Case-based review

Ten percent to 20% of Americans will develop gallstones. Bile salts and bile acids may be interchangeably used, although their strict physicochemical properties differ [1,2]. The basis for most biliary tract disease, gallstones are a significant health care burden in the United States, where more than 700,000 cholecystectomies are performed annually. The resultant cost from symptoms and complications approach $10 billion [3].

Most (about 85%) gallstones consist of cholesterol. Cholesterol gallstones primarily form because of an imbalance in the composition of bile [4]. Bile is 95% water. Its 3 major organic solids are lipids: bile acids, phospholipids (lecithin), and cholesterol. Cholesterol and lecithin are water insoluble, being predominantly hydrophobic molecules. The remaining constituents are electrolytes plus a rather small amount of pigment (conjugated bilirubin). In the first stage of cholesterol gallstone formation, the liver secretes excess cholesterol relative to the solubilizing components, bile salts and lecithin. This results in supersaturated bile. The next stage is nucleation in which factors like certain proteins in bile hasten the precipitation of the excess cholesterol out of solution, forming microcrystals. Mucin, a glycoprotein secreted in excess by the gallbladder mucosa, then acts as a matrix scaffold to retain these cholesterol microcrystals. An early stage in gallstone formation is the appearance of biliary sludge (“microlithiasis”). Sludge consists of cholesterol microcrystals, mucin, and pigment material (bilirubinate). In the last stage, retention and growth, impaired gallbladder contractility holds on to this precipitated material, allowing the microcrystals to agglomerate and grow into overt gallstones.

The interaction of multiple genetic and environmental factors predisposes certain individuals to form gallstones [1,5]. Genes contribute 25% to the phenotype, most evident as the basis for ethnicity and a familial predisposition. A combination is necessary: genetic traits predisposing to stone formation triggered by exogenous and dietary factors, yielding the phenotypic expression. Gallstones reach epidemic proportions in the North and South American Indian populations, in which 60% to 70% develop gallstones. The risk is also...
increased in Hispanics. In contrast, the rate in sub-Saharan Africa and Asia is quite low. Obesity, a major risk factor, likely relates to insulin resistance (the metabolic syndrome) and leads to excessive cholesterol secretion by the liver. Evolution and circumstance in Native American Indians may have ironically selected those with “thrifty” genes that conserve energy; these genes likely had a survival advantage in the distant past. Abundant access to food now has placed such individuals at an increased risk for obesity and cholelithiasis. Hence, a genetic trait complicated by obesity (and the metabolic syndrome) elicits excessive cholesterol secretion into bile and results in a cascade that yields a gallstone.

In addition to cholesterol gallstones, there are pigmented stones. Black pigment stones, which make up a minority of gallstones (< 15%), consist of a polymer of calcium bilirubinate. They develop in cirrhosis (likely from altered bilirubin metabolism), hemolytic states (from excess bilirubin production), and ileal Crohn’s disease (enhanced bilirubin absorption in the intestine and return to the liver for re-secretion). Altered bilirubin metabolism may, in part, account for age increasing the prevalence in both sexes. Brown pigment stones, in contrast, develop in the bile ducts as a result of bacteria and inflammation that degrade (deconjugate) bilirubin and other bile constituents. They are associated with infection/inflammation from biliary strictures in developed countries and with parasitic infestations in Asia.

CASE STUDY
Initial Presentation
A 27-year-old pregnant Hispanic women is found to have gallbladder sludge at routine ultrasonographic evaluation done as part of her prenatal assessment.

History
The pregnancy, her first, has been uneventful. In the first trimester, she experienced morning nausea and vomiting that disappeared after 6 weeks. She also developed heartburn, manifest by retrosternal burning and occasional acid regurgitation, occurring 2 to 3 times a week and responding to periodic use of ranitidine 300 mg. The ultrasound was performed at 12 weeks as part of a routine prenatal screen. The fetus was normal, but the ultrasound incidentally revealed the presence of biliary sludge in the gallbladder (Figure 1).

