymptomatic common bile duct stones are stones that have moved out of the gallbladder and into the biliary system. Complications caused by common bile duct stones are not confined to the gallbladder and can affect other organs in the biliary system, such as the pancreas. Complications such as pancreatitis and cholangitis are more likely to be life threatening than acute cholecystitis, and deaths from these conditions commonly occur in

	people without other comorbidities. The group agreed that the risks associated with leaving asymptomatic common bile duct stones untreated outweighed the risks of treatment, and that common bile stones have an increased risk of serious complications than asymptomatic gallbladder stones. Therefore, the GDG agreed that asymptomatic common bile duct stones should be managed in the same way as symptomatic common bile duct stones (see section 4.6.5 for a discussion of this evidence). Recommendations about managing asymptomatic common bile duct stones are in section 4.6.
Consideration of Health Benefits and Resource Use	No health economic evidence was found.
Quality of evidence	No evidence was available.
Other considerations	The discussions around asymptomatic gallbladder stones that were linked to discussions around asymptomatic common bile duct stones were reviewed as part of review question 4c in section 4.6. The GDG discussed whether it would be useful to make a research recommendation about treating asymptomatic gallbladder stones, since there was no evidence to base their decisions on. The group agreed that an appropriate trial would be one that screened a large population to identify sufficient people with asymptomatic gallbladder stones, who would then need to be followed up for many years. The GDG felt that ideally, people included in such a trial should not be told that they have asymptomatic gallbladder stones identified, as it was felt that this knowledge could confound the findings of a trial. This is because once people are aware they have asymptomatic gallbladder stones they may report symptoms they would not have otherwise have noticed, or seek medical attention for symptoms that they would not have normally sought attention for. Since it would not be ethical to withhold information from patients, the GDG agreed that in reality there is no appropriate way to conduct primary research in this area. Therefore it was decided that a research recommendation should not be made.

4.4.6 Recommendations

5. Reassure people with asymptomatic gallbladder stones found in a normal gallbladder and normal biliary tree that they do not need treatment unless they develop symptoms.

4.4.7 Research Recommendations

No research recommendations were made in relation to this review question.

4.4.8 References

No references

4.5 Managing symptomatic gallbladder stones

4.5.1 Review Question 4b

Which strategies should be used for managing symptomatic gallbladder stones?

This question aimed to establish which management strategies offer optimal outcomes for patients with symptomatic gallbladder stones, including patients with acute cholecystitis.

4.5.2 Evidence Review

A single search was performed for review questions 4a, 4b, 4c and 5, which identified 10,976 references. After removing duplicates and screening the references based on their titles and abstracts, 210 references were obtained and reviewed against the inclusion and exclusion criteria for this review question (appendix C), and 47 references met the overall inclusion criteria. Details of excluded studies and reasons for their exclusion are in appendix F.4.

Of the 47 included references, 15 references relating to 9 randomised controlled trials met the inclusion criteria for this review question (see study flow chart in appendix E.4), which specifically focussed on comparisons of the following strategies for managing symptomatic gallbladder stones:

- Laparoscopic cholecystectomy alone vs laparoscopic cholecystectomy with intraoperative cholangiography (3 studies)
- Laparoscopic cholecystectomy vs cholecystostomy (no studies)
- Laparoscopic cholecystectomy vs conservative management (1 study, 6 references)
- Day-case laparoscopic cholecystectomy vs inpatient laparoscopic cholecystectomy for acute cholecystitis (5 studies)

Data from the 9 included randomised controlled trials were extracted into detailed evidence tables (see appendix G) and are summarised in Table 6 below. The included studies were critically appraised using randomised controlled trial methodology checklists. Data were then analysed using meta-analysis wherever appropriate (see appendix H.5 for all data analysis outputs).

Outcomes were assessed using the standard GRADE approach (see appendix I.5 for full GRADE profiles). In this approach, randomised controlled trials are started with a ‘high’ quality rating and are further downgraded as appropriate. Overall the evidence was moderate to low in quality.

Table 6: Summary of included studies for question 4b

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
(Amott et al. 2005) Australia N=315	Laparoscopic cholecystectomy with routine intraoperative cholangiography	Laparoscopic cholecystectomy with selective intraoperative cholangiography	Patients undergoing laparoscopic cholecystectomy between February 1995 and November 2002	Patients with a preoperative diagnosis of common bile duct stones and people who had undergone preoperative ERCP for suspected or proven CBDS.	No differences in operating times, retained CBDS or CBD injury, but recurrent biliary symptoms were easier to manage if IOC had been performed.
(Khan et al. 2011) UK N=190	Laparoscopic cholecystectomy	Laparoscopic cholecystectomy with intraoperative cholangiography	Patients referred to the upper GI surgical outpatient clinic for consideration for laparoscopic cholecystectomy	Under the age of 18 years, suspected of CBDS, history of allergic reaction to contrast material, previous major upper abdominal surgery ASA grade III or more, acalculous cholecystitis, patients with gallbladder polyps	Routine IOC does not seem justified for people with a low risk of CBDS
(Soper and Dunnegan 1992) USA N=115	Laparoscopic cholecystectomy	Laparoscopic cholecystectomy with intraoperative cholangiography	Consecutive patients undergoing attempted laparoscopic cholecystectomy	Patients with compelling reasons for or against intraoperative cholangiography were excluded	Laparoscopic cholecystectomy can be performed safely in the absence of IOC with little risk of CBD injury or retained CBDS
(Schmidt et al. 2011a; Schmidt et al. 2011b; Vetrhus et al. 2002; Vetrhus et al. 2003; Vetrhus et al. 2004; Vetrhus et al. 2005) Norway N= 201	Laparoscopic cholecystectomy	Conservative management	Patients with complicated and non-complicated gallbladder stones recruited between October 1991 and May 1994	Under 18 or over 80 years of age, severe concomitant disease, suspected common bile duct stones, acalculous cholecystitis, patients with localised peritonitis suggestive of gallbladder perforation or gangrenous cholecystitis	Conservative management carries a risk of subsequent gallstone events, but escalation of disease severity or increased mortality was not observed.
(Barthelsson et	Day-case	Planned inpatient	Ultrasonography documented	Not stated	Patients in both groups

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
al. 2008) Sweden N=100	laparoscopic cholecystectomy	admission for laparoscopic cholecystectomy	cholelithiasis, scheduled for planned laparoscopic cholecystectomy, ASA I-II, 20 to 70 years old.		recover equally well, indicating patients should be offered day-case procedures.
(Hollington 1999) Australia N=150	Day-case laparoscopic cholecystectomy	Planned inpatient admission for laparoscopic cholecystectomy	Patients presenting for elective cholecystectomy, who had an ASA status less than IV, adequate motivation levels	Patients who were assessed as being at risk of conversion to open surgery	Day-case management did not compromise patient outcomes. There was no advantage in cost savings compared with inpatient management.
(Johansson et al. 2006) Sweden N= 107	Day-case laparoscopic cholecystectomy	Planned inpatient admission for laparoscopic cholecystectomy	Patients presenting for gallstone disease surgery between the ages of 18 and 70 years	ASA score of III or IV, extreme obesity, patients with extensive abominal surgery, those with a clincial suspicion of common bile duct stones or a history of acute cholecystitis or pancreatitis were considered unsuitable for outpatient surgery	Day-case procedures can be performed and have a low rate of complications and admissions / readmissions. Day-case options are acceptable to patients and are associated with reduced cost.
(Keulemans et al. 1998) The Netherlands N= 80	Day-case laparoscopic cholecystectomy	Planned inpatient admission for laparoscopic cholecystectomy	Patients indicated for cholecystectomy due to symptomatic cholelithiasis confirmed by ultrasound	ASA III and IV, patients older than 70 years, and patients with extensive previous abdominal surgery, clinical suspicion of bile duct stones, acute cholecystitis, and calcified gallbladder	Effectiveness was equal in both groups and patients appear satisfied with their treatment. Day-case procedures are preferable because it is less expensive.
Young (2008) Australia N= 28	Day-case laparoscopic cholecystectomy	Planned inpatient admission for laparoscopic cholecystectomy	Patients undergoing laparoscopic cholecystectomy aged 50 and under, ASA II or less, and who spoke English were approached in the preadmission clinic.	Not stated	With careful selection of patients, LC cases performed as day procedures did not impact at all on the patients' recovery trajectory

4.5.3 Health economic evidence

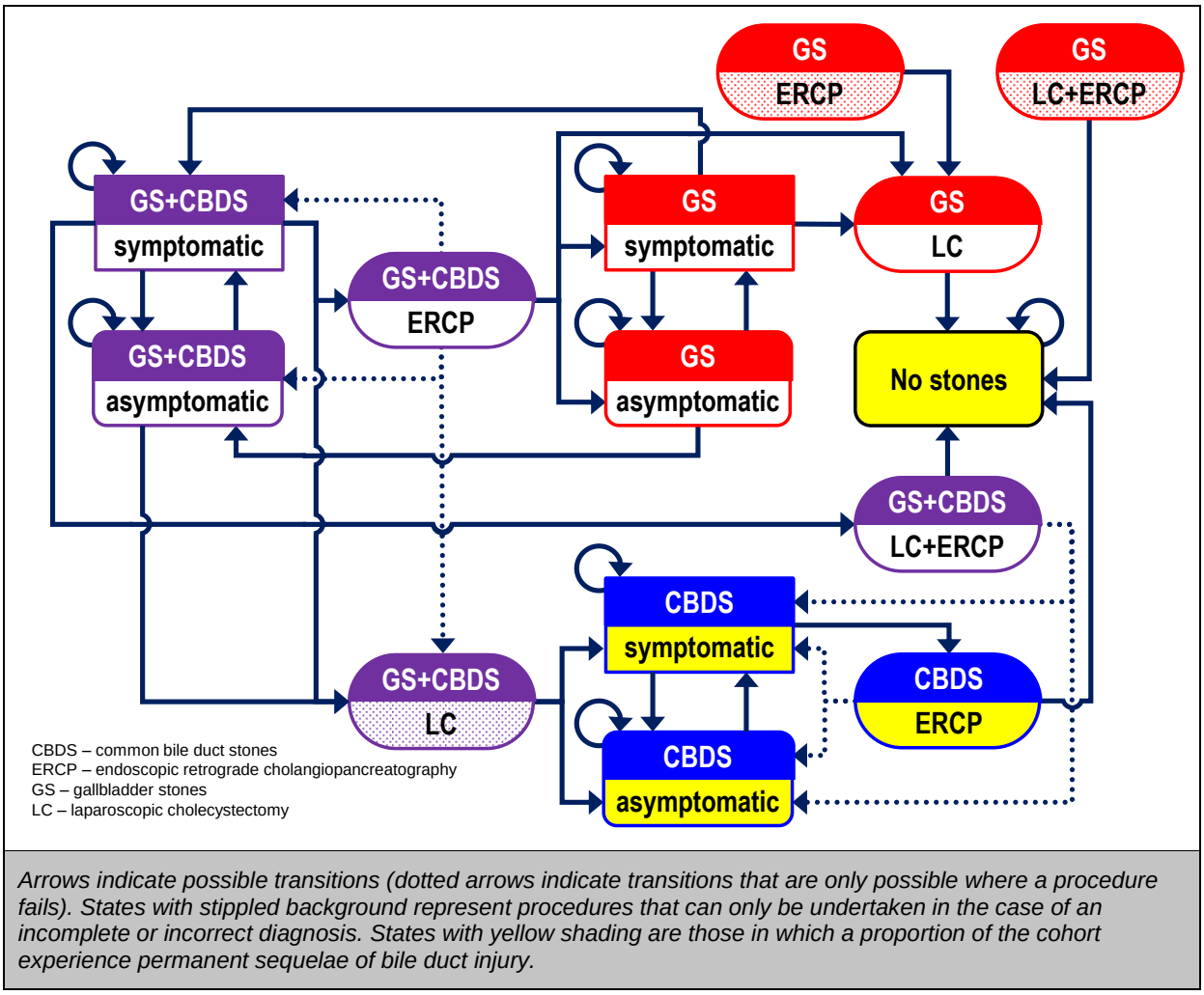
A literature search was conducted jointly for questions 4 and 5 by applying standard health economic filters to the clinical search strategies (see Appendix D). From the search, 1,396 references were retrieved for questions 4 and 5, of which 1 was retained for question 4b and 1 was retained for question 5. As no existing health economic studies were found that addressed all the comparisons in questions 4 and 5, an original economic model was constructed.

