

David Ivan Croteau, MD,  
FAAFP  
Lakeland Regional  
Medical Center, Lakeland,  
Fla

✉ david.croteau@lrmc.  
com

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# Speed your diagnosis of this gallbladder disorder

Fatty infiltration of the internal organs—and the inflammation associated with it—is an increasingly common cause of gallbladder dysfunction. Here’s what to keep in mind to identify it without delay.

## PRACTICE RECOMMENDATIONS

› Use the Rome III guidelines to diagnose and treat functional gallbladder disorder; when this benchmark is followed, cholecystectomy results in ~90% resolution rate. **(B)**

› Keep in mind that classic biliary symptoms, particularly right upper quadrant pain, pain after eating, and reproduction of pain with cholecystokinin injection, are highly predictive of a successful postoperative outcome. **(C)**

› Offer cholecystectomy to patients who present with classic biliary symptoms and an abnormal hepatobiliary iminodiacetic acid (HIDA) scan. **(C)**

### Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

**CASE ▶** Dionne J, a 38-year-old woman with a BMI of 32, presents with a 2-month history of right upper abdominal pain. The pain is intermittent and often begins after eating, she reports, particularly when a meal includes fatty foods. She has no nausea, vomiting, diarrhea, constipation, or fever, and the pain is not getting progressively worse.

When the pain comes on, Ms. J says, it lasts about an hour, sometimes less. It is colicky in nature, and not relieved with bowel movements or position change. The patient tried ranitidine 150 mg twice a day for 2 weeks, with no relief. You suspect functional gallbladder disorder. But is Ms. J a candidate for a cholecystectomy? What would you do next?

**O**ver the past 2 decades, the incidence of cholecystectomies due to functional gallbladder disorder (FGBD) has multiplied, going from about 5% to 20% to 25%.<sup>1</sup> But definitive information about the etiology of FGBD has not kept pace.

Although the Rome III diagnostic guidelines for FGBD, published in 2006,<sup>2</sup> remain the standard of care, a number of more recent studies have added to our understanding of this disorder. This review of the diagnosis and treatment of FGBD incorporates both the Rome III guidelines and the latest findings. The text and tables that follow can help you recognize this clinical entity earlier, minimize the number of tests needed to arrive at a definitive diagnosis, and establish a plan of care that is consistent with both the guidelines and the evidence.

## As obesity rates rise, so does gallbladder dysfunction

Obesity has been shown to produce a chronic proinflammatory state throughout the body,<sup>3-6</sup> which has been linked to fatty

### Pain after gallbladder surgery? Consider sphincter of Oddi dysfunction

David Ivan Croteau, MD,  
FAAFP

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TABLE

## Rome III diagnostic criteria for functional gallbladder disorder

Must include episodes of pain located in the epigastrium and/or right upper quadrant and *all* of the following findings:

- Gallbladder is present
- Normal liver enzymes, conjugated bilirubin, and amylase/lipase
- Episodes lasting  $\geq 30$  minutes
- Recurrent symptoms occurring at different intervals (not daily)
- The pain builds up to a steady level
- The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
- The pain is not relieved by bowel movements
- The pain is not relieved by postural change
- The pain is not relieved by antacids
- Exclusion of other structural disease that would explain the symptoms

### Supportive criteria

The pain may present with one or more of the following findings:

- Pain is associated with nausea and vomiting
- Pain radiates to the back and/or right infrascapular region
- Pain awakens the patient from sleep in the middle of the night

Source: Behar et al. *Gastroenterology*. 2006;130:1498-1509.<sup>2</sup> Used with permission from Elsevier.

infiltration of the gallbladder (among other organs) and impaired contractility.<sup>3,6-9</sup>

A study by Al-Azzawi et al highlighted the importance of increased fat in the gallbladder wall as a key cause of dysmotility.<sup>10</sup> The researchers compared wall thickness, inflammation, and the amount of fat in the walls of gallbladders that had been removed for both acalculous and calculous disease with the characteristics of gallbladders removed for reasons unrelated to organ dysfunction (the controls). Those with dysmotility, they found, had more fat in the wall but the same wall thickness as the controls. The amount of fat in the walls was similar for the acalculous and the calculous groups, but the gallbladders in which stones were found had more inflammation and increased wall thickness.<sup>10</sup>