The patient has had gut problems dating back to childhood. She had had chronic constipation that recently worsened with the pregnancy. She also experiences bloating and lower abdominal crampy pains, usually relieved by defecation. She has had indigestion for the past few years. Fatty foods are a particular problem, aggravating the abdominal discomfort and occasionally precipitating diarrhea in the form of 2 to 4 loose bowel movements. Investigations several years ago for these digestive complaints led to her being told that she had irritable bowel syndrome (IBS). Celiac serology was negative. Family history is pertinent. Her mother and 2 of 3 sisters have had gallbladder surgeries as did the maternal grandmother. None have known liver disease. The patient uses no drugs other than supplemental vitamins and folic acid. She has always been overweight: her body mass index prior to the pregnancy had been 32 kg/m². Her weight gain in the first trimester was somewhat higher than that recommended by her physician.

Physical Examination
The patient appears healthy and has normal vital signs. She is afebrile. Abdominal examination reveals a gravid uterus at the expected gestational age. There is no tenderness or other abnormal findings. The fetal heart sounds are normal at 130 bpm.

Investigations
Laboratory tests show a normal complete blood count (white blood cell count, 7500/mm³), elevated alkaline phosphatase of 367 U/L (normal, < 150 U/L), and normal total bilirubin 9.6 μmol/L (normal, < 20 μmol/L). Other biochemistries (aminotransferase, δGT, and lipase) are normal. On the abdominal ultrasound done at 12 weeks, no gallstones are evident. The gallbladder wall is not thickened. There is no sonographic Murphy’s sign.

• How common is gallbladder disease during pregnancy?

Biliary sludge develops in one third of women during pregnancy but commonly resolves in the postpartum period.
After delivery, 5% of women continue to have sludge. Gallstones appear in 3% of pregnant women and may not disappear in the puerperium.

Biliary sludge is a precursor to gallstones. When aggregates of sludge grow above 2 to 3 mm in size, they produce higher amplitude echoes with acoustic shadowing, evolving into gallstones that possess different characteristics on ultrasonography (Figure 2). Sludge and gallstone formation during pregnancy relate to the accompanying changes that predispose to each stage: the excessive secretion of cholesterol (from estrogens) and gallbladder stasis (from progestins). Additional factors in this particular patient are her obesity and genetic background. Hispanics with some admixture of Native American have a predilection to cholesterol gallstone formation [1].

- **How are complications of biliary stone disease managed in pregnancy?**

Sludge and/or gallstones can lead to a range of complications, from episodes of self-limiting biliary colic to acute cholecystitis to either biliary tract obstruction and cholangitis or pancreatic duct obstruction and acute pancreatitis [6]. Such biliary tract complications of gallstones represent the second most common non-gynecologic condition requiring surgery in pregnancy, with cholecystectomy performed in 1 to 8 of every 10,000 pregnancies. The presence of biliary sludge or gallstones, however, does not necessarily mean that a complication will ensue.

The appropriate management of biliary tract complications during pregnancy has been controversial. Some advocate avoiding surgery, whereas more recent evidence favors an aggressive surgical management. Despite the attendant grave implications for maternal and fetal morbidity, surgery in appropriate cases can be safe. It reduces the need for labor induction, preterm deliveries, and fetal morbidity [7,8]. Thus, should acute cholecystitis, cholangitis, or pancreatitis develop during a pregnancy, early cholecystectomy and, when appropriate, endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP), become quite reasonable. In the past, ERCP and MRCP have been contraindicated in pregnancy because of the perceived concerns that exposure of the fetus to ionizing radiation and magnetic fields posed a risk. The quantity of radiation during ERCP is estimated at 18 to 310 mrad, much lower than the harmful dose (5–20 mrad) at which fetal damage occurs [8]. Radiation risk is highest during the first trimester. Another precaution is to limit the fluoroscopy time. Case reports on the use of MRCP indicate that this too does not yield any increased risk to the fetus or the mother [8].