4.5.3.1 Original health economic modelling – methods

A full description of the health economic model can be found in in Appendix J; a summary is presented here. The model was developed in line with the NICE reference case (National Institute for Health and Care Excellence 2013). A single health economic model structure was developed to address all prioritised comparisons under questions 4b, 4c and 5. For question 4b, no evidence was found to enable the modelling of the percutaneous cholecystostomy comparison.

A single Markov structure with 2-week cycles was used to assess all comparisons (see Figure 1). Not all states and transitions were used in each comparison (see Appendix J for descriptions of the states and transitions available for each comparison). A lifetime horizon was adopted to capture the long term impact of bile duct injuries and mortality differences. The model is a natural history rather than a diagnosis model, so the model “knows” whether a patient has CBDS, irrespective of whether the patient or clinician knows.

Surgical interventions (laparoscopic cholecystectomy and ERCP, or both together) are represented as 2-week states, with short term surgical consequences (including mortality) modelled as cost and QALY impacts within one 2-week state. Laparoscopic cholecystectomy can cause bile duct injury.



Arrows indicate possible transitions (dotted arrows indicate transitions that are only possible where a procedure fails). States with stippled background represent procedures that can only be undertaken in the case of an incomplete or incorrect diagnosis. States with yellow shading are those in which a proportion of the cohort experience permanent sequelae of bile duct injury.

Figure 1: Gallstones Health Economic Model Diagram

Symptoms modelled are mutually exclusive and specific to gallbladder stones (biliary colic, acute cholecystitis) or CBDS (cholangitis, jaundice, pancreatitis [with associated mortality risk], sepsis).

Where possible, model parameters (symptoms at baseline or during treatment, operative consequences as prioritised by the GDG) are sourced from the included clinical studies, with data from standard laparoscopic cholecystectomy or ERCP trial arms combined to increase parameter accuracy.

Costs are based on 2011–12 NHS reference costs (Department of Health 2012). As the GDG identified length of stay as a critical outcome, resource use was based on length of stay differences reported in the included clinical studies.

There are few EQ-5D-based utility values for gallstones, so SF36 data were converted to utility values (Ara and Brazier 2008). The quality of life impact of interventional procedures reflects length of stay, but is assumed to return to normal within 2 weeks, unless a bile duct injury occurred (assumed to have lifelong impact). All symptoms are assumed to have the same utility impact. The utility impact of living with asymptomatic gallbladder stones were taken from a study of urinary stones (Penniston and Nakada 2007).

The health economic model has a number of limitations that should be considered. A number of key parameters are based on the included clinical evidence that has wide confidence intervals; zero event rates in 1 arm are common. A lack of gallstone-specific utility values required a number of assumptions to be made regarding the QALY outcomes. Interventions

are costed using average costs – micro-costing of interventions may help identify differences between options, but may limit the generalisability of the model.

4.5.3.2 Original health economic modelling – results

Table 7: Cost effectiveness results for laparoscopic cholecystectomy versus conservative management

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Laparoscopic cholecystectomy	£2516.33	16.009			
Conservative Management	£11,028.41	15.323	£8512.07	−0.686	Dominated

(a) Results represent means of 1,000 probabilistic model runs

The health economic model found that conservative management is more costly and produces fewer QALYs than laparoscopic cholecystectomy and is therefore said to be dominated (see Table 7). This remained true in 100% of probabilistic model runs. It appears that not removing the gallbladder increases the need for and exposure to further ERCPs and also gallbladder cancer.

Table 8: Cost effectiveness results for laparoscopic cholecystectomy with intraoperative cholangiography versus laparoscopic cholangiography alone

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Laparoscopic cholecystectomy	£2475.10	16.008			
Laparoscopic cholecystectomy with IOC	£2612.50	15.997	£137.41	−0.010	Dominated

(a) Results represent means of 1,000 probabilistic model runs

The health economic model found that, on average, laparoscopic cholecystectomy with routine intraoperative cholangiography is more costly and produces fewer QALYs than laparoscopic cholecystectomy alone and is therefore said to be dominated (see Table 8). This result is driven by the increased costs of higher laparoscopic to open cholecystectomy conversion rates and uncertain rates of bile duct injury and bile leak in the intraoperative cholangiography arm - neither of the latter were statistically significant. In probabilistic sensitivity analysis, laparoscopic cholecystectomy alone has a 67% chance of being cost effective at a threshold of £20,000 per QALY compared with laparoscopic cholecystectomy with intraoperative cholangiography.

Table 9: Cost Effectiveness Results for Day Case versus Inpatient Laparoscopic Cholecystectomy

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Day-case laparoscopic cholecystectomy	£2534,65	15.887			
Inpatient laparoscopic cholecystectomy	£2932.24	15.998	£397.59	0.111	£3568 / QALY

(a) Results represent means of 1,000 probabilistic model runs

Inpatient laparoscopic cholecystectomy costs more and produces more QALYs than day-case laparoscopic cholecystectomy, at an acceptable cost of QALY of £3568/QALY (see Table 9). The increased costs are driven by the additional length of stay in the inpatient arm. The QALY gains result from a higher estimated bile duct injury rate in the day-case cohort; however, this rate should be interpreted with caution as it is based on 1 event in the day-case arm and 0 events in the inpatient arm. This uncertainty is reflected in probabilistic sensitivity analysis, in which inpatient laparoscopic cholecystectomy has a 56% chance of being cost effective at a threshold of £20,000 per QALY compared with day case laparoscopic cholecystectomy. Therefore, it may be more appropriate to view inpatient

laparoscopic cholecystectomy as more expensive than day-case laparoscopic cholecystectomy with comparable QALY outcomes.

4.5.4 Evidence Statements

One study provided low quality evidence about conservative management in comparison with laparoscopic cholecystectomy, and there was some evidence that laparoscopic cholecystectomy was superior to conservative management. Readmission rates were lower in the laparoscopic cholecystectomy group than the conservative management group, and 44% of people in the conservative management group also required cholecystectomy

Three studies provided moderate to low quality evidence about laparoscopic cholecystectomy in comparison with laparoscopic cholecystectomy with intraoperative cholangiography and there was uncertainty about whether the addition of intraoperative cholangiography was beneficial or not since there were no significant differences between the groups on any of the outcomes.

No evidence was available comparing cholecystostomy to laparoscopic cholecystectomy, and so no conclusions can be drawn.

Five studies providing moderate to low quality evidence compared day-case laparoscopic cholecystectomy with planned inpatient laparoscopic cholecystectomy. No differences in readmission rate or quality of life were found. Unplanned inpatient admissions were required in 12.1% of planned day case procedures.

A directly applicable original health economic model analysis with minor limitations suggests laparoscopic cholecystectomy is cost effective compared with conservative management. Comparisons of laparoscopic cholecystectomy with laparoscopic cholecystectomy and intra-operative cholangiography and day-case with inpatient laparoscopic cholecystectomy were limited by the quality of the clinical evidence.

4.5.5 Evidence to Recommendations

Relative value of different outcomes	In general, studies were underpowered for the outcomes that the GDG had chosen and so confidence intervals relating to effect estimates for many outcomes were wide. This was expected, since events such as mortality and bile duct injury are relatively rare and sample sizes would need to be very large to observe sufficient rare events. There was also a lack of randomised controlled trial (RCT) evidence for some of the comparisons that were considered as part of this review. The GDG felt that it is generally accepted that cholecystectomy is safe and effective, and that conducting clinical trials where participants for whom cholecystectomy is appropriate are randomised to a treatment that may be less effective may be seen as unethical, thus limiting the amount of RCT evidence that is available.
Trade off between benefits and harms	**Laparoscopic cholecystectomy compared with conservative management** The evidence comparing conservative management to laparoscopic cholecystectomy was limited. Only 1 underpowered study met the inclusion criteria. The evidence showed that disease progression was statistically significantly lower in patients offered cholecystectomy compared with conservative management, but there were no statistically significant differences between the groups in terms of

readmission, or mortality. Other outcomes that the GDG felt were critical to their decision making (requirement for additional intervention, and length of stay) were not reported by the study. The GDG agreed that the results imply that conservative management is only suitable as a temporary management strategy, as patients offered conservative management continued to have recurrent biliary events. This supports the GDG's views that once a gallbladder develops gallstones, it will continue to do so, and that the only way of stopping gallstone formation and preventing recurrent biliary events is cholecystectomy.

The GDG agreed that laparoscopic cholecystectomy has been established as a relatively safe procedure, and the risks of disease progression outweigh the risks of this type of surgery. Of course all surgeries carry some risks, particularly for people with complex, multiple conditions and for these patients the risk of surgery may well outweigh the risk of disease progression. Furthermore, some patients may choose not to opt for surgical treatment. Thus, the GDG agreed that conservative management should only be considered when cholecystectomy is not appropriate, and felt that this is standard practice across the NHS already and so did not require a specific recommendation to be made.

However, the GDG did feel that sometimes older patients and those with comorbidities may be assumed to be inappropriate for laparoscopic cholecystectomy before they have even been assessed. Therefore the group felt the need to reinforce the message that laparoscopic cholecystectomy is becoming increasingly safer and that it is inappropriate not to offer this treatment to someone where the risks of disease progression outweigh the risks of surgery. The GDG felt justified in making a strong recommendation to offer laparoscopic cholecystectomy to all patients with symptomatic gallbladder stones, since there is sufficient acceptance of this procedure in the clinical community which is supported by the GDG's experience, health economic evidence, and by a small amount of clinical evidence found in this review.

Laparoscopic cholecystectomy compared with percutaneous cholecystostomy

No evidence that met the inclusion criteria was available about comparing percutaneous cholecystostomy to laparoscopic cholecystectomy and so the GDG discussed this treatment option by reflecting on its knowledge and experience.

Percutaneous cholecystostomy is widely accepted to be a safe and effective treatment for patients with a gallbladder obstruction. The GDG felt that percutaneous cholecystostomy is only used when cholecystectomy is not an appropriate treatment option (either because of patient preferences or clinical judgement), and that this is standard practice across the NHS. However, the GDG agreed that there is inappropriate variation in the way that patients are managed once a percutaneous cholecystostomy has been placed. This was attributed to the fact that patients presenting with symptomatic gallbladder stones will usually be admitted to a surgeon, and when surgery is identified as not being an appropriate treatment option, the patient is then considered for percutaneous cholecystostomy. The GDG felt that some patients are never reassessed for cholecystectomy, even when their clinical condition has improved

making surgery an appropriate option for them. The GDG agreed that there is a high incidence of recurrent gallbladder sepsis in this group of patients which has a high risk of mortality associated with it. Thus, the GDG agreed to recommend that patients with percutaneous cholecystostomy should be reviewed for reconsideration for cholecystectomy once adequate drainage has been established and the acute episode has resolved in order to minimise the risk of recurrent sepsis and mortality.

Laparoscopic cholecystectomy compared with laparoscopic cholecystectomy with intraoperative cholangiography (IOC)

Intraoperative cholangiography is performed during laparoscopic cholecystectomy to improve the safety of the procedure, by improving visualisation of the biliary anatomy and therefore reducing bile duct injuries, and it can also identify common bile duct stones that weren't suspected at earlier diagnostic work up. The evidence review considered the use of routine IOC, selective IOC, and not using IOC at all, but there were no statistically significant differences for any of the outcomes that the GDG had chosen to base its decisions on. The GDG felt that this was because the studies were underpowered, and so were not confident in these findings. Thus, the discussions about IOC were based on the knowledge and experience of the GDG.

