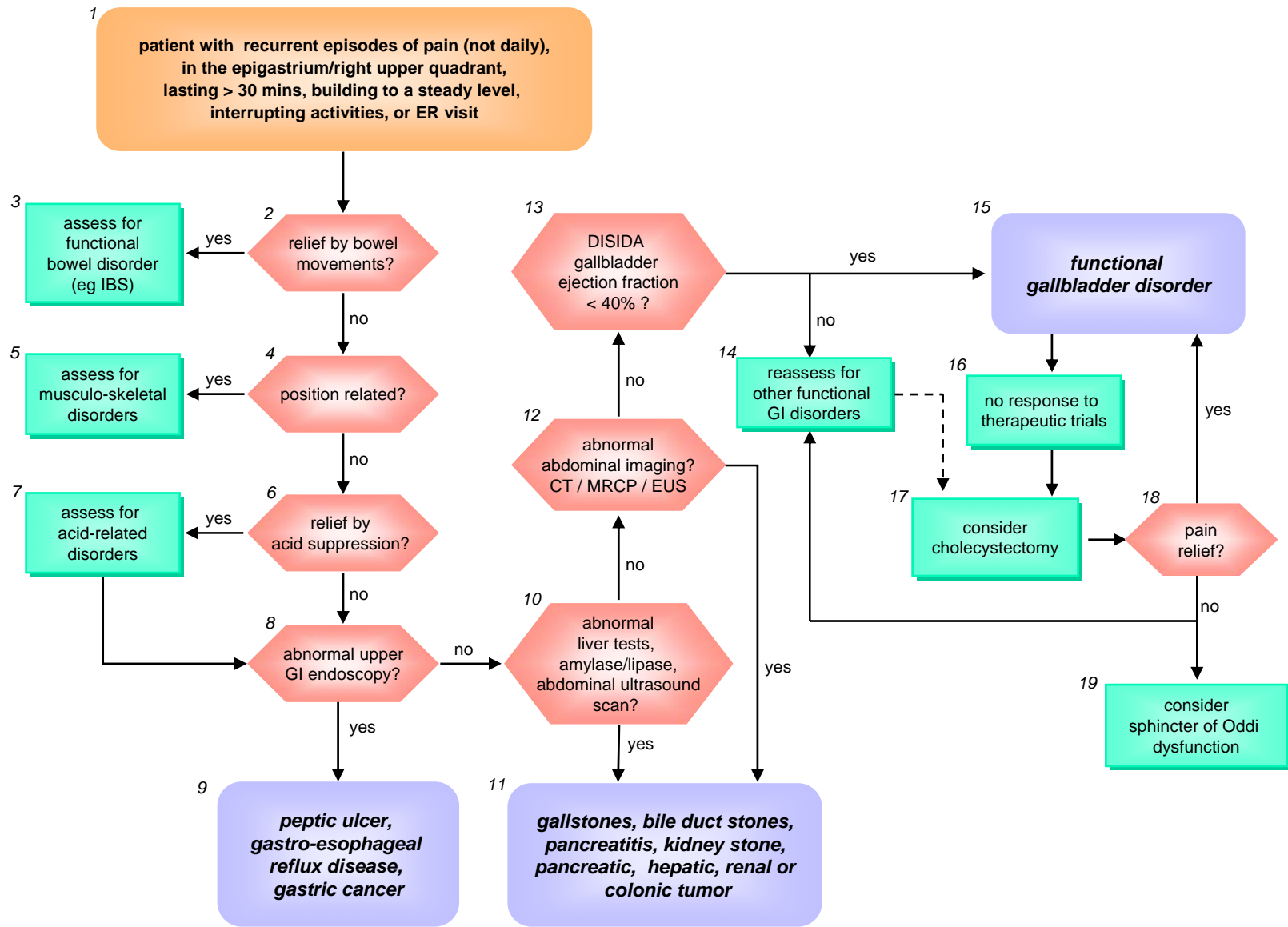


# Figure 1: Recurrent biliary-like pain: gallbladder in place



## **Recurrent biliary-like pain: gallbladder in place**

### ***Case history***

A 35 year old nurse of Hispanic origin is referred to a gastroenterologist by her primary care physician (PCP) because of several episodes of severe upper abdominal pain that have occurred over a six month period. When it occurs, the pain is always located in the right upper quadrant of the abdomen, builds up to a steady and intense level, lasts 30 minutes to one hour, and is of sufficient severity to disrupt her normal activities (Box 1, Fig 1). It often radiates to the right subscapular region. She has not been able to identify any definite precipitating factors to the pain, although on two occasions it has occurred soon after her evening meal. The pain has woken her from sleep on one occasion. On several occasions she has experienced diaphoresis and nausea and vomiting during the episode of pain. The pain is not relieved by defecation or passage of flatus (Box 2), and she reports that it is not triggered by movements or lifting (Box 4). She has taken an antacid on two occasions during an episode of pain but this did not produce any improvement in the pain (Box 6). In between attacks, she does not suffer from other gastrointestinal symptoms apart from occasional heartburn, and her weight has been steady. The patient has no significant past medical history. She takes no regular medications and does not smoke or drink alcohol. In her family history, the patient reports that her mother suffered from “gallbladder trouble” that had been difficult to diagnose, but had eventually been cured by cholecystectomy.

The gastroenterologist obtains the further history that one attack of severe pain had caused her to be taken to the emergency room, where she was found to be afebrile and to have no specific abdominal abnormalities on physical examination. The discharge summary from that hospital visit states that her white cell count was normal, as were standard liver biochemistry and serum amylase and lipase. An abdominal ultrasound scan (Box 10) had also been performed and was reported as unremarkable, although the quality of the images was poor because of her body habitus and the presence of bowel gas.