- **What is the significance of the patient’s abdominal complaints?**

This patient does not exhibit features of typical biliary colic. True biliary pain (biliary colic) consists of episodes of steady right upper abdominal or epigastric pain that persists for 30 minutes to less than 6 hours. It may be accompanied by nausea and vomiting but not fever. Laboratory features of inflammation or cholestasis are absent. In this patient, only the alkaline phosphatase is elevated, a common finding during pregnancy; the source of the alkaline phosphatase is not the liver but instead arises from the placenta.

The patient does not have symptoms of gallstone disease. True biliary pain (biliary colic) from gallstone disease is characteristically pain in the right hypochondrium and/or epigastrium [3,9]. This patient’s symptoms are more reflective of functional dyspepsia and IBS. Dyspepsia as defined in an American Gastroenterological Association position statement is “a chronic or recurrent pain or discomfort centered in the upper abdomen [10].” The Rome III diagnostic criteria for functional dyspepsia includes a negative gastroscopy to rule out organic disease (Table 1) [11], something that is not warranted in this case. There is nothing to suggest a peptic ulcer. The symptoms are not recent, and there are no “alarm” features. Further, her crampy abdominal pain relieved by defecation, bloating, and altered bowel habits are more in line with the IBS. IBS is characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause [12] and includes a wide array of symptoms.
GALLSTONE DISEASE

Table 1. Rome III Diagnostic Criteria for Functional Dyspepsia

One or more of:
- Bothersome postprandial fullness
- Early satiety
- Epigastric pain
- Epigastric burning

AND

No evidence of structural disease (including a negative upper endoscopy) that is likely to explain the symptoms

These criteria should be present for the last 3 months with symptom onset at least 6 months before diagnosis


Table 2. Rome III Diagnostic Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months

Associated with 2 or more of the following:
- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

These criteria should be present for the last 3 months with symptom onset at least 6 months before diagnosis


with both gastrointestinal and extraintestinal complaints (Table 2). Clinical overlap between these functional gut disorders is common.

In the past, the abdominal discomfort and bloating that follow a heavy, particularly fatty meal has been termed “fatty food” intolerance. In fact, dyspepsia is not a particular manifestation of gallstone disease, while fatty foods do not necessarily precipitate attacks of biliary colic [9,13].

- What is the association between gallstones and biliary pain?

Biliary-type pain is common. In a U.S. household survey of presumed “healthy” individuals, 0.6% of men and 2.3% of women had biliary pain [7]. In an Italian ultrasound study, biliary pain occurred in as many as 7.6% of men and 20.7% of women, none of whom had gallstones [14,15]. From a different perspective, up to 82% of patients with gallstones incidentally detected on ultrasonography do not have any biliary symptoms [14,16]. These “silent” gallstones remain clinically innocuous in most individuals. Only 13% of people with gallstones develop biliary pain when followed for 15 to 20 years [17].

If symptoms develop in a person with documented cholelithiasis, the likelihood of recurrent symptoms is high (30%–50% per year) [9,15]. Pain severity appears to progressively increase from clinically silent to overt symptoms (sufficient to stop activity or the development of gallstone complications) parallel to the natural history of gallstone disease: from silent gallstones to symptomatic gallstones to cholecystectomy [9]. Although stone characteristics do not predict pain, sex differences exist in terms of pain frequency in those with gallstones. In men, the prevalence of biliary-type pain is no different in those with stones (7.6%) than those without gallstones (7.8%). In women, pain is more common, approaching 34.8% in those with gallstones versus 20.7% in those without gallstones. Such frequency differences may be iatrogenic because women have more regular visits to their physicians or perhaps reflect their natural history: women develop stones earlier in life. Thus, gallstones and abdominal pain are not synonymous, and biliary-type pain can occur in the absence of gallstones. It is therefore not surprising that biliary pain occurs without gallstones, and chronic abdominal pain can persist in 20% to 50% of patients following cholecystectomy [18,19]. Many of these postcholecystectomy complaints are rather nonspecific. In the “postcholecystectomy syndrome,” only 14% of patients experience true biliary pain. Hence, routine cholecystectomy is not warranted for gallstones that are clinically silent [17].