The GDG acknowledged that the individual studies included in the review drew mixed conclusions about whether IOC was useful or not, and this reflected current differences in clinical opinions about the usefulness of the procedure. The GDG reflected on its knowledge and experience and agreed that using IOC to improve visualisation of biliary anatomy offers clear benefits during laparoscopic cholecystectomy. This is because improved visualisation improves the surgeon's ability to plan and progress with laparoscopic cholecystectomy, making it safer for the patient. Because of this the GDG agreed that it is desirable for all surgeons performing laparoscopic cholecystectomy to be competent in IOC.

However, there was further debate in relation to the benefits and harms of IOC for detecting common bile duct stones, and these discussions linked to evidence about managing common bile duct stones which is presented in section 4.6 of this guideline, where it was agreed that all common bile duct stones need to be removed, regardless of whether they are causing symptoms or not.

Common bile duct stones found during IOC can be removed laparoscopically by a surgeon who has undergone specialist training. Most surgeons trained to do laparoscopic cholecystectomy do not have this specialist training and will not remove bile duct stones laparoscopically. Alternatively, common bile duct stones can be removed endoscopically. This can be done pre-, intra-, or post-operatively by someone who has undergone specific endoscopy training. Although some surgeons are appropriately trained for performing endoscopies, the majority of surgeons trained to perform laparoscopic cholecystectomy are not, and surgical lists are not usually planned with both a surgeon and an endoscopist in attendance. Thus the GDG agreed that few teams would be equipped to deal with common bile duct stones that might be identified. The GDG felt that once common bile duct stones are discovered, they

need removing either at the time of discovery or within 2 or 3 days. Thus, if an unequipped team discovered stones the team would need to make an unplanned and urgent call for an appropriately trained person to remove the stones during the operation. Alternatively stones would need to be left in situ and the patient rescheduled for another intervention, thus exposing the patient to the risk of the stone developing serious complications during the wait, and the risks associated with undergoing a second intervention (such as risks of anaesthesia and procedural errors). Thus the group agreed that there was insufficient evidence of benefit to support a recommendation about using IOC for diagnosing common bile duct stones, or when inadequate preoperative diagnostic tests have been performed. Instead, the GDG felt that good preoperative examinations using diagnostic methods outlined in section 4.2 would improve the chances of common bile duct stones being identified preoperatively so that subsequent cholecystectomy can be planned to deal with common bile duct stones by appropriate surgeons and/or endoscopists.

Overall, the GDG felt that IOC is beneficial for visualising the biliary anatomy and making laparoscopic cholecystectomy safer, and because of this surgeons performing laparoscopic cholecystectomy should be competent to use the procedure. However, the use of IOC varies in current clinical practice as there are uncertainties about its potential harms when unexpected common bile duct stones are discovered by surgeons who do not have specialist training to remove the stones laparoscopically. Thus the GDG decided not to make a recommendation about IOC. Instead a research recommendation was made to support the development of more research to explore the potential benefits and harms of this procedure.

The GDG also wanted to stress that the lack of a recommendation should not preclude suitably trained individuals from using IOC at their discretion in the appropriate clinical situations.

Day-case laparoscopic cholecystectomy compared with inpatient stay laparoscopic cholecystectomy

The choice about whether to perform laparoscopic cholecystectomy as a day-case procedure or as planned inpatient admission was also reviewed. The evidence revealed that there were no statistically significant differences for any of the outcomes that the GDG had chosen to base their decisions on. Furthermore, the GDG acknowledged that some of the evidence included in this comparison came from older studies that might not accurately reflect continuing improvements in surgical outcomes that have occurred over time. Thus the discussions about day-case or planned inpatient admission were based on the knowledge and experience of the GDG.

The GDG agreed that there are no differences in important outcomes between day-case and inpatient procedures. The GDG discussed whether day-case surgery should always be offered to patients, since it offers the benefits of enabling the patient to return home sooner, reducing the risk of hospital acquired infections, and reducing the use of NHS resources.

However, there are various patient and clinical factors that need to be taken into consideration. For example, patients require adult

	supervision for 24hours after cholecystectomy and people who do not have someone at home to supervise them will require an inpatient stay. Similarly, some patients with comorbidities may need admitting to hospital before or after the operation to manage their other conditions. Thus the GDG felt that decisions about whether to plan day-case or inpatient cholecystectomy should be decided at a local level on a case by case basis to take the various patient and clinical factors into account.
Consideration of Health Benefits and Resource Use	For laparoscopic cholecystectomy compared with conservative management, the economic model suggests the costs and health benefits of surgery outweigh the health detriment of leaving the gallbladder in situ and having recurrent biliary events. The GDG noted the economic model considered this question as a binary choice – either removing the gallbladder or leaving it in situ – that is unlikely to occur in clinical practice. In sensitivity analyses, the economic model almost always produces higher costs and lower QALYs, but did not specifically consider older patients with comorbidities. For laparoscopic cholecystectomy versus laparoscopic cholecystectomy with intra-operative cholangiography, the economic model suggests laparoscopic cholecystectomy is a more cost-effective option. However, this reflects clinical evidence of small non-statistically significant differences in rates of operative consequences, in which the GDG were not confident. Probabilistic analysis of the model suggested laparoscopic cholecystectomy was the cost-effective option in around 2/3 of cases over a wide range of assumed values of 1 QALY, so intra-operative cholangiography may be cost effective in some situations and when done by appropriately trained surgeons Whilst the comparison of day case to inpatient laparoscopic cholecystectomy suggests inpatient laparoscopic cholecystectomy is more cost effective, this again is based on clinical evidence of small non-statistically significant differences (in bile duct injury rates) in which the GDG were not confident. Increased costs of inpatient laparoscopic cholecystectomy were driven by higher lengths of stay. It may be more appropriate to view inpatient laparoscopic cholecystectomy as more expensive than day-case laparoscopic cholecystectomy with comparable QALY outcomes.
Quality of evidence	Evidence was of moderate to low quality, and some comparisons had no evidence at all.
Other considerations	None

4.5.6 Recommendations

6. **Offer laparoscopic cholecystectomy to people diagnosed with symptomatic gallbladder stones.**

7. **Offer day-case laparoscopic cholecystectomy for people having it as an elective planned procedure, unless their circumstances or clinical condition make an inpatient stay more appropriate.**

8. **Offer percutaneous cholecystostomy to manage gallbladder empyema when:**
   - **surgery is not appropriate at presentation and**
   - **conservative management is unsuccessful.**

9. **Reconsider laparoscopic cholecystectomy for people who have had percutaneous cholecystostomy once they are well enough for surgery.**

4.5.7 Research recommendations

2. **What are the benefits and harms, and cost effectiveness of routine intraoperative cholangiography in people with low to intermediate risk of common bile duct stones?**

Why this is important

In the evidence reviewed for this guideline, there was a lack of randomised controlled trials of intraoperative cholangiography. Therefore, there is a need for large, high-quality trials to address clinical questions about the benefits and harms of intraoperative cholangiography.

4.5.8 References

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Vetrhus M, Soreide O, Nesvik I et al. (2003) Acute cholecystitis: delayed surgery or observation. A randomized clinical trial. Scandinavian Journal of Gastroenterology 38: 985-90

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4.6 Managing common bile duct stones

4.6.1 Review Question 4c

Which strategies should be used for managing common bile duct stones?

4.6.2 Evidence Review

A single search was performed for questions 4a, 4b, 4c and 5 which identified 10,976 references. After removing duplicates and screening the references based on their titles and abstracts, 210 references were obtained and reviewed against the inclusion and exclusion criteria for this review question (appendix C), and 47 references met the inclusion criteria overall. Details of excluded studies and reasons for their exclusion are in appendix F.4.

Of the 47 included references, 24 references relating to 24 randomised controlled trials were included in this review question (see study flow chart, appendix E.4) which specifically addressed the following comparisons for managing common bile duct stones:

- ERCP vs conservative management (9 studies)
- ERCP and laparoscopic cholecystectomy vs ERCP alone (2 studies)
- (pre-, intra-, post- operative) ERCP clearance of the bile duct plus laparoscopic cholecystectomy compared with surgical clearance of the bile duct plus laparoscopic cholecystectomy (12 studies)
- Uncleared duct with biliary stent vs cleared duct (1 study)
- Day-case ERCP vs planned inpatient ERCP (no studies)

Data were extracted into detailed evidence tables (see appendix G.4) and are summarised in Table 10 below. Each study was assessed for methodological quality using randomised controlled trial checklists, and some studies had methodological flaws which impacted on the overall quality of the evidence. For example, some studies didn't report randomisation procedures and those that did sometimes used inappropriate methods (patient identifying numbers – Hong, 2006), or had methods that led to differences in baseline characteristics of the groups (for example, Hui, 2002) which could bias results.

Data from multiple studies were available for most of the comparisons; therefore, meta-analysis was performed wherever possible (see appendix H.7). In addition, network meta-analysis was possible to compare the different methods for ERCP clearance of the duct (pre-, intra-, or post- operative) in comparison with surgical clearance. Standard GRADE approaches were used to assess pairwise comparisons, and a modified version of the GRADE framework was used to assess the evidence analysed using network meta analysis (see appendix I.6 for full GRADE profiles). In the modified approach, the standard GRADE criteria still apply but additional factors are also considered such as how each 'link' or pairwise comparison within the network applies to the others (see NICE clinical guideline CG173, appendix D for details of the additional factors that may be considered in a network meta analysis). However, since the network of evidence for this review question was relatively small, very few of the additional criteria actually applied. Details of the specific reasons for downgrading are stated in the footnotes of the relevant GRADE profiles in appendix I.6.

Table 10: Summary of included studies for question 4c

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
(Boerma et al. 2002) The Netherlands N=120	ERCP with laparoscopic cholecystectomy 6 weeks later	ERCP alone	Patients who underwent sucessful endoscopic sphincterotomy and extraction of common bile duct stones who had radiologically proven stones in the gallbladder	Patients unfit for surgery (ASA IV and V)	A wait and see policy after ERCP cannot be recommended since 47% of patients in the ERCP alone group developed recurrent biliary events.
(Lau et al. 2006) China N=178	ERCP with laparoscopic cholecystectomy as soon as practical	ERCP alone	Patients older than 60 years of age, who received complete endoscopic sphincterotomy, radiological evidence of an intact gallbladder containing gallbladder stones, no previous hospitalisation for cholecystitis.	Evidence of intrahepatic stones, radiological evidence of recurrent pyogenic cholangitis, intercurrent malignancy with a limited life span, or deemed unfit for cholecystectomy (ASA IV or V)	Cholecystectomy after ERCP reduces recurrent biliary events and should be recommended.
(Acosta et al. 2006) USA N=61	ERCP	Conservative management	Age over 18 years, symptoms consistent with gallstone pancreatitis and ampullary obstruction, admission within 48hrs of onset of symptoms, serum amylase or lipase levels at least 2 times the upper normal limit, serum bilirubin grater or equal to 1.4mg/dL, objective demonstration of gallstones,	Alcoholism or other causes of pancreatitis, severe cholangitis, coagulation disorder, cirrhosis, contraindication to general anaesthesia, previous Billroth II procedure.	In patients with gallstone pancreatitis and ampulary obstruction, limiting the duration of obstruction to no longer than 48hrs by ERCP decreased morbidity.
(Fan et al. 1993) Hong Kong N= 195	ERCP during acute phase	Conservative management followed by ERCP after the acute episode had subsided	Patients with acute pancreatitis	Not stated	Emergency ERCP is indicated in patients with acute pancreatitis
(Folsch et al.	ERCP	Conservative	Patients with pain in the upper	Pregnant, coagulation	In patients with acute