Physical examination performed by the gastroenterologist does not reveal any specific abnormalities. Despite the apparent lack of response to non-prescription antacids, the gastroenterologist recommends upper GI endoscopy (Box 8). This reveals no relevant abnormality. The gastroenterologist then requests a CT scan to exclude any intra-abdominal lesion, and to obtain better images of the gall bladder (Box 12). The CT scan is also negative, with a normal appearing gallbladder and normal bile duct size, and a normal appearing pancreas.

The patient continues to experience similar episodes of severe abdominal pain, despite avoiding high-fat meals. A trial of antispasmodic therapy prescribed by her PCP does not produce any improvement in the pain. The patient and her mother are both convinced that the gallbladder is causing her symptoms, and press the gastroenterologist for a surgical referral. However the gastroenterologist feels that further investigation is warranted; she discusses with the patient the pros and cons of several possible additional tests to more definitively exclude gallstone and gallbladder disease, including magnetic resonance cholangio-pancreatography (MRCP), endoscopic ultrasound (EUS) of the gallbladder and biliary tree, and duodenal aspiration for biliary crystals (Box 12). EUS is only available at a town 50 miles away, while the gastroenterologist is not convinced of the value of examination for biliary crystals. After discussion, she recommends a nuclear medicine DISIDA scan, to determine the ejection fraction of the gallbladder, having confirmed that the patient is not taking any medications that could affect the results of the test. The investigation reports her ejection fraction to be only 20% (Box 13). On this basis the gastroenterologist makes a diagnosis of **functional gallbladder disorder** (Box 15). She suggests a two month therapeutic trial with a low dose tricyclic antidepressant agent (Box 16), but the pain episodes continue despite this. She then recommends that the patient see a biliary surgeon for consideration of cholecystectomy (Box 17).