- What causes biliary pain?

The basis for biliary pain when the gallbladder is intact has been attributed to obstruction: the gallbladder contracting against a fixed (eg, gallstone) or functional obstacle either at the cystic duct or at the sphincter of Oddi (eg, sphincter of Oddi spasm). Such obstruction might then stimulate the gallbladder mucosa to produce a phospholipase, which hydrolyses one fatty acid from the phospholipid (lecithin) in bile, producing lysolecithin. This biological detergent will initiate an inflammatory reaction (cholecystitis); the attendant inflammatory mediators then contribute to the pain. Prostaglandin, for example, might mediate the inflammatory response. The pathogenesis of biliary pain is less clear in cholesterol gallstone disease without cholecystitis, where the excessive cholesterol in bile actually
leads to defective signal transduction (at the level of the sarcolemma) and depressed smooth muscle contractility, begging the question as to how reduced gallbladder contraction can result in pain [20]. In fact, the normal biliary tract is a low-pressure conduit for bile secreted from the liver. During the interdigestive period, the gallbladder should function as a reservoir to decompress and modulate any marked increases of intrabiliary pressure. With meals, the gallbladder contracts and the sphincter of Oddi customarily relaxes to expedite bile entering the duodenum. Other than the gallbladder and sphincter of Oddi, the biliary tract is devoid of smooth muscle. In acute cholecystitis, the basis for biliary pain resides in the inflammatory process. In a setting of biliary colic without overt inflammation or clear cut mechanical obstruction, the origin remains obscure at this time.

**Patient Follow-up**

The patient is not having any biliary symptoms, but her 18-week (routine follow-up screen) ultrasound examination still shows evidence of sludge in the gallbladder. She subsequently has a rather normal delivery. Because of the potential confusion with her functional gut symptoms, another ultrasound is performed at 6 weeks postpartum. This time, the gallbladder is free of sludge (Figure 3). However, the mid-abdominal, crampy pain relieved by defecation, chronic constipation, bloating, and flatulence continue.

Four years later she returns with slightly different symptoms. She has been having rather severe, steady right upper quadrant pain that is sufficient in severity to bring her to her physician. Attacks are quite discrete, lasting 1 to several hours. Between episodes, she is otherwise well, although the IBS features have not resolved.

Her physical examination is unremarkable except that she continues to be obese with a body mass index of 34 kg/m². Laboratory testing shows normal complete blood count, liver biochemistries, and lipase. An abdominal ultrasound is normal. There is no sludge or stones; the wall is not thickened.

The primary care physician arranges a cholecystokinin (CCK)-cholescintigraphic scan. The CCK-8 (octapeptide of cholecystokinin) infusion causes some abdominal discomfort but does not reproduce her pain. Gallbladder emptying is impaired with an ejection fraction less than 30% (Figure 4).

- **What is the patient’s diagnosis?**

The gallbladder and the sphincter of Oddi normally function as an integrated unit, regulating the delivery of bile from the liver through the biliary tract and into the duodenum. The sphincter of Oddi also controls pancreatic secretions. The gallbladder collects and stores hepatic bile during fasting, concentrating it to reduce the volume. The gallbladder accommodates this volume through receptive relaxation, limiting any rise in pressure [20]. Eating causes the gallbladder to evacuate 75% of its contents through neural (cholinergic and local gastroduodenal reflexes) and hormonal (CCK acting via cholinergic nerves) mechanisms. Emptying occurs through smooth muscle contraction of the gallbladder, coordinated with a reduction in sphincter of Oddi tone. CCK also relaxes the sphincter of Oddi through neural (nitric oxide–mediated) pathways. Biliary tract pressures therefore should normally remain rather low, well below the maximal secretory pressure generated by the liver that can be as high as 40 mm Hg.