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
1997) Germany N=238		management	abdomen, serum amylase or lipase 3 times higher than the upper normal limit, Signs of acute pancreatitis on ultrasound or CT scan, bilirubin level lower than 5mg per deciliter, ability to perform ERCP within 72 hours of pain, age over 18 years, biliary origin of pancreatitis	abnormalities, alcoholism or metabolic cause of pancreatitis, included in this study or another study simultaneously	biliary pancreatitis but without obstructive jaundice, ERCP was not beneficial.
(Hui et al. 2002) China N=111	ERCP	Conservative management	Patients admitted to the department of medicine for acute cholangitis with gallbladder stones	Patients were excluded if ERCP detected common bile duct stones, interhepatic choellithiasis, or malignant obstruction.	ERCP in patients with acute cholangitis without CBDS decreased the duration of cholangitis and reduced hospital stay, but did not decrease the incidence of recurrent acute cholangitis
(Neoptolemos et al. 1988) UK N= 121	ERCP	Conservative management	Consecutive patients with acute pancreatitis	Pregnant, under 18 years of age, history of chronic alcoholism or acute alcohol intake, presence of an identifiable secondary cause of the attack of pancreatitis such as drugs, hyperlipidaemia, trauma or surgery	ERCP, in comparison with conservative management, offered fewer complications, and shorter hospital stay for patients with severe pancreatitis
(Nitsche et al. 1995) Germany N=138	ERCP	Conservative management	Acute biliary pancreatitis, pain in the upper abdomen, amylase or lipase more than 3 times the upper normal limit, bilirubin <5mg/dl, ERCP can be performed within 72 hours of onset of pain	Obstructive jaundice, under 18 years of age, pregnant, coagulopathy, alcoholism or metabolic cause for pancreatitis, included in this or another study simultaneously.	ERCP is not superior to conservative management for acute biliary pancreatitis, but people with biliary complications (jaundice, sepsis, and cholangitis) should receive urgent ERCP.
(Oria et al. 2007)	ERCP	Conservative management	All patients who presented to the emergency ward within 48hrs of the onset of gallstone	Serious comorbid conditions that precluded ERCP, under the age of 18 years, pregnant,	No evidence that ERCP reduces systemic and local inflammation in

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
Argentina N= 103			pancreatitis	acute cholangitis	patients with gallstone pancreatitis and acute biliary obstruction. If acute cholangitis can be excluded, ERCP is not mandatory.
(Vracko et al. 2006) Sweden/ Slovenia N=105	ERCP	Conservative management	Consecutive and unselected series of elderly patients over 65years of age with acute cholecystitis	Not stated	ERCP improves the clinical course for the majority of elderly patients suffering from acute cholangitis.
(Zhou and Prasoon 2012) China N= 45	ERCP	Conservative management	Patients admitted to hospital for acute gallstone pancreatitis	Not stated	It is safe to apply ERCP in the treatment of severe acute gallstone pancreatitis.
(Chopra et al. 1996) UK N= 43	Biliary stent in uncleared bile duct	Ductal clearance using ERCP	Patients aged 70 and older, or younger with serious debilitating disease with a single duct stone greater than 10mm in diameter or 2 or more stones of any size	Not stated	For immediate bile duct drainage, stent insertion proved safe and effective alternative to duct clearance.
(Bansal et al. 2010) India N=30	Preoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Patients with symptomatic gallstones and CBDS with a diameter more than 10mm	Not stated	The results showed equivalent success rate in terms of mortality and hospital stay. Laparoscopic approach seems to be favourable because of the smaller number of procedures and hospital visits
(Cuschieri et al. 1999) UK, Italy, Spain, Australia, Portugal, The	Preoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	ASA I or II patients who were suspected or had proved ductal calculi based on clinical features (jaundice, recent acute pancreatitis), liver function tests (elevated bilirubin, alkaline	Not stated	The results demonstrate equivalent success rates and patient morbidity for the two management options but significantly shorter hospital stay with

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
Netherlands N=300			phosphatase) and external ultrasound findings. Investigations such as CT was optional.		the single stage laparoscopic treatment.
(Ding et al. 2013) China N=221	Preoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Patients aged 16 to 70 years, clinical presentation with biliary colic with or without jaundice, serum elevation of at least one of the following: aspartate aminotransferase, alanine aminotransferase, glutamyl transpeptidase, alkaline phosphatase, total bilirubin, Radiological findings suggestive of gallstones and concomitant common bile duct stones, with abdominal ultrasound showing possible CBDS or a dilated CBD >8mm in diameter. Patients meeting these criteria underwent MRCP and only those with MRCP evidence of CBDS were randomised	Active acute pancreatitis. Pregnancy, septic shock, intrahepatic gallstones, malignant pancreatic or biliary tumours, prior sphincterotomy, unfit for anaesthesia and surgery, contraindications for to MRCP and ERCP, liver cirrhosis, pervious history of abdominal surgery, inability to give informed consent	Single stage and multistage approaches were equally effective in achieving initial clearance of CBDS. However, recurrent CBDS occurred more commonly in patients who had undergone two stage treatment.
(ElGeidie 2011a) Egypt N=226	Intraoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Patients with suspected common bile duct stones based on positive ultrasound, laboratory data, MRCP and intraoperative cholangiography. Patients were included if they satisfied the following criteria: aged between 16 and 80 years; clinical, radiological and laboratory evidence suggestive of biliary obstruction, MRCP findings suggestive of choledocholithiasis,	Acute cholangitis, gallstone pancreatitis, ASA grades IV and V, suspected CBD malignancy, previous cholecystectomy, pregnancy, contraindications to MRCP or ERCP due to previous gastrectomy, contraindications to laparoscopic surgery due to previous upper abdominal surgery and marked liver cirrhosis.	Both procedures were shown to be safe, effective and minimally invasive, but the intraoperative ERCP approach may be preferred when facilities and experience in endoscopic therapy exist.

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
			intraoperative cholangiogram findings of choledocholithiasis		
(ElGeidie 2011b) Egypt N=198	Preoperative ERCP plus laparoscopic cholecystectomy	Intraoperative ERCP plus laparoscopic cholecystectomy	Patients with suspected CBDS who were admitted to hospital. Pre-operative diagnosis was based on a combination of clinical assessment (biliary colic with or without jaundice), liver chemistry (Serum elevation of at least one of the following enzymes: aspartate amino transferase, alanine amino transferase, gamma glutamyl transpeptidase, alkaline phosphatase, total bilirubin), and abdominal ultrasound (Showing possible CBD stones or a dilated CBD >8mm). Patients meeting the inclusion criteria underwent MRCP and only patients with MRCP evidence of CBDS were included.	Patients without evidence of CBDS of MRCP, patients with cholangitis, pancreatitis, patients <18 years or >80 years of age, ASA IV and V, suspected CBD malignancy, previous cholecystectomy, pregnancy, contraindications to laparoscopic surgery as previous upper abdominal surgery and marked liver cirrhosis.	Both treatments are good options for dealing with preoperatively diagnosed CBDS, but when there is enough experience and facilities intraoperative ERCP as a single stage treatment would be preferable.
(Hong et al. 2006) China N= 234	Intraoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Patients with cholelithiasis and extrahepatic duct stones diagnosed by history, physical examination, ultrasonography, MRCP, or cholangiogram through cystic duct cannulation.	Not stated	Both treatments were shown to be safe, effective and minimally invasive treatments for CBDS
(Koc et al. 2013) Turkey N=120	Preoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Classic biliary pain, at least 1 episode within the past year, at least 4 weeks after the acute symptoms, gallstones detected by ultrasonography, CBD diameter >8mm	Clinical, radiologic, or biochemical evidence of cholangitis and pancreatitis; Evidence of cirrhosis, intrahepatic gallbladder, liver mass or abscess, neoplasm; Suppurative or necrotising cholecystitis, gallbladder	Laparoscopic CBD exploration provides an alternative therapeutic approach that has less morbidity, is cost-effective, and allows earlier recovery with a reduced period of short-

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
				empyema, or perforation; Pregnancy; Recurrent choledocholithiasis.	term disability.
(Nathanson et al. 2005) Australia N=85	Postoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Patients with suspected common bile duct stones who had undergone laparoscopic cholecystectomy, intraoperative cholangiography and had a failed trans cystic duct clearance were randomised to intraoperative choledochotomy or post-operative ERCP.	ERCP prior to referral for cholecystectomy, severe cholangitis or pancreatitis requiring immediate ERCP drainage, common bile duct diameter less than 7mm on operative cholangiography, bilioenteric drainage required in addition to stone clearance.	The data suggest that the majority of secondary CBDS can be diagnosed at the time of cholecystectomy and cleared transcystically, with those failing having either choledochotomy or postoperative ERCP.
(Noble et al. 2009) UK N=91	Preoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	High risk patients (over 70 years of age, over 60 years of age with comorbidity, or those over 50 years of age with a body mass index greater than 40) with bile duct stones proven on radiographic imaging, or with strong evidence of them (dilated CBD on ultrasound and abnormal liver tests), who were fit to undergo general anaesthesia and cholecystectomy.	Previous endoscopic sphincterotomy, required emergency sphincterotomy for severe cholangitis or pancreatitis, had a Billroth II gastrectomy, or if they were unfit for anaesthesia and cholecystectomy.	There was no difference between the approaches to duct clearance in terms of postoperative stay, complications or conversion in higher risk patients, but the laparoscopic approach was more effective and efficient and avoided unnecessary procedures.
(Rhodes et al. 1998) UK N=80	Postoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Patients undergoing cholecystectomy who had common bile duct stones detected at peroperative cholangiography Laparoscopic cholecystectomy was done with 4 ports, and cholangiography was always done. After cholangiography patients with common bile duct stones were randomised to bile	Not stated	Surgical bile duct exploration is as effective as ERCP in clearing the CBD of stones. There is a non-significant trend to shorter time in the operating theatre and a significantly shorter hospital stay in patients treated by surgical bile duct exploration.

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
			duct exploration or ERCP		
(Rogers et al. 2010) USA N=122	Preoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	ASA I or II patients with classic signs and symptoms of gallstone disease (clinical and/or laboratory data and/or radiographic imaging suggestive of cholecystitis, cholelithiasis, cholangitis, gallstone pancreatitis, choledocholithiasis). Patients were over 18 years of age, with classic biliary type pain, at least one episode in the last 6 months, ultrasound demonstration of cholecystolithiasis, likely choledocholithiasis (suggested by one of the following: CBD 6mm or larger in diameter on US or CT, interhepatic duct dilation as determined by US or CT, elevated serum bilirubin, alkaline phosphatase and/or lipase)	Patients without ASA I or II status, patients with suppurative cholangitis or clinically severe pancreatitis.	Both techniques were highly effective in detecting and removing CBDS and were equivalent in overall costs and patient acceptance. However, overall duration of hospitalisation was shorter and physician fees lower for surgical bile duct exploration
(Sgourakis and Karaliotas 2002) Greece N=78	Preoperative ERCP plus laparoscopic cholecystectomy	Surgical bile duct exploration plus laparoscopic cholecystectomy	Patients suspected of common bile duct stones based on high SGOT (aspartate trans aminase), bilirubin, alkaline phosphatase and CBD diameter (greater than or equal to 10mm).	Not stated	Surgical bile duct exploration is not yet established as the gold standard procedure for CBDS and there is need for further randomised trials and possibly future meta analyses.

4.6.3 Health economic evidence

A literature search was conducted jointly for questions 4 and 5 by applying standard health economic filters to the clinical search strategies (see Appendix D). For questions 4 and 5, 1,396 references were retrieved, of which 1 was retained for question 4b and 1 was retained for question 5.

Gurusamy et al. (2012) (see Table 11) used a decision tree to compare intraoperative and preoperative ERCP for patients with gallbladder stones and CBDS. The study modelled the success or failure (and subsequent repeat ERCP) of CBDS extraction, complications of ERCP, consequent cholecystectomy (laparoscopic or open) and mortality from symptoms and open operations. Whilst this analysis was directly relevant to the UK NHS, the model did not compare all the interventions included in this guideline question (as postoperative ERCP and intraoperative bile duct exploration were not included).