Several other studies have found evidence of both inflammation and fatty deposits in the walls of gallbladders removed for acalculous disease.<sup>2,4,11-13</sup>

In one study, researchers found chronic inflammation in 99% of gallbladders re-

moved from patients who had classic biliary symptoms but no gallstones.<sup>11</sup>

FGBD appears to be initiated by fatty infiltration of the gallbladder wall, causing increasing levels of inflammation and steatocholecystitis that lead to poor motility.<sup>3,4,6-10</sup> This in turn alters bile composition, which can lead to sludge and stone formation.<sup>2,6,10</sup> The finding by Al-Azzawi et al of greater thickness and inflammation in the walls of gallbladders with calculi suggests that gallstones result from progressively worsening inflammation and dysmotility.<sup>10</sup>

### Steps to take for a definitive diagnosis

A diagnosis of FGBD requires a history of classic gallbladder symptoms, many but not all of which are specified in the Rome III diagnostic criteria (TABLE). Classic symptoms include nausea, vomiting, right upper quadrant pain, pain after eating, and reproduction of pain with cholecystokinin (CCK) injection. Cramping, bloating, reflux, diarrhea, fullness, and epigastric pain are atypical symptoms.<sup>2,11</sup>

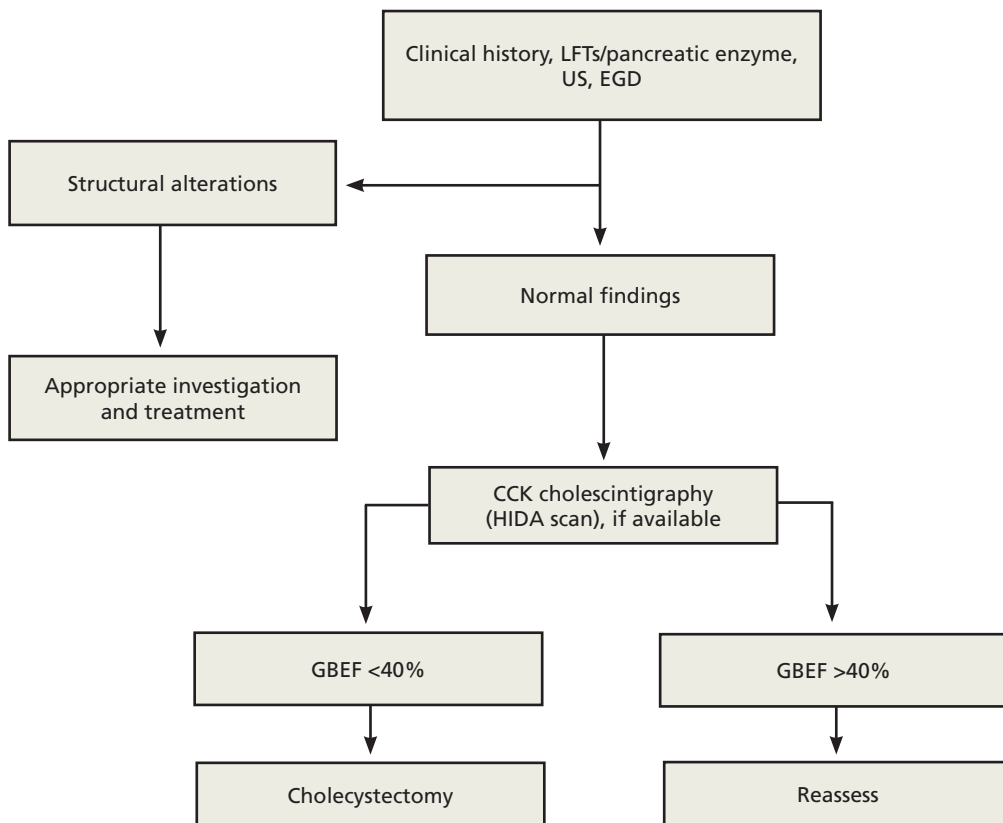
CONTINUED



**Evidence suggests that gallstones develop as a result of progressively worsening inflammation and dysmotility.**

**ALGORITHM**

**Diagnostic workup and management of functional gallbladder disorder (Rome III)**



CCK, cholecystokinin; EGD, esophagogastroduodenoscopy; GBEF, gallbladder ejection fraction; HIDA, hepatobiliary iminodiacetic acid; LFTs, liver function tests; US, ultrasound.