Gallbladder dyskinesia represents true biliary-type pain occurring in the absence of gallstones: the gallbladder appears normal on abdominal ultrasound. Functional disorders of the gallbladder and the sphincter of Oddi must be distinguished from such common conditions as gastroesophageal reflux disease, functional dyspepsia, IBS, and more sinister entities like cholecystitis and pancreatitis [21] (Table 3). The basis has been attributed to impaired gallbladder emptying, hence the term dyskinesia [20]. This may occur from reduced gallbladder contraction [22] due to inflammation (hence the synonym, chronic acalculous cholecystitis) or an intrinsic contractile problem (perhaps related to excess cholesterol in the membrane as occurs in cholesterolosis). Changes of chronic cholecystitis are variable and not predictive of a therapeutic success [23,24].

Perhaps there is a spectrum of gallbladder disease commencing with cholesterol saturation of bile, followed by gallbladder dysmotility leading to microcrystal growth and culminating in gallstone formation and gallbladder...
Figure 4. Cholecystokinin (CCK)-cholescintigraphy showing normal gallbladder filling and emptying in response to cholecystokinin (CCK). Continuous imaging of the gallbladder is acquired for 60 minutes, following the intravenous IV administration of 2 mCi technetium ($^{99m}$Tc)-labeled hepatominodiacetic acid (HIDA). Gallbladder emptying is then assessed in response to CCK-8 infused intravenously at 0.02 µg/kg over 30 minutes. Representative scans are shown for 5, 30, and 60 minutes after the $^{99m}$Tc-HIDA injection and then at 60 minutes following the CCK infusion. (A) The radiolabel has been taken up by the liver. (B) At 30 minutes, activity has declined over the liver as it fills the gallbladder and enters the duodenum. (C) By 60 minutes, little remains in the liver while the gallbladder is well-delineated with the reminder of activity seen in the small intestine. (D) 60 minutes after initiating the CCK infusion, the gallbladder has become quite empty. Most radioactivity is now in the small intestine. CCK-cholescintigraphy showing impaired emptying in response to CCK. (E) Shows normal gallbladder filling. At 30 minutes after $^{99m}$Tc-HIDA injection, radioactivity is clearing the liver and filling the gallbladder. Following CCK administration, the gallbladder retains most of its contents at 60 (F) and at 90 minutes (G), indicating that emptying is impaired, as it is in this case.
inflammation [25]. The common occurrence of dysmotility-
like symptoms (eg, constipation, gastroparesis) in those
with gallbladder dyskinesia has lead to the suggestion that
the basis may reflect a generalized motility disorder of the
gut [26,27]. Another cause of impaired gallbladder empty-
ing might result from partial obstruction of outflow from the
gallbladder. Such obstruction might reside at the level of the
gallbladder neck or cystic duct (termed the cystic duct syn-
drome, the “fighting gallbladder”), or the sphincter of Oddi
(sphincter of Oddi dysfunction). Alternatively, the source of
pain might be a feature of visceral hypersensitivity involv-
ing the gallbladder, biliary tree, or an adjacent structure, just
as it occurs with other functional gut problems [20,28]. In
fact, there might be more than one origin of the symptoms,
explaining some of the difficulty in identifying adequate
diagnostic tests and the reported differences in outcome
following cholecystectomy: In some individuals, the under-
lying problem may relate to dysfunction of the sphincter
of Oddi rather than the gallbladder [29]. Others may have
stone disease that was missed by standard diagnostic imag-
ing. Transabdominal ultrasound, although over 95% sensi-
tive, has its limitations, particularly for small stones. Some
reports have found gallstones at cholecystectomy performed
for presumed gallbladder dyskinesia [27,30,31]. Endoscopic
ultrasound and the microscopic analysis have been used to
better exclude gallstone disease [32,33], but validated stan-
dards do not exist at this time.