Table 11: Health Economic Evidence – Intra-Operative Versus Pre-Operative ERCP for CBDS

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusion	Uncertainty
			Cost	Effect	ICER		
Gurusamy et al. (2012) Patients with gallbladder and CBD stones suitable for LC UK **Directly Applicable**[a] **Potentially Serious Limitations**[b,c,d,e,f]	**Effects:** authors' own systematic review, other sources, some assumptions. Rare events modelled using non-informative priors **Costs:** reference costs £UK, 2008. Some assumptions **Utilities:** small non-UK time trade-off and standard gamble studies, not from patients, some assumptions	Decision tree (3 year horizon) Pre-operative ERCP and LC done in separate hospital admissions Discounting applied to both costs and QALYs at 3.5%	−£623	0.008	Intraoperative ERCP dominates preoperative ERCP	Intraoperative ERCP is less expensive and resulted in better QALYs than preoperative ERCP	ICER sensitive to extreme values of operative success that would not be seen in clinical practice Complications and conversion rates Cost savings predicated on necessary resource scheduling In PSA, intra-operative ERCP has 93% chance of being cost effective at £20,000/QALY

a Utilities not from patients and not scored by UK general public
b Time horizon may be limited
c Some assumptions made in all data sources
d Decision tree does not allow recurrence of symptoms
e Delay between ERCP and LC not specified
f No consideration of ERCP or laparoscopic cholecystectomy mortality, or background mortality

Abbreviations
CBDS: Common bile duct stones
ERCP: Endoscopic retrograde cholangiopancreatography
ICER: Incremental cost effectiveness ratio
LC: Laparoscopic Cholecystectomy
PSA: Probabilistic Sensitivity Analysis
QALY: Quality adjusted life years
UK: United Kingdom

4.6.3.1 Original health economic modelling – methods

As no existing health economic studies were found that addressed all the comparisons in questions 4 and 5, an original economic model was constructed. A full description of the health economic model can be found in in Appendix J; a summary is presented in section 4.5.3). For questions 4c (managing symptomatic CBDS), the GDG did not prioritise the biliary stents comparison and no evidence was found to enable the modelling of the day case versus inpatient ERCP comparison.

4.6.3.2 Original health economic modelling – results

Table 12: Cost effectiveness results for ERCP versus conservative management

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
ERCP	£3366.72	15.923			
Conservative management	£11,437.11	15.476	£8070.39	−0.446	Dominated

(a) Results represent means of 1,000 probabilistic model runs

The health economic model found that conservative management is more costly and produces fewer QALYs than ERCP and is therefore said to be dominated (see Table 12). This remained true in 100% of probabilistic model runs. The increased costs and decreased QALYs are driven by patients retaining their gallstones, having further symptomatic episodes and requiring additional ERCPs that would be undertaken non-electively in the conservative management arm.

Table 13: Cost effectiveness results for ERCP with laparoscopic cholecystectomy versus ERCP alone

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
ERCP alone	£1873.52	15.919			
ERCP and laparoscopic cholecystectomy	£2310.48	16.012	£436.96	0.093	£4680 / QALY

(a) Results represent means of 1,000 probabilistic model runs

ERCP and laparoscopic cholecystectomy is more costly and produces more QALYs than ERCP alone, at an acceptable cost per QALY of £4680 (see Table 13). The increased costs and QALYs are driven by all patients having a laparoscopic cholecystectomy that avoids patients living with asymptomatic gallstones or having further symptomatic episodes. In probabilistic sensitivity analysis, ERCP with laparoscopic cholecystectomy has a 98.5% chance of being cost effective at a threshold of £20,000 per QALY, compared with ERCP alone.

Table 14: Cost effectiveness results for laparoscopic cholecystectomy with bile duct exploration versus laparoscopic cholecystectomy with pre-, intra- or postoperative ERCP

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
LC with intraoperative ERCP	£3013.21	15.941			
LC with bile duct exploration	£3672.46	15.930	£659.24	−0.011	Dominated
LC with preoperative ERCP	£4124.08	15.919	£1110.87	−0.022	Dominated
LC with postoperative ERCP	£8712.44	15.896	£5699.23	−0.045	Dominated

(a) Results represent means of 1,000 probabilistic model runs

In an incremental analysis of the 4 options for managing CBDS with laparoscopic cholecystectomy, laparoscopic cholecystectomy with intraoperative ERCP was less costly and produced more QALYS than either laparoscopic cholecystectomy with bile duct exploration, laparoscopic cholecystectomy with preoperative ERCP or laparoscopic cholecystectomy with postoperative ERCP. Therefore, laparoscopic cholecystectomy with intraoperative ERCP is the dominant option (Table 14). In probabilistic sensitivity analysis, laparoscopic cholecystectomy with intraoperative ERCP is cost effective in 84.6% of simulations (see Table 15).

Pre- and postoperative ERCP options have increased costs as they require 2 hospital admissions. The differences between intraoperative ERCP and bile duct exploration are driven by higher rates of bile leaks and extra ERCPs required to clear the CBDS, both of which are worse for bile duct exploration. However, the QALY differences are small and both these parameters are based on non-statistically significant differences from 1 or 2 RCTs.

The model does not take account of any additional implementation costs or wider opportunity costs that occur to facilitate laparoscopic cholecystectomy with intraoperative ERCP or bile duct exploration.

Table 15: Probabilistic Sensitivity Analysis Results

Strategy	Replications cost effective at £20,000 per QALY threshold
LC with intraoperative ERCP	84.6%
LC with intraoperative bile duct exploration	13.5%
LC with preoperative ERCP	1.9%
LC with postoperative ERCP	0.0%

4.6.4 Evidence Statements

Low to very low quality evidence provided by up to 8 randomised controlled trials showed that there were no significant differences between ERCP and conservative management. The only exception to this was a statistically significantly lower requirement for additional ERCP in the ERCP group than the conservative management group.

Moderate quality evidence was provided by 2 randomised controlled trials and showed that ERCP followed by laparoscopic cholecystectomy was preferable to ERCP alone.

Very low quality evidence provided by up to 11 randomised controlled trials comparing ERCP clearance of the bile duct plus laparoscopic cholecystectomy with surgical clearance of the bile duct plus laparoscopic cholecystectomy was inconclusive. Where network meta-analyses were conducted, all options had wide credibility intervals meaning there was uncertainty about which option was best. Furthermore, some outcomes had evidence that couldn't be meaningfully compared.

Low quality evidence was provided by a single study and showed there were no statistically significant differences between biliary stenting and clearing the bile duct. The only exception to this was a statistically significantly lower requirement for additional ERCP in the stent group than in the cleared duct group.

No evidence comparing day-case ERCP to planned inpatient ERCP was found

A directly applicable published cost–utility study with potentially serious limitations suggested that intraoperative ERCP is cost saving and generates more QALYs when compared with preoperative ERCP.

A directly applicable original health economic model analysis with minor limitations suggests ERCP is cost effective compared with conservative management and ERCP with laparoscopic cholecystectomy is cost effective compared with ERCP alone. Based on limited and inconclusive clinical evidence, laparoscopic cholecystectomy with intra-operative ERCP dominates other options but without taking account of any additional implementation costs.

4.6.5 Evidence to Recommendations

Relative value of different outcomes	In general, studies were underpowered for the outcomes that the GDG had chosen and so confidence intervals relating to effect estimates for many outcomes were wide. This was expected, since events such as mortality and bile duct injury are relatively rare and sample sizes would need to be very large to observe sufficient rare events. There was a lack of randomised controlled trial evidence for some of the comparisons that were considered as part of this review. The GDG felt that this is because surgical removal of the gallbladder, and surgical and/or endoscopic stone extraction of stones in the common bile duct are accepted as best practice. Alternative management options are only considered for patients for whom surgery/endoscopy is not appropriate, such as those who have complex, comorbid conditions, or those who make an informed choice not to opt for surgery/endoscopy. Continual improvements in clinical outcomes for surgery and endoscopy has meant that surgery and/or endoscopy can be offered to an increasing number of people for whom traditionally these options would not be appropriate. It would be seen as highly unethical to randomise patients for whom surgery and/or endoscopy is appropriate to inferior treatments, and thus randomised controlled trial evidence in this area is limited. The absence of evidence and the wide confidence intervals surrounding most effect estimates meant the GDG relied on their knowledge and experience for most of the discussions of the interventions under review.
Trade off between benefits and harms	**ERCP compared with conservative management** Evidence about conservative management in comparison with ERCP for common bile duct stones was inconclusive. There were no significant differences in any of the critical or important outcomes and this was attributed to lack of statistical power in the evidence. GDG experience is that ERCP is a safe procedure and is being increasingly offered to a wide range of clinically compromised and complex patients, but there was no evidence to say that ERCP should always be performed. The GDG agreed that there will always be patients where the risks of intervening with ERCP outweigh the risks associated with not intervening, and for these patients conservative management is an appropriate treatment option. The GDG felt that decisions about who should be offered conservative management should be taken locally, since such cases will be complex and dependent on the skills and experience of local health care professionals. The GDG felt it was not necessary to make a recommendation about conservative management, as doing so may make it seem that conservative management is an appropriate option for all patients, which they agreed it wasn't. **ERCP + laparoscopic cholecystectomy compared with ERCP alone**

The GDG discussed whether laparoscopic cholecystectomy should always be offered to people who have ERCP, in order to prevent recurrent disease. Evidence about this came from 2 studies, where statistically significant differences on 2 of the 3 critical outcomes that the GDG had specified were found. The evidence showed significant reductions in disease progression/recurrence, and in the requirement for additional ERCP in the group who received laparoscopic cholecystectomy after ERCP, compared with the group that had ERCP alone. Furthermore, subsequent cholecystectomy was required for 25% of patients who had ERCP alone. The evidence supported the knowledge and experience of the group, where it was agreed that disease recurrence is common, and the only way to prevent this is to remove the gallbladder to stop new gallstones forming. Thus the GDG recommended that laparoscopic cholecystectomy should be offered to patients who have common bile duct stones since the harms of recurrent events outweighed the harms of laparoscopic cholecystectomy.

Pre/post/intra operative ERCP + LC compared with BDE+LC

The evidence relating to these comparisons came from 9 studies that were analysed using network meta-analysis whenever possible. In some instances there was insufficient evidence to form a network so pairwise meta-analysis was performed instead. For some outcomes it wasn't possible to meta analyse at all. This was usually when an outcome was possible in one arm of the comparison but not in the other (for example, requirement for cholecystectomy isn't possible in people who have already had cholecystectomy, but is possible in those waiting for cholecystectomy). In these cases simple rates were presented.

Network meta-analysis was possible for one critical outcome (length of stay) and three important outcomes (missed stones, failed procedure, conversion to open surgery). The results of the network analyses were inconclusive. All of the options had wide credibility intervals on all of the outcomes, indicating there was uncertainty about which options offered the best outcomes and which offered the worst.

Mortality was also chosen as a critical outcome by the GDG, and although mortality data were reported by most of the studies included in these comparisons, the event rates were often zero in both arms of the trial. Since zero event data cannot be meaningfully analysed, only evidence from studies where deaths were observed were compared. It was only possible to compare mortality data in a pairwise comparison between preoperative ERCP+LC versus BDE+LC. The results of this comparison were not statistically significant, and this was attributed to a lack of statistical power in the analysis. The point estimate did indicate that deaths were lower in preoperative ERCP group than the bile duct exploration group.

Requirement for more than 1 ERCP was chosen as an important outcome by the GDG, but this outcome was not possible to observe in the surgical bile duct exploration arm, since ERCP was not part of treatment. Furthermore, not all studies reported this outcome so it was not possible to meta-analyse the data. Rates of multiple ERCP were provided but it was not possible to calculate confidence intervals around the rates, and so this outcome had unknown levels of uncertainty.

Thus, the GDG agreed that the mixed and unclear evidence was a

reflection of current clinical reality as there are lots of different options for managing common bile duct stones that are used in different clinical scenarios. However, the GDG acknowledged that the studies used within this evidence often excluded patients who were older, complex, and had comorbidities from their protocols. Thus, the range of clinical scenarios that the evidence covered does not reflect reality. Since there was insufficient evidence, decisions were based on knowledge and experience of the group.