Source: Behar J et al. *Gastroenterology*. 2006;130:1498-1509.<sup>2</sup> Used with permission from Elsevier.

**Rule out structural causes**

There is no single test for FGBD, and a definitive diagnosis can be made only after structural causes of the symptoms (eg, gallstones, tumor, sclerosis, and cirrhosis) have been ruled out (ALGORITHM).<sup>2</sup> Initial tests include liver and pancreatic enzyme laboratory screening and an ultrasound of the upper right quadrant. In patients with FGBD, both the lab tests and the ultrasound will be normal.

The Rome III guidelines also call for an esophagogastroduodenoscopy (EGD) to rule out esophagitis, gastritis, and duodenitis, although some researchers have held that if the other tests are normal, this test need not be done.<sup>12</sup> If the EGD is also normal—or not

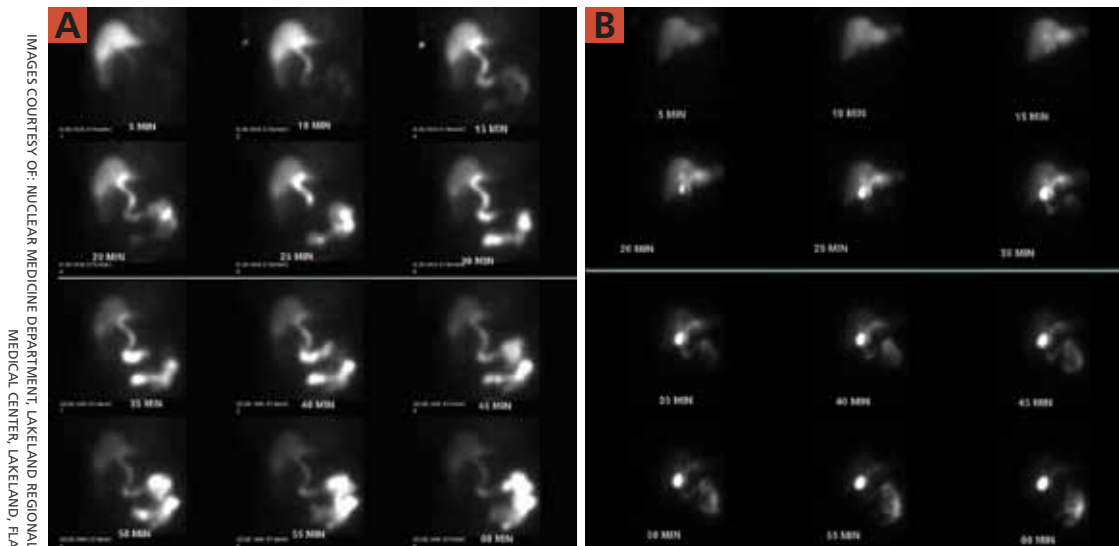
done—a hepatobiliary iminodiacetic acid (HIDA) scan is the next step in the diagnostic pathway. The scan tests the gallbladder's ejection fraction (EF), revealing the percentage of radioactive dye ejected from the organ after CCK is injected (FIGURE).<sup>2</sup> The injection of CCK should be done over a minimum of 30 minutes, the guidelines specify. The shorter the time frame used for the injection, the less likely that the pain will be reproduced or that the EF findings will be reliable.<sup>14</sup>

Most researchers define a normal EF as >35%,<sup>10,11,13</sup> but the Rome III criteria use a cutoff of 40%. A patient who has an EF <40% and meets the other guideline criteria is diagnosed with FGBD.