- **How is functional gallbladder disorder diagnosed?**

The diagnosis of functional disorder of the gallbladder cur-
rently rests on demonstrating impaired gallbladder empty-
ing, using cholecintigraphy to quantitate a decrease in the
gallbladder ejection fraction induced by CCK (Figure 5) [21].
This nuclear scanning technique generates time-activity
curves for the gallbladder after intravenous CCK-8 ad-
ministration [34]. The radionuclide originally used was
technetium 99m-labeled hydroxy iminodiacetic acid, hence
the term HIDA scan. Gallbladder emptying is expressed as
an ejection fraction, which is the percentage change of gall-
bladder counts after the CCK stimulus. The dose of CCK-8
used and the duration of administration have not been
uniformly established. Most reasonable is to infuse CCK
at a low dose and slowly over 30 minutes rather than 3 to
5 minutes. The long, slower infusion simulates CCK release
after a meal rather than the acute pharmacologic bolus that
likely has poorer reproducibility. The “normal” response to
the 30-minute CCK infusion is commonly set at an ejection
fraction greater than 30% to 35% although one (Rome III)
consensus placed the normal gallbladder ejection fraction
at greater than 40% [21]. Further confounding the value of
CCK-cholescintigraphy are the multiple causes of impaired
gallbladder emptying (Table 4). All these factors limit the
value of gallbladder emptying to predict those who might
benefit from cholecystectomy [20,23]. Critical analysis of
reports suggests that CCK-cholescintigraphy is not reliable
in predicting a positive outcome following cholecystectomy
[35,36]. The various methods used to perform cholescintig-
raphy (particularly the rapid CCK bolus dosing) undoubt-
edly detract from the ability of this test to accurately predict
those who would benefit from cholecystectomy [37]. Fur-
ger, the entity may well represent more than just impaired
gallbladder emptying [20]. Laparoscopic cholecystectomy,
intuitively the definitive therapy for a disorder affecting the
gallbladder, is therefore not warranted except in exceptional
cases or in a research protocol.

**Additional Follow-up**

The patient has additional episodes that lead to a
surgical opinion and an uneventful laparoscopic
cholecystectomy. The gallbladder shows an increase infil-
tration of chronic inflammatory cells, sufficient for the
pathologist to label it as chronic mild cholecystitis. Within a few
weeks of the surgery, the patient begins noticing a change

### Table 3. Rome III Diagnostic Criteria for Functional
Gallbladder Disorder

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Episodes of pain located in the epigastrium and/or right upper quadrant</td>
<td>Episodes lasting &gt; 30 minutes</td>
</tr>
<tr>
<td>The gallbladder is normal—no stones or sludge. Tests of the liver (enzymes, conjugated bilirubin) and pancreatic (lipase/amylase) are normal</td>
<td>Recurrent symptoms occurring at different intervals (not daily)</td>
</tr>
<tr>
<td>The pain builds up to a steady level</td>
<td>The pain is moderate to severe, enough to interrupt daily activities or lead to an emergency department visit</td>
</tr>
<tr>
<td>The pain is not relieved by:</td>
<td>The pain is not relieved by:</td>
</tr>
<tr>
<td>Bowel movements</td>
<td>Postural change or Antacids</td>
</tr>
</tbody>
</table>

Supportive criteria:

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

GALLSTONE DISEASE

in her bowel motions. She has 4 to 5 loose stools during the day in association with crampy abdominal pain, which is relieved by defecation. Soon thereafter, the troublesome bloating recurs. The diarrhea becomes a significant problem in her daily existence.

• What is the cause of this patient’s diarrhea?

The “postcholecystectomy syndrome” is an ill-defined entity, ranging from mild digestive symptoms to severe attacks of abdominal pain and jaundice. Following removal of the gallbladder for symptomatic cholelithiasis, most patients experience a satisfactory outcome with relief of symptoms. Depending upon the original indications for the cholecystectomy, however, 20% to 50% of patients will continue to have a variety of abdominal symptoms, including dyspepsia, flatulence, eructation, and food intolerances [38]. As there are over 700,000 cholecystectomies performed annually in the United States, a frequency that has been rising with the advent of laparoscopic cholecystectomy [39], this syndrome could represent an ever-increasing health problem. An overt, structural problem, such as retained common duct stones, biliary stricture, pancreatitis, or a neoplasm, is an obvious cause of continued symptoms in some individuals following cholecystectomy. They will experience rather classical biliary-type pain, cholestasis, or cholangitis. Others with less specific complaints have no obvious disease. Whether or not a cystic duct remnant might give rise to symptoms in some patients is unclear. In this case, the indications for performing the cholecystectomy were flawed, and the patient developed a postcholecystectomy complication, diarrhea.