A discussion about the merits of ERCP+LC and BDE+LC took place. ERCP+LC requires two separate procedures, ERCP to remove the stone and LC to remove the gallbladder. Usually these procedures are done days or weeks apart from each other. Thus the patient will require a prolonged hospital stay during the wait, or will be admitted to hospital twice for each individual procedure. Furthermore, the patient would be exposed to the risks of anaesthesia/sedation twice, and there is a risk that their clinical condition could deteriorate in the time between the two procedures. BDE+LC on the other hand is performed as a single procedure and would usually result in the patient having a shorter total hospital stay (since multiple or prolonged admission is not necessary), is only exposed to one anaesthesia, and has their condition treated definitively in one procedure. Thus, the GDG agreed that in principle BDE+LC is superior to ERCP+LC.

The GDG acknowledged that only a minority of surgeons can perform BDE+LC safely, as this is highly complex surgery that requires specialist knowledge and experience. The GDG felt that surgeons not trained to do bile duct exploration would not and should not undertake this procedure. Conversely, laparoscopic cholecystectomy performed after bile duct stones have been removed does not require a surgeon trained in bile duct exploration, and can be performed by any surgeon trained to perform laparoscopic cholecystectomy. Since ERCP is widely available throughout the NHS, the GDG felt that it could recommend that bile duct stones should be removed by ERCP before laparoscopic cholecystectomy, or by surgical bile duct exploration during laparoscopic cholecystectomy in order to reduce the risk of subsequent surgical complications. The GDG felt that the decision to use ERCP or bile duct exploration to clear the duct should be taken locally depending on the skills and experience of the team.

Uncleared duct + biliary stent compared with cleared duct

Only one study was identified that met the inclusion criteria. The study had a low rate of stone clearance which the GDG felt reflected the age of the paper as it was published in 1996, and higher rates of clearance are usually observed today. The GDG also acknowledged that the study randomised patients to biliary stents without attempting to clear the duct first, which is not ethical and wouldn't be done in practice today. The study was underpowered and so no clear conclusions could be drawn about the efficacy and safety of biliary stenting in comparison with ductal clearance.

Biliary stenting is widely accepted to be an appropriate management strategy when stones cannot be cleared from the bile duct and surgery is not an appropriate treatment option. Biliary stenting is associated with complications that can be life-threatening, and clinicians must balance the risks of using stents with those associated with

persevering in the attempt to clear the duct. The GDG felt that in general, most clinicians would strive for a cleared duct and the decision to abort ductal clearance would be taken locally depending on the individual patient's condition and the clinical experience of the team. Thus, the GDG did not feel it would be of use to make recommendations about when biliary stenting should be considered. However, the GDG felt that there was inappropriate variation in the management of patients once a biliary stent has been placed. Often biliary stents are used as long term treatment option with patients never getting reassessed for further surgical or endoscopic ductal clearance, even when their clinical condition has improved. Instead patients will go on to have their stent replaced indefinitely. The GDG were concerned about this, since patients would be at increased risk of recurrent events and would be at risk of experiencing cholangitis, one of the most serious complications associated with the use of stents.

Although the evidence was inconclusive since the single study it was based on was underpowered, the point estimates showed that risk of death and disease progression were higher in the stent group than in the cleared duct group. Furthermore, the study did find a statistically significant difference in risk of cholangitis, with those in the stent group having a significantly greater risk of cholangitis than those in the cleared duct group. The GDG had not specified cholangitis as a specific outcome for this evidence review, instead it chose a composite outcome that included all types of progressive disease including cholangitis, pancreatitis and jaundice. So although the individual study observed a statistical difference in cholangitis risk, this was not observed in the analysis for this review, since the use of the composite outcome 'disease progression' had diluted the evidence. Since cholangitis is such a serious and life threatening complication, the GDG could not ignore the study findings and were satisfied that the evidence did support their knowledge and experience. Thus recommendations about managing stents once they have been placed were made.

Day-case ERCP vs planned inpatient ERCP

There was no evidence in relation to this comparison and so the GDG based its discussions on the knowledge and experience of the group, and also extrapolated from evidence presented in chapter 4.6 relating to day-case versus inpatient laparoscopic cholecystectomy.

The GDG discussed whether day-case surgery should always be offered to patients, since it offers the benefits of enabling the patient to return home sooner, reducing the risk of hospital acquired infections, and reducing the use of NHS resources.

However, there are various patient and clinical factors that need to be taken into consideration. For example, patients require adult supervision for 24hours after sedation and people who do not have someone at home to supervise them will require an inpatient stay. Similarly, some patients with comorbidities may need admitting to hospital before or after the operation to manage their other conditions. The GDG also acknowledged that definitions of inpatient admission and day-cases may vary, and that considerations of other aspects of hospital performance may influence decisions around length of stay.

Thus, the GDG felt that decisions about whether to plan day-case or inpatient ERCP should be decided at a local level on a case by case

	basis to take the various patient and clinical factors into account.
Consideration of health benefits and resource use	For ERCP compared with conservative management, the economic model suggests that leaving patients with common bile duct stones results in net health losses (due to symptoms) and cost increases (due to extra non-elective interventional procedures being required). The GDG noted that the economic model considered a binary choice between ERCP and no intervention that is unlikely to occur in clinical practice. The economic model suggests that ERCP with laparoscopic cholecystectomy is cost effective compared with ERCP alone with an ICER of around £4,700 / QALY. The GDG agreed that the extra cost of laparoscopic cholecystectomy would be an appropriate trade off against the extra QALYs gained by relief of recurrent biliary symptoms. The economic analysis of laparoscopic cholecystectomy with laparoscopic bile duct exploration compared with laparoscopic cholecystectomy with pre-, intra- or postoperative ERCP suggests that intraoperative ERCP dominates other options. However, the GDG interpreted this result cautiously. They noted the underlying network meta-analysis was inconclusive. They also noted options modelled with 1 (intraoperative ERCP, laparoscopic bile duct exploration) rather than 2 (pre- and post-operative ERCP) hospital admissions are cheaper and also limited the time patients could become symptomatic and lose QALYs. However, the GDG were concerned that the economic model did not reflect implementation costs that would be associated with recommending intra-operative ERCP or laparoscopic bile duct exploration. The GDG felt that the economic analysis supported their view that laparoscopic cholecystectomy with bile duct exploration is superior to laparoscopic cholecystectomy with ERCP, but the decision on which method should be used to clear the bile duct should be taken locally based on the skills and experience of staff. The economic model did not consider biliary stents or day-case versus inpatient ERCP treatment.
Quality of evidence	The overall quality of the evidence was mixed, with the majority of evidence being low in quality.
Other considerations	None

4.6.6 Recommendations

10. Offer bile duct clearance and laparoscopic cholecystectomy to people with symptomatic or asymptomatic common bile duct stones.

11. Clear the bile duct:

- **surgically at the time of laparoscopic cholecystectomy or**
- **with endoscopic retrograde cholangiopancreatography (ERCP) before or at the time of laparoscopic cholecystectomy.**

12. **If the bile duct cannot be cleared with ERCP, use biliary stenting to achieve biliary drainage only as a temporary measure until definitive endoscopic or surgical clearance.**

13. **Use the lowest-cost option suitable for the clinical situation when choosing between day-case and inpatient procedures for elective ERCP.**

4.6.7 Research recommendations

3. **What models of service delivery enable intraoperative endoscopic retrograde cholangiopancreatography (ERCP) for bile duct clearance to be delivered within the NHS? What are the costs and benefits of different models of service delivery?**

Why this is important

Evidence reviewed for this guideline identified that intraoperative ERCP is both clinically and cost effective, but it is unclear whether delivery of this intervention is feasible in the NHS because of the way current services are organised. It is also unclear whether intraoperative ERCP will remain cost effective if services are reorganised.

4.6.8 References

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4.7 Timing of laparoscopic cholecystectomy

4.7.1 Review Question 5

In adults with acute cholecystitis or symptomatic common bile duct stones, should cholecystectomy be performed during the acute episode (early) or should intervention be delayed until the acute episode has subsided (delayed)?

4.7.2 Evidence Review

A single search was performed for questions 4a, 4b, 4c and 5 which identified 10,976 references. After removing duplicates and screening the references based on their titles and abstracts, 210 references were obtained and reviewed against the inclusion and exclusion criteria for this review question (appendix C), and 47 references met the inclusion criteria overall. Details of excluded studies and reasons for their exclusion are in appendix F.4

Of the 47 included references, 8 references relating to 8 randomised controlled trials were included in this review question (see study flow chart) which specifically addressed the timing of intervention for gallstone disease, and for the purposes of this review the following definitions were used:

- early laparoscopic cholecystectomy: performed within the first 7 days of the acute presentation
- delayed laparoscopic cholecystectomy: performed more than 4 weeks after presentation.

Studies that didn't use these definitions were not eligible for inclusion.

Of the 8 included studies, 7 related to acute cholecystitis (Gul, 2013; Johansson, 2003; Kolla, 2004; Lai, 1998; Lo, 1998; Macafee, 2009; Yadav, 2009) and one related to common bile duct stones (Reinders, 2010). All studies were assessed for methodological quality using randomised controlled trial checklists, and meta-analysis was performed wherever possible (see appendix H.7).

Standard GRADE processes were applied to assess the quality of the evidence in relation to the following outcomes:

- Readmission due to symptoms
- Readmission due to surgical complications
- Length of stay
- Mortality
- Quality of life

Full GRADE profiles are available in appendix (I.7).

Overall, the individual studies had good methodological quality, with adequate randomisation and appropriate study conduct. Evidence was available in relation to readmission and length of stay, but outcomes such as mortality and quality of life were not reported by any of the studies. There was a lack of evidence in relation to common bile duct stones.

Table 16: Summary of included studies for question 5

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
(Gul 2013) India N= 60	Early laparoscopic cholecystectomy	Delayed laparoscopic cholecystectomy	Patients diagnosed with acute cholecystitis	Patients with symptoms for more than 72 hours before surgery, patients with surgical jaundice (bilirubin level above 3.5mg/dl) ultrasound proved common bile duct stones, malignancy, preoperatively diagnosed gallstone pancreatitis, previous upper abdominal surgery, significant medical disease rendering them unfit for laparoscopic surgery, those who refused laparoscopic surgery	Early laparoscopic cholecystectomy within 72 hours of onset of symptoms has both medical as well as socioeconomic benefits and should be the preferred approach for patients managed by surgeons with adequate experience in laparoscopic cholecystectomy.
(Johansson et al. 2003) Sweden N= 145	Early laparoscopic cholecystectomy	Delayed laparoscopic cholecystectomy	Patients diagnosed with acute cholecystitis	Patients were excluded if (1) they had bilirubin greater than 3.5mg/dl or (2) they had symptoms for more than 1 week, (3) if they were incapable of understanding written information regarding the study, or (4) if they were elderly (>90 years).	Despite a high conversion rate, early laparoscopic cholecystectomy offered significant advantages in the management of acute cholecystitis compared with a conservative strategy.
(Kolla et al. 2004) India N=40	Early laparoscopic cholecystectomy	Delayed laparoscopic cholecystectomy	Patients diagnosed with acute cholecystitis	Patients with symptoms for more than 96h, previous upper abdominal surgery, coexisting common bile duct stones, or significant medical disease rendering them unfit for laparoscopic surgery	Early laparoscopic cholecystectomy for acute cholecystitis is safe and feasible, offering additional benefit of shorter hospital stay.
(Lai et al. 1998) Hong Kong N= 104	Early laparoscopic cholecystectomy	Delayed laparoscopic cholecystectomy	Patients diagnosed with acute cholecystitis	Patients were excluded if they had symptoms for more than 1 week, had previous upper abdominal surgery, had	Early laparoscopic cholecystectomy for acute cholecystitis is safe and feasible, offering

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
				significant medical diseases that rendered them unfit for laparoscopic surgery, or had coexisting bile duct stones with ductal dilation, acute cholangitis, or acute pancreatitis.	additional benefit of shorter hospital stay
(Lo 1998) China N=99	Early laparoscopic cholecystectomy	Delayed laparoscopic cholecystectomy	Patients diagnosed with acute cholecystitis	Spreading peritonitis or uncertain diagnosis, previous upper abdominal surgery, absolute contraindications for surgery, concomitant malignant disease or pregnancy, conservative treatment for 72 hours before the diagnosis was made, refused surgery, had symptoms for more than 7 days before admission	Early operation within 72 hours of admission has both medical and socioeconomic benefits and is the preferred approach.
(Macafee et al. 2009) UK N= 72	Early laparoscopic cholecystectomy	Delayed laparoscopic cholecystectomy	Patients aged 18 to 80 years presenting with biliary colic or acute cholecystitis and admitted as an emergency	Patients who had a comorbidity deeming them unfit for laparoscopic cholecystectomy, those previously diagnosed with gallstone disease, those with deranged liver function tests, acute pancreatitis, or ascending cholangitis	This trial confirmed equivalent clinical outcomes regardless of the timing of operative intervention.
(Yadav et al. 2009) Nepal N= 50	Early laparoscopic cholecystectomy	Delayed laparoscopic cholecystectomy	Patients diagnosed with acute cholecystitis presenting within 7 days of onset.	Patients presenting with AC more than 7 days duration, those with common bile duct stones or ductal dilation, patients with serious medical disease for whom surgery was inappropriate were excluded.	Both early and delayed laparoscopic cholecystectomy is possible and safe in the treatment of acute cholecystitis
(Reinders et al.	Preoperative	Preoperative ERCP	Patients over the age of 18	Patients unfit for surgery (ASA	Early laparoscopic

Study	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Authors conclusions
2010) The Netherlands N= 96	ERCP and early cholecystectomy	and delayed laparoscopic cholecystectomy	years who underwent successful endoscopic sphincterotomy and stone extraction for choledocholithiasis and who had radiologically proven residual gallbladder stones	III IV), patients with biliary pancreatitis or acute cholecystitis	cholecystectomy after ERCP appears to be safe and might prevent the majority of biliary events in the period following ERCP

4.7.3 Health economic evidence

A literature search was conducted jointly for questions 4 and 5,by applying standard health economic filters to the clinical search strategies (see Appendix D). 1,396 references were retrieved for questions 4 and 5, of which 1 was retained for question 4b and 1 was retained for question 5.

Wilson et al. (2010) (see Table 17) used a decision tree to compare early and delayed laparoscopic cholecystectomy for acute cholecystitis. The model estimated the development of 4 symptoms at 9 weeks during an 18-week delay period, with a time horizon of 1 year.

Whilst Wilson et al. (2010) was directly relevant, it had a number of limitations, including the delay length, time horizon, no consideration of CBDS and utility data.

4.7.3.1 Original health economic modelling – methods

Because Wilson et al.'s (2010) analysis had potentially serious limitations, and did not address all relevant questions in this area, an original economic model was constructed. A full description of the health economic model can be found in in Appendix J, a summary is presented in section 4.5.3.

Table 17: Health Economic Evidence – Early versus Delayed Laparoscopic Cholecystectomy For Acute Cholecystitis

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusion	Uncertainty
			Cost	Effect	ICER		
Wilson et al (2010) Acute cholecystitis UK **Directly Applicable**[a] **Potentially Serious Limitations**[b, c,d,e,f,g,h]	**Effects:** authors' own systematic review, other sources, some assumptions. Rare events modelled using non-informative priors **Costs:** reference costs £UK, 2006. Adjustments made for longer early LC operations and for increased delayed LC length of stay **Utilities:** small time trade off study, not from patients or UK, some assumptions	Decision tree (1 year horizon) 18 week delay period; symptoms develop after 9 weeks LC all done as inpatients Discounting not applied due to short time horizon	−£820	0.05 QALYs	Early LC dominates delayed LC	Early LC is less expensive and results in better QoL than delayed LC	ICER sensitive to extreme values of surgical complications that would not be seen in clinical practice Differences driven by symptoms in delay and extra delayed LC length of stay Quality of life estimates are most uncertain part of model In PSA, early LC has 71% chance of being cost effective at £20,000/QALY

a Utilities not from patients and not scored by UK general public
b No consideration of common bile duct stones
c Time horizon may be limited
d Some assumptions made in all data sources
e Decision tree does not allow recurrence of symptoms or common bile duct stones
f Delay period longer than found in most clinical papers
g Development of symptoms occurs later than advised by Guideline Development Group
h No consideration of operative or background mortality

Abbreviations
ICER: Incremental cost effectiveness ratio
LC: Laparoscopic cholecystectomy
PSA: Probabilistic Sensitivity Analysis
QALY: Quality adjusted life years
UK: United Kingdom

4.7.3.2 Original health economic modelling – results

Table 18: Cost effectiveness results for early laparoscopic cholecystectomy versus delayed laparoscopic cholecystectomy

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Early laparoscopic cholecystectomy	£2728.27	15.983			
Delayed laparoscopic cholecystectomy	£3686.21	15.988	£957.94	0.005	£201,896/ QALY

(a) Results represent means of 1,000 probabilistic model runs

The health economic model found that delayed laparoscopic cholecystectomy is more costly and produces more QALYs than early laparoscopic cholecystectomy, but an ICER of over £200,000 per QALY is above that which is usually accepted as being cost effective (see Table 18). In probabilistic sensitivity analysis, early laparoscopic cholecystectomy has an 88% chance of being cost effective at a threshold of £20,000 per QALY compared with delayed laparoscopic cholecystectomy. The increased costs are driven by the additional length of stay and the small QALY gains are sensitive to estimated rates of bile duct injury.

Table 19: Cost effectiveness results for early laparoscopic cholecystectomy after ERCP versus delayed laparoscopic cholecystectomy after ERCP

Strategy	Discounted		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Early laparoscopic cholecystectomy post ERCP	£2322,14	16.007			
Delayed laparoscopic cholecystectomy post ERCP	£2402.41	16.002	£80.06	−0.005	Dominated

(b) Results represent means of 1,000 probabilistic model runs

Delayed laparoscopic cholecystectomy after ERCP is more costly and produces fewer QALYs than early laparoscopic cholecystectomy after ERCP and is therefore said to be dominated (see Table 19). In probabilistic sensitivity analysis, early laparoscopic cholecystectomy post ERCP has a 100% chance of being cost effective at a threshold of £20,000 per QALY compared with delayed laparoscopic cholecystectomy after ERCP. The increased costs are driven by the additional length of stay and the QALY differences are small.

4.7.4 Evidence Statements

Acute cholecystitis

Moderate to low quality evidence was provided by 6 randomised controlled trials comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis, and demonstrated that readmission rates and length of stay were lower in the early compared with the delayed group and quality of life was higher.

A published cost–utility analysis and an original health economic model both suggest that early laparoscopic cholecystectomy for acute cholecystitis is cost effective compared with delayed laparoscopic cholecystectomy.

Common bile duct stones

One randomised controlled trial provided low quality evidence comparing early versus delayed laparoscopic cholecystectomy following ERCP for common bile duct stones. Evidence was provided for only 1 of the 5 outcomes for this comparison. This is because the study either didn't report the data, or because data were reported but zero events occurred. The 1 outcome for which moderate quality evidence was available showed that there was no statistically significant difference in length of stay between the 2 groups.

A directly applicable original health economic model analysis with minor limitations suggests that early laparoscopic cholecystectomy following ERCP for common bile duct stones is cost effective compared with delayed laparoscopic cholecystectomy.

4.7.5 Evidence to Recommendations

Relative value of different outcomes	The GDG chose readmission due to symptoms and readmission due to surgical complications as outcomes that were critical to their decision making, since it was felt that these outcomes would capture important differences between groups in relation to the complications of surgery. Readmission due to symptoms was reported in some of the studies relating to acute cholecystitis but was not reported in the study relating to common bile duct stones. Readmission due to surgical complications was not reported by any of the studies included in this review question. The GDG felt that the studies that didn't report these critical outcomes probably didn't observe any readmissions, although there was no way that they could be certain of this. The GDG felt that in reality, readmission rates are low and the individual studies were underpowered to observe these relatively rare events. Likewise, mortality was reported by most of the included studies, but no events were observed since the studies were underpowered to detect this relatively rare event. The GDG felt that it is more likely for studies to report zero mortality events than zero readmission events due to the greater importance placed on mortality than readmission. The GDG felt that the lack of evidence supports their views that readmission and mortality are rare, and focused their attention on the evidence relating to length of stay which was felt to be the best measure of clinically important differences between early and delayed laparoscopic cholecystectomy (LC) for the majority of patients.
Trade off between benefits and harms	The earlier LC is performed the less potential there is for recurrent events during the wait for surgery, therefore there are expected benefits in terms of patient quality of life and resource utilisation. However, there are concerns that early intervention could cause harm to patients by increasing the complication rate and extending length of stay. Thus delayed surgery may have greater benefits in the longer term if surgery is safer, although patients may experience recurrent events during the period of delay which could necessitate emergency intervention. In the evidence relating to acute cholecystitis, the early LC group had significantly fewer readmissions than the delayed group as well as a significantly shorter length of stay, which the GDG interpreted as meaning that early intervention does not increase complications. The patient representatives on the group also expressed a preference for

	early LC due to their personal experiences of having to wait for surgery. The patient members expressed that their quality of life was compromised during the wait by avoiding foods that triggered their symptoms, worrying about social activities and not feeling confident to return to work until treatment has been completed due to worries about pain and other complications, although no evidence relating to quality of life was found in this review. The GDG also felt that the absence of evidence relating to harm, especially mortality, probably reflected the fact that these events are rare, and in the majority of cases the benefits of early intervention would far outweigh the risks. Thus the GDG felt that there was sufficient evidence relating to the benefits of early LC to enable them to recommend that early LC should be offered to patients with acute cholecystitis. There was limited evidence in relation to common bile duct stones. The only evidence available for this population came from one small study for the outcome 'length of stay'. The study did not find a significant difference and this was attributed to a lack of statistical power. Furthermore the GDG identified that the study had excluded patients with biliary pancreatitis, which represents a large proportion of people with common bile duct stones. Thus the paper lacks transferability to routine clinical settings. Overall, the lack of evidence meant the GDG were uncertain about whether early or delayed LC was the optimum management strategy for common bile duct stones. The group felt that in reality there was great variation in when people were offered LC following removal of bile duct stones, and agreed that the delay is not necessarily based on clinical decision making and is more often due to a lack of capacity. The GDG felt that it probably wasn't appropriate to recommend the same time frame for LC for common bile duct stones as for acute cholecystitis. This is because common bile duct stones are more complicated and associated with higher risks than gallbladder stones that cause acute cholecystitis, particularly when severe pancreatitis has developed. Performing early surgery may therefore increase the risk of bile duct injury and mortality. Since there was no evidence to support or refute this notion, the GDG were not confident about the optimum time frame in which to offer LC and did not make a specific recommendation.
Consideration of Health Benefits and Resource Use	In both health economic comparisons, the higher cost of delayed laparoscopic cholecystectomy is driven by the longer length of stay associated with delayed laparoscopic cholecystectomy. QALY differences are small, but suggest that delaying surgery is associated with similar or worse net quality of life than early surgery.
Quality of evidence	The GDG agreed that the evidence was of moderate to low quality.
Other considerations	The GDG acknowledged that decisions about when to perform LC may be based on capacity issues rather than clinical appropriateness. Thus, the GDG wanted to emphasise that the recommendations made here should improve patient flow and release capacity, rather than put additional constrains on it. This is because the number of people requiring LC in a given year is a finite, and operating on them earlier will not increase the number of people requiring LC. Instead, offering early cholecystectomy may actually reduce the number of

	readmissions, emergency operations, and length of stay. The GDG felt the recommendations are achievable but acknowledged that some providers may need to focus on redesigning their services in order to implement them.

4.7.6 Recommendations

14. Offer early laparoscopic cholecystectomy (to be carried out within 1 week of diagnosis) to people with acute cholecystitis.

4.7.7 Research recommendations

4. In adults with common bile duct stones, should laparoscopic cholecystectomy be performed early (within 2 weeks of bile duct clearance), or should it be delayed (until 6 weeks after bile duct clearance)?