The surgeon had just attended a seminar which raised doubt on the value of the DISIDA test in this setting, as several studies had shown little or no correlation with the outcome after cholecystectomy. However, he agrees with the gastroenterologist that the clinical features are strong, that the family history adds some further

support, and that there is no evidence for other disorders that may explain the pain. He performs laparoscopic cholecystectomy (Box 17) without complication. Histology of the gallbladder reveals a mild degree of “chronic cholecystitis”. The patient made a good recovery and was free of symptoms when seen a year later by her internist for a routine check-up (Box 18). Had the outcome not been satisfactory, the gastroenterologist had planned to reassess the patient for other functional GI disorders (Box 14), and to consider the possibility of sphincter of Oddi dysfunction (Box 19) (see ‘post-cholecystectomy biliary-like pain’ algorithm).

## Figure legend

1. The typical features of biliary (and pancreatic) pain have been defined (2) as:- episodes of epigastric and/or right upper quadrant pain, lasting 30 minutes or longer and occurring at different intervals (not daily), with the pain building up to a steady level, and being severe enough to interrupt the patient's daily activities or lead to an emergency room visit. It is important to emphasize that the following diagnostic algorithm and discussion refers specifically to pain fulfilling all the above characteristics for biliary-like pain, and especially if one or more of the additional features of the pain outlined below are present. These additional features of the pain that should be established are: whether the pain radiates to the back and/or subscapular region, and whether the pain awakens the patient from sleep; also whether there is associated nausea and vomiting. Pancreatic pain is usually focussed in the epigastrium, with radiation to the mid-back.
2. Abdominal pain consistently relieved by defecation or the passage of flatus, in the absence of alarm features, suggests a functional bowel disorder (1). Alarm features include unintentional weight loss, lymphadenopathy, abdominal mass, bleeding and evidence of anemia.
3. Further evaluation should be undertaken as appropriate; see 'recurrent abdominal pain and disordered bowel habit' algorithm
4. Pain precipitated by movement, coughing or laughing suggests a musculo-skeletal origin.
5. Right upper quadrant/costal margin pain aggravated by sitting up (Carnett's sign) suggests costochondritis, which may respond to local therapy.
6. Pain relieved consistently by antacids or proton pump inhibitors (PPIs) suggests peptic ulceration or gastroesophageal reflux disease.
- 7-9. Upper GI endoscopy is the primary tool for diagnosing mucosal disease of the esophagus, stomach and duodenum. It is also usually undertaken for completeness even when the pain is not relieved by acid

suppression, but ultrasound scanning should take precedence. Note that gallbladder pain and pain from other sources may co-exist, so it may still be appropriate to investigate further for gallbladder disease.

10, 11. Abdominal ultrasound (US) scan and relevant blood tests should be performed initially when gallbladder disease is suspected. US has high accuracy for the detection of gallstones >3 mm in diameter, and for cholecystitis (4). The extent to which it can detect or exclude other conditions (eg bile duct stones, pancreatitis and pancreatic tumors) is highly dependant on the operator, and on the size of any lesion. When symptoms are typical and especially if there are other pointers to gallbladder disease (eg transient liver test abnormalities or a strong family history), there should be no hesitation to repeat the ultrasound scan. Liver biochemistry and serum amylase/lipase are normal in patients with functional gallbladder disorder.

12. With a negative US scan, or scans, of good quality, the next step depends on the degree of continuing clinical suspicion for gallstones or gallbladder disease as opposed to other rarer conditions (eg pancreatitis). In many circumstances, abdominal CT scanning will be chosen to provide a broader survey for abdominal pathology. Good quality CT scans can detect most cases of active and chronic pancreatitis and pancreatic tumors, and intra- and retro-peritoneal masses.

Endoscopic ultrasound (EUS) is the most sensitive test for small gallstones, bile duct stones, and pancreatic disease, but it is not universally available, is operator dependent and is also somewhat invasive.

MR scanning with MRCP provides good images of the abdominal organs and both biliary and pancreatic ductal systems (especially with secretin infusion). It has provided an excellent risk-free alternative to ERCP, which should be reserved for treatment of conditions detected by non-invasive means. The extent to which these scans are used in a particular case should depend on the clinician's level of suspicion for different sources of the pain. For instance, a broader search may be appropriate in a patient aged 65 years (especially someone who is losing weight) than would be reasonable in a fit 30 year old patient.

Gallbladder bile can be sampled for cholesterol crystals with duodenal aspiration after CCK stimulation. The finding of microlithiasis may justify cholecystectomy if there are no confounding factors (eg prolonged fasting). However, this test is cumbersome, requires small bowel intubation, is not well standardized, and has been largely superseded by EUS.

13. Dynamic DISIDA gallbladder scanning (with CCK provocation) can be used to assess gallbladder dysfunction, and is appropriate when suspicion is high and scans are negative. An ejection fraction of <40% is usually taken to define abnormality. However this test is not standardized and may be performed differently in different institutions. Moreover, low ejection fraction can occur in other conditions (diabetes, obesity, celiac disease, and with certain medications such as narcotic and anticholinergic agents) so the result must be interpreted in context, and with caution. The extent to which the results predict the results of surgery is controversial (5,6). Reproduction of pain on injection of CCK has been taken to indicate a gallbladder disorder, but this is not a good predictor of a good surgical outcome. CCK is not universally available for human use.

14. Patients with comprehensive negative investigations, including DISIDA scanning, should be reassessed carefully, especially for other functional gastrointestinal disorders. In a few cases cholecystectomy can still be considered, if the pain is typical and disabling, and especially if there are other pointers, such as a strong family history of gallbladder disease, or transient disturbances of liver enzymes. There is no proven role for sphincter of Oddi manometry (at ERCP) in patients with a gallbladder in place.

15, 16, 17. In this context, the diagnosis of functional gallbladder disorder is suggested by abnormal isotope scanning of the gallbladder.

**Rome III diagnostic criteria (1) for functional gallbladder disorder are 1) episodes of epigastric and/or right upper quadrant pain, lasting 30 minutes or longer and occurring at different intervals (not daily), with the pain building up to a steady level, being moderate to severe enough to interrupt the patient's daily activities or lead to an ER visit, and not being relieved by bowel movements, postural change or antacids 2) exclusion**

**of other structural disease that would explain the symptoms 3) gallbladder present, and 4) normal liver enzymes, conjugated bilirubin, and amylase/lipase. Supportive criteria are: associated nausea and vomiting, pain radiating to the back and/or subscapular region, and pain awakening the patient from sleep.**

However, it is important to note that an abnormal test does not exclude another overlapping functional gastrointestinal disorder as being the cause of the patient's symptoms. For this reason it is appropriate to give a therapeutic trial of medication and to only consider further more invasive treatments on a case by case basis. Thus, if not previously undertaken, an adequate therapeutic trial with an antispasmodic agent, a psychotropic agent or other appropriate agents should be undertaken before consideration of cholecystectomy. Lack of any symptomatic response further supports the consideration for cholecystectomy.

As indicated above, however, clinical studies evaluating the role of cholecystectomy in symptomatic patients without gallstones but with positive dynamic biliary imaging have provided variable results. One systematic review and meta-analysis found that patients with suspected functional biliary pain with decreased gallbladder ejection fraction did not have a better symptomatic outcome after cholecystectomy than those with normal ejection fraction (7). A recent systematic review, however, addressed a different question, concluding that patients with biliary-like pain without gallstones but with a decreased gallbladder ejection fraction are more likely to experience symptom relief following cholecystectomy than those treated medically (8). An earlier analysis examining this question came to a similar conclusion (9). It is clear that further prospective randomised clinical studies are required to determine definitively the role of dynamic isotope biliary scanning in the investigation and management of acalculous biliary-like pain.

18. The diagnosis of a functional gallbladder disorder is confirmed by the relief of pain following cholecystectomy, for a period longer than 12 months.

18,19. Lack of pain relief following cholecystectomy requires reassessment, initially to rule out a complication of surgery or residual pathology (eg duct stones). If the pain remains the same as pre-operatively, diagnostic



considerations would include sphincter of Oddi dysfunction (see algorithm for 'post-cholecystectomy biliary-like pain'), or a non-biliary source, including other functional gastrointestinal disorders.