A continuation of symptoms following cholecystectomy is usually construed as “functional” when no organically defined basis exists for the discomfort or complaint. Sphincter of Oddi dysfunction is an uncommon entity [21]. It characteristically is accompanied by features of transient biliary obstruction with elevated liver enzymes. If the pancreatic component of the sphincter is involved, pain, elevated pancreatic enzymes, and even pancreatitis can result. Measuring pressure in the sphincter of Oddi requires ERCP, which is invasive and carries a high risk of complications. Suspected patients should be referred to an expert unit for such assessment, but only in the presence of compelling clinical evidence and after noninvasive tests are negative.

In the present case, the patient’s symptoms of abdominal pain, altered bowel movements, and bloating remain in keeping with the diagnosis of IBS. The development of diarrhea might be a feature of this entity. Alternatively, it could be an unmasking of a congenital defect in bile salt absorption in the terminal ileum [40]. Removal of the gallbladder and its reservoir function provides a rather continuous delivery of bile to the small intestine. Failure to actively absorb bile salts/bile acids in the ileum allows their spill

### Table 4. Causes of Impaired Gallbladder Emptying

<table>
<thead>
<tr>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Primary gallbladder disease</td>
</tr>
<tr>
<td>Cholesterol gallstones</td>
</tr>
<tr>
<td>Prior to stone formation as evidenced by microcrystals of cholesterol and following medical dissolution</td>
</tr>
<tr>
<td>Pigment stones</td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
</tr>
<tr>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Acute or chronic, with or without stones</td>
</tr>
<tr>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>Obesity, diabetes, pregnancy, VIPoma, sickle hemoglobinopathy</td>
</tr>
<tr>
<td>Neuromuscular defects</td>
</tr>
<tr>
<td>Myotonia dystrophic</td>
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<tr>
<td>Denervation (spinal cord injury, vagotomy)</td>
</tr>
<tr>
<td>Functional abdominal pain</td>
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<tr>
<td>Irritable bowel syndrome including functional dyspepsia</td>
</tr>
<tr>
<td>Deficiency of cholecystokinin</td>
</tr>
<tr>
<td>Celiac disease, fasting/TPN</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Anticholinergic agents, calcium channel blockers, opioids, ursodeoxycholic acid, octreotide, cholecystokinin-A receptor antagonist, nitric oxide donors, female sex hormones (progestins)</td>
</tr>
</tbody>
</table>

Figure 5. Algorithm for the management of acalculous biliary pain (gallbladder dyskinesia) as suggested by the Rome III consensus [21]. Cholescintigraphy (hepatoiminoiodiacetic acid scan) assesses gallbladder emptying in response to a slow infusion of cholecystokinin (CCK) infusion over 30 minutes.
into the colon, leading to net water and electrolyte secretion, termed cholerheic diarrhea. Bile salts and bile acids may be interchangeably used although their specific physicochemical properties differ. Bile salt malabsorption also may be a component of the diarrhea associated with microscopic colitis. Malabsorption of bile salts arises in Crohn’s disease or from ileal loss. It can also be idiopathic (presumably the result of a congenital absence of the bile salt transporter in the ileum) and therefore cause diarrhea after cholecystectomy [41]. Diagnosis may come from a therapeutic trial of a bile salt sequestering agent such as cholestyramine but more reliably warrants measuring the turnover of a synthetic radiolabeled bile acid. The $^{75}$SeHCAT scan involves the ingestion of the radiolabeled bile salt selenium-75 homologous acid taurine. Retention of the radiopharmaceutical is assessed by whole body counts at 7 days. Less than 15% retention indicates marked loss from the intestines and bile salt malabsorption. Therapy employs an anionic, bile salt-binding resin, either cholestyramine or colestipol. The $^{75}$SeHCAT test is not available in the United States. The diagnosis of bile acid–related diarrhea often depends on the clinical response to treatment with a bile acid–binding agent.

