Acute Cholecystitis, Biliary Obstruction, and Biliary Leakage

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The use of cholescintigraphy to diagnose acute cholecystitis, biliary obstruction, and biliary leakage dates back to the late 1970s. Today, despite the many advances in imaging instrumentation, radiopharmaceuticals, and methodology over these years, cholescintigraphy still plays an important role in confirming or excluding these diagnoses in acutely ill patients. Acute calculous and acalculous cholecystitis, gallbladder perforation, biliary obstruction, and biliary leakage often present as acute abdominal pain, and must be differentiated from other surgical and nonsurgical etiologies with similar symptoms and presentation. Understanding the pathophysiology of acute hepatobiliary diseases is vital for deciding on the most advantageous imaging work-up and for interpretation of the studies. To optimize the value of cholescintigraphy, up-to-date methology, proper use of appropriate pharmacologic interventions, and recognition of characteristic image findings are critical.

ACUTE CHOLECYSTITIS

ACUTE ABDOMINAL pain is a common emergency room complaint and not uncommon in ill, hospitalized patients. Its etiology must be differentiated from various other acute abdominal conditions (eg, acute appendicitis, perforated/penetrating duodenal or gastric ulcer, acute pancreatitis, small bowel obstruction, lower lobe pneumonia, ureteral calculus). The pathophysiology of biliary colic and acute cholecystitis begins with cystic duct obstruction. Obstruction to venous and lymphatic outflow increases intraluminal pressure, resulting in gallbladder edema and distention. If patency is not reestablished, neutrophils infiltrate the gallbladder wall, followed by mucosal hemorrhage and necrosis. Gangrenous cholecystitis occurs in 20% and perforation in 10% of patients. A severely inflamed gallbladder may become adherent to contiguous structures (eg, the liver, omentum, and duodenum). Although gallstones are the hallmark of cholecystitis, they do not signify acute disease. Cholelithiasis is seen in 60% of patients with acute abdominal pain, however, fewer than 50% have acute cholecystitis. The majority of patients with gallstones remain asymptomatic during their lifetime.[1]

Clinical Manifestations of Biliary Colic and Acute Cholecystitis

The pain of biliary colic results from gallbladder contraction against a fixed obstruction or passage of the stone through the cystic duct. The abdominal pain lasts minutes to hours, followed by a diminution in intensity. Nausea and vomiting are common. The pain of acute cholecystitis is unremitting for days, accompanied by fever and leukocytosis. Mild jaundice occurs in 10% of patients caused by inflammation of contiguous biliary ducts (Mirizzi syndrome) or concomitant choledocholithiasis. Symptoms are often self-limited due to the dislodgement of the cystic duct stone. Repeated bouts of acute cholecystitis result in lymphocytic infiltration and fibrotic wall thickening. Thus, the histopathologic changes of acute cholecystitis are often superimposed upon chronic inflammatory changes. The fibrotic processes may hinder or prevent acute transmural inflammatory changes.

Complications

Complications of acute cholecystitis include hydrops (ie, gallbladder filled with a clear or white mucoid material), emphysematous cholecystitis (ie, gas within the gallbladder lumen or wall), and empyema. Perforation is the most serious complication and has a high mortality rate. There are 3 types of perforation: (1) free flow into the peritoneum (acute), (2) pericholecystitic abscess (subacute), and (3) cholecystoenteric or cholecystocutaneous fistula (chronic). In subacute or chronic perforations with fistula formation, repeated bouts of cholecystitis lead to fibrosis with adherence to adjacent structures. Inflammation and pressure necrosis can develop around gallstones impacted in the gallbladder wall, with erosion into contiguous organs. A gallstone may pass through a sinus tract and become lodged within bowel, causing obstruction (eg, gallstone "ileus").

Acute Acalculous Cholecystitis

It occurs in 5% to 15% of patients with acute cholecystitis. There are no stones in the gallbladder or cystic duct. These patients are critically ill, often are postoperative, have had severe trauma, extensive burns, and other serious illnesses. Diagnosis is difficult and delayed due to the patient's multiple medical problems, resulting in high morbidity and mortality. The incidence of gangrene and perforation is high. A minority of patients have cystic duct obstruction caused by kinking, fibrosis, adhesive bands, anomalous vessels, tumor, or lymphadenopathy. In many others, the obstruction is caused by edema, inspissated bile, and/or cellular debris. However, some patients have direct inflammation of the gallbladder wall from sepsis, ischemia, or toxins without

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obstruction. Bile stasis, caused by decreased gallbladder emptying during prolonged fasting or total parenteral nutrition (TPN), plays an important role in this disease. The concentrated bile salts produce inflammation of the gallbladder mucosa.