Why this is important

In the evidence reviewed for this guideline, there was a lack of randomised controlled trials of intraoperative cholangiography, and the evidence that was available did not support the knowledge and experience of the Guideline Development Group. Therefore, there is a need for large, high-quality trials to address clinical questions about the benefits and harms of intraoperative cholangiography

4.7.8 References

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Macafee DA, Humes DJ, Bouliotis G et al. (2009) Prospective randomized trial using cost-utility analysis of early versus delayed laparoscopic cholecystectomy for acute gallbladder disease. British Journal of Surgery 96: 1031-40

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4.8 Information for patients and their carers

4.8.1 Review Question 6

What are the information and education needs of patients and carers of people with gallstone disease?

4.8.2 Evidence Review

The aim of this review question was to identify areas for which information and education should be provided. This question did not aim to compare the effectiveness of different education programmes/strategies.

A systematic search was conducted (see appendix D) which identified 7,862 references. After removing duplicates the references were screened on their titles and abstracts and 61 references were obtained and reviewed against the inclusion and exclusion criteria as described in the review protocols (appendix C).

Overall, 56 studies were excluded as they did not meet the eligibility criteria. A list of excluded studies and reasons for their exclusion is provided in appendix F.

Five studies met the eligibility criteria and were included. Data were extracted into detailed evidence tables (see appendix G) and are summarised in the table below.

Table 20: Summary of included studies for question 6

Study details	Aims of the study	Authors conclusions
(Barthelsson et al. 2003) Sweden N= 12	Explore patient experiences in relation to laparoscopic cholecystectomy	Although most patients were satisfied with day-case LC, a number of problem areas were expressed- preoperative anxiety, post-operative amnesia, experience of pain, need for additional pain medication, feelings of nausea, vomiting, bloating and swelling, information about wound care, additional telephone follow up, difficulties having small children at home.
(Blay and Donoghue 2005) Australia N=93	Determine if a preadmission education intervention reduced pain, increased self-care and decreased postoperative symptoms after laparoscopic cholecystectomy	Pre admission education intervention helps reduce post-operative pain levels following LC and significantly increases patient's knowledge of self-care and complication management.
(Blay and Donoghue 2006) Australia N= 100	Determine what information pre admission nurses provided to elective laparoscopic cholecystectomy patients.	Patients sourced information from a variety of sources, including communicating with friends and relatives for the personal perspective. Personal communication should not be replacing education by nurses. Unfortunately patients did not cite the preadmission nurse as the major source of information in this study.
(Tamhankar et al. 2009) UK N=105	Establish the proportion of people undergoing elective hernia repair or cholecystectomy who access the internet for information about their operations	A significant proportion of patients used the internet and about one third of them specifically sought information about their operation. Such information can cause worry and confusion in patients. The study highlights the need for regulated, comprehensible patient information on

Study details	Aims of the study	Authors conclusions
		hospital websites to which patients should be directed.
(Young and O'Connell 2008) Australia N=28	A randomised controlled trial of inpatient vs day-case cholecystectomy, with a telephone survey to identify if discharge information was sufficient.	With careful patient selection and enhanced discharge education, LC procedures performed as a day-case offer safe and effective alternative to inpatient care.

Studies were quality assessed using methodology checklists. For qualitative studies, the NICE qualitative checklist was used. The NICE guidelines manual does not provide a checklist for surveys, and so a checklist originally published in the British Medical Journal (see appendix K) was used to aid the quality assessment of these studies.

The GRADE framework for assessing quality was modified for this review in that studies, rather than outcomes, were assessed for quality (see appendix I.8) on the following basis. Overall, the studies were of very low quality and had serious limitations; Survey studies lacked detailed analysis and qualitative studies lacked rigour as they did not utilise adequate research design and methodology, and they failed to provide rich data to support findings; studies were limited because 4 of the 5 studies were conducted outside the UK and so lack transferability, and most studies were from the perspective of elective cholecystectomy, meaning that non elective surgery and other treatment options are not adequately represented in the evidence base. Specific details about the reasons for this approach and the judgements made are provided in the footnotes of the profiles in appendix I.8.

4.8.3 Health economic evidence

A literature search was conducted for review question 6, by applying standard health economic filters to the clinical search strategies (see Appendix D). From the search, 504 references were retrieved, of which none were retained at title and abstract screening. Health economic modelling was not prioritised for this review question.

4.8.4 Evidence Statements

Very low quality evidence from 5 studies on people waiting for or undergoing surgery for gallbladder disease showed that patients requested more information on diet, wound management, pain management, and resuming normal activities. Some patients had no memory of the information that was provided to them, and some consulted the internet to acquire additional information. Some people did not know why they had to wait for elective surgery.

4.8.5 Evidence to Recommendations

Relative value of different outcomes	The GDG considered all themes/outcomes that arose from the evidence, but focused its discussions on the theme/outcome of diet. This is because most themes that arose such as wound management, resuming activity, memory and so on, were not specific to gallstone disease and the GDG agreed that other NICE products that already exist or that are in development (such as Patient experience in adult NHS services, Hospital admission pathway, Surgery pathway) would cover these general themes more appropriately. The group chose to focus discussions on diet because this is the area the patient representatives felt was most important, because diet was

	a key issue in the evidence, and because this issue was specific to gallstone disease. Previous review questions did not find sufficient evidence to support or refute a link between diet and gallstone disease, and diet as an intervention for managing gallstone disease was not evaluated in any of the review questions. Thus, discussions about diet were based on the knowledge and experience of the GDG and a co-opted expert dietician.
Trade off between benefits and harms	Some patients with gallstone disease find that eating and/or drinking triggers gallbladder pain and discomfort. This could be due to the mechanics of digestion because the gallbladder contracts on consuming food and drink in order to release bile to aid digestion, and when a person has gallstone disease the gallbladder can become inflamed and infected, and this contracting process can be painful. The GDG decided that it would not be useful to provide information to patients about food and drink that may potentially trigger symptoms because not everyone with gallstone disease experiences pain and discomfort when eating or drinking, not all food and drink triggers gallbladder pain, and the type of triggers vary for different individuals. Instead, the GDG felt that individual patients are best placed to identify which food and drink triggers their own pain. The GDG agreed that once a gallbladder has been removed the mechanism for experiencing pain is no longer there (since there is no gallbladder to contract and cause pain). The time between diagnosis and treatment for gallbladder disease is relatively short (usually less than 3 months), so the GDG felt that there was no harm in recommending that patients should avoid food and drink that triggers their pain between diagnosis and treatment, since harms to health or quality of life were expected to be very low. However, long term avoidance of specific foods, especially once gallstones or the gallbladder have been removed could be detrimental and are not recommended. The group acknowledged that some patients with gallstone disease continue to report symptoms or experience new symptoms once their gallbladder has been removed. The GDG felt this is probably due to some underlying condition that the patient either didn't notice before they experienced gallstone disease, or that coincidentally began at the same time as the symptoms of gallstone disease or cholecystectomy. The GDG felt that these symptoms are often misattributed to the absence of a gallbladder by both health professionals and patients themselves, and because of this patients may not receive appropriate investigations to identify the real cause of the symptoms. Thus, people may continue to experience unnecessary symptoms, or restrict trigger food and drink over the long term to avoid ongoing symptoms. Since long term dietary restriction may be harmful, and because patient quality of life is affected by on-going symptoms, the GDG felt that people experiencing new or existing symptoms after they have recovered from cholecystectomy should be encouraged to return to their health professional, and health professionals should investigate

	the patient appropriately.
Consideration of Health Benefits and Resource Use	Health economics were not considered as a priority for this review question. No economic studies were found.
Quality of evidence	The quality of the evidence was very low, and the studies contributing to the evidence did not provide adequate information about the particular aspects of dietary advice that should be provided. Therefore the GDG developed the recommendations using their knowledge and experience.
Other considerations	None.

4.8.6 Recommendations

15. **Advise people to avoid food and drink that triggers their symptoms until they have their gallbladder or gallstones removed.**

16. **Advise people that they should not need to avoid food and drink that triggered their symptoms after they have their gallbladder or gallstones removed.**

17. **Advise people to seek further advice from their GP if eating or drinking triggers existing symptoms or causes new symptoms to develop after they have recovered from having their gallbladder or gallstones removed.**

4.8.7 Research recommendations

5. **What is the long-term effect of laparoscopic cholecystectomy on outcomes that are important to patients?**

Why this is important

There is a lack of information on the long-term impact of cholecystectomy on patient outcomes. Many patients report a continuation of symptoms or the onset of new symptoms after laparoscopic cholecystectomy, and these affect quality of life. Research is needed to establish the long-term patient benefits and harms, so that appropriate information can be provided to patients to aid decision-making and long-term management of their condition.

4.8.8 References

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5 Glossary & Abbreviations

Table 21: Glossary

Acalculous cholecystitis	Inflammation or infection of the gallbladder not caused by gallstones. Acalculous cholecystitis is not covered by this guideline.
Asymptomatic	For the purposes of this guideline only, asymptomatic refers to stones that are found incidentally by imaging investigations unrelated to gallstone disease, in people who have had no symptoms for at least 12 months before diagnosis.
Biliary colic	Pain caused by the gallbladder or bile duct contracting around a gallstone.
Biliary system/biliary tract/biliary tree	Organs involved in the production and secretion of bile into the digestive system to aid in the digestion of food. Includes the gallbladder, bile ducts, and some specialised cells in the liver.
Cholecystitis	Inflammation or infection of the gallbladder. This guideline only includes cholecystitis caused by gallstones.
Cholecystolithiasis	See gallbladder stones
Choledocholithiasis	See common bile duct stones
Cholelithiasis	May refer specifically to the presence of gallbladder stones or it may refer generally to the presence of gallstone disease.
Cholangitis	Inflammation or infection of the common bile duct. This guideline only includes cholangitis caused by gallstones
Common bile duct stones (CBDS)	Gallstones that have travelled from the gallbladder into the common bile duct, or stones that have formed in the bile duct. Stones in the bile duct may be found by gallbladder imaging or incidentally by unrelated imaging investigations.
Gallbladder stones	Gallstones in the gallbladder
Gallstones	Discreet, hard, fatty mineral deposits that develop in the gallbladder
Gallstone disease	The presence of gallstones in the gallbladder and/or common bile duct and/or the associated complications that gallstones cause
Gold standard	A term used in studies of diagnostic test accuracy to describe a method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease. Also known as the reference standard
Index test	A term used in studies of diagnostic test accuracy to describe the test being evaluated
Mirrizi syndrome	Compression of the common bile duct caused by a gallstone becoming trapped in the neck of the gallbladder. A rare condition.
Obstructive jaundice	An obstruction in the common bile duct preventing the flow of bile from the gallbladder to the liver. This guideline only includes obstructive jaundice caused by gallstones
Pancreatitis	Inflammation or infection of the pancreas. This guideline only includes pancreatitis caused by gallstones.
Reference standard	A term used in studies of diagnostic test accuracy to describe a method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease. Also known as the gold standard
Symptomatic	For the purposes of this guideline only, symptomatic refers to stones found on gallbladder imaging in people who have

	experienced symptoms at any time up to 12 months before diagnosis.
Suspected gallstone disease	Gallstone disease is the term used in this guideline to refer to the presence of stones in the gallbladder or common bile duct and the symptoms and complications they cause. Most people with gallstone disease have asymptomatic gallbladder stones, meaning the stones are confined to the gallbladder and they do not have any symptoms, and disease is often identified coincidentally as a result of investigations for other conditions. In suspected gallstone disease the symptoms may range from mild, non-specific symptoms that can be difficult to diagnose, to severe pain and/or complications which are often easily recognised as gallstone disease by healthcare professionals.
Xanthogranulomatous cholecystitis	A destructive inflammatory process that causes damage to the gallbladder. A rare condition caused by gallstone disease.

Table 22: Abbreviations

BDE	Bile duct exploration
CBDS	Common bile duct stones
CT	Computer tomography
CTC	Computer tomography cholangiography
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
GDG	Guideline development group
HIDA	Hepatobiliary iminodiacetic acid
IOC	Intraoperative cholangiography
LC	Laparoscopic cholecystectomy
LFTs	Liver function tests
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance image
US	Ultrasound