**Treatment and Case Conclusion**

The patient is placed on 5-g packets of colestipol daily in a therapeutic trial. She experiences a marked improvement in her bowel function, having formed bowel movements once a day. Nevertheless, the bloating and abdominal pains continue. Management focuses on IBS. A trial of low-dose, tricyclic antidepressant agent in the form of nortriptyline 10 to 20 mg at night improves the abdominal pain. Its presumed mechanism is to reduce the visceral hypersensitivity component of functional gut pain. Supportive care and stress management alleviate the other symptoms.

**SUMMARY**

Biliary sludge is a common feature that may develop during pregnancy. In a few women, sludge can progress to gallstones or cause obstruction leading to biliary or pancreatic complications. Most have no true biliary symptoms and the sludge disappears in the postpartum period.

The management of gallstones is clear. Gallstones without symptoms (“silent” stones) need no treatment with few exceptions [3]. Abdominal pain is the most common symptom. The term “colic” is a misnomer, as this pain is not colicky in nature but instead is rather steady. A typical episode persists for several hours. Once symptoms develop in a person with documented cholelithiasis, the likelihood of recurrence is high. Laparoscopic cholecystectomy represents definitive treatment for such symptomatic gallstones and is usually successful.

Not all right upper quadrant abdominal pain is biliary colic. Dyspeptic symptoms are not valid features of biliary tract disease. In the absence of cholelithiasis, functional abdominal pain (eg, IBS) can account for pain simulating biliary colic. Biliary dyskinesia represents a functional gallbladder problem that has been characterized by absence of an overt, identifiable (organic) cause. Rather, the current hallmark is impaired gallbladder emptying as detected by nuclear medicine scan (CCK-cholescintigraphy). This test, although valuable, has not been uniformly standardized. Further, its sensitivity and specificity is in question, a factor leading to mixed results in identifying those with acalculous biliary pain who might benefit from cholecystectomy. People with IBS who undergo cholecystectomy will likely continue to have symptoms after the surgery. Removal of the gallbladder has its own inherent risks and can also unmask bile acid diarrhea.

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**Financial disclosures:** None.

**References**

GALLSTONE DISEASE


CME EVALUATION: Gallstone Disease: From Dyspepsia to Biliary Complications

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. What percentage of Americans will develop gallstones in their lifetime?
   A. 1% to 5%
   B. 5% to 10%
   C. 10% to 20%
   D. 20% to 30%
   E. 30% to 40%

2. All of the following are risk factors for developing cholesterol gallstones EXCEPT
   A. Insulin resistance
   B. Male sex
   C. Native American ethnicity
   D. Obesity
   E. Pregnancy

3. All of the following are included in the Rome III diagnostic criteria for a functional gallbladder disorder EXCEPT
   A. Episodes lasting less than 30 minutes
   B. Normal gallbladder with no sludge or stones
   C. Pain in the epigastrium and/or right upper quadrant
   D. Pain not relieved by bowel movements
   E. Recurrent symptoms occurring at different intervals

4. All of the following can cause impaired gallbladder emptying EXCEPT
   A. Cholecystitis
   B. Cholesterol and pigment gallstones
   C. Inflammatory bowel disease
   D. Irritable bowel syndrome
   E. Pregnancy

5. Which of the following is commonly considered a normal gallbladder ejection fraction in response to the 30-minute cholecystokinin infusion initiated during cholecintigraphy?
   A. ≥ 10% to 15%
   B. ≥ 15% to 20%
   C. ≥ 20% to 25%
   D. ≥ 30% to 35%
EVALUATION FORM: Gallstone Disease: From Dyspepsia to Biliary Complications

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