>  
 Right upper quadrant pain, pain after meals, and pain reproduced with an injection of cholecystokinin are the most highly predictive of long-term symptom relief from cholecystectomy.

## FIGURE

## Abnormal vs normal HIDA scans: What you'll see



IMAGES COURTESY OF: NUCLEAR MEDICINE DEPARTMENT, LAKELAND REGIONAL MEDICAL CENTER, LAKELAND, FLA

The larger amount of contrast dye retained in the abnormal scan (A) compared with the normal scan (B) is evidence of a poor ejection fraction.

**CASE ►** On physical examination, Ms. J has pain in the right upper quadrant, with no guarding or rebound, and normal bowel sounds. Her liver and pancreatic enzyme tests are normal, and an ultrasound shows no sludge, no stones, and mild edema of the gallbladder wall. The patient declines an EGD because of the cost but undergoes a HIDA scan—which reveals that she has an EF of 25%.

### Will cholecystectomy bring long-term relief?

There are 2 options for a patient diagnosed with FGBD—medical management, consisting of lifestyle modifications such as dietary change and weight loss and medication for symptom relief—or cholecystectomy. Surgery should be offered to any individual who, like Ms. J, meets the Rome III diagnostic criteria and has an abnormal HIDA scan. Recent studies have raised questions about the correlation between HIDA results and postoperative relief,<sup>11,12</sup> however, and indicate that patients who have classic biliary symptoms and a *normal* HIDA scan often have good postoperative outcomes, as well.<sup>11,15</sup>

A careful workup is key to ensuring maximal benefit from surgery. The resolution

of symptoms with a cholecystectomy when the Rome III criteria are followed for patient selection has been found to be close to 90%.<sup>11,15-20</sup> Two recent studies have examined the resolution rate for FGBD, with conflicting results.<sup>11,12</sup> Both studies were based on long-term postoperative follow-up, ranging from 6 to 24 months. The main difference was the selection bias used in determining eligibility for the study.

The initial selection criteria for the study by Carr et al (N=93) were presenting symptoms (either classic or atypical), followed by a typical workup. The long-term resolution rate for those with classic gallbladder symptoms was 88%<sup>11</sup>—close to the 90% associated with the Rome III guidelines. The study by Singhal et al (N=141)<sup>12</sup> was done retrospectively, using objective data from tests (ie, normal ultrasound and liver biochemistries and abnormal HIDA) rather than patient history as the criteria for inclusion. Among participants in the Singhal study, the long-term resolution rate was just 57%.

Ironically, the patients in the Carr study who had atypical symptoms had mixed postoperative results. The rate of long-term resolution for this cohort was 57%—the same as the overall resolution rate found by Singhal et

al.<sup>11,12</sup> The fact that a group of patients who presented atypically had the same postoperative resolution rate as those for whom tests (rather than symptoms) were used as the selection criteria illustrates the importance of presenting symptoms as a prognostic indicator.

**CASE ►** Ms. J opts for a cholecystectomy and

you refer her to a general surgeon. At her annual exam the following year, she reports that she has been symptom free since the surgery. **JFP**

**CORRESPONDENCE**

David I. Croteau, MD, FAAFP, LPMC Family Medical Center, 300 Parkview Place, Lakeland, FL 33805; David.Croteau@lrmc.com

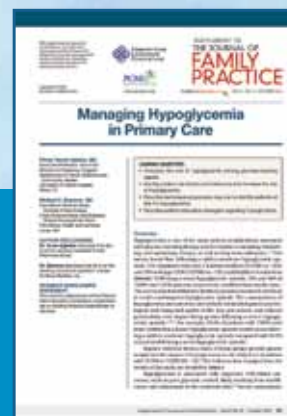
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# Managing Hypoglycemia in Primary Care

This supplement on hypoglycemia will help you to:

- ▶ Educate patients about their risk of hypoglycemia
- ▶ Identify risk factors and behaviors that increase the risk of hypoglycemia in patients
- ▶ Compare glucose-lowering agents and the risk of hypoglycemia associated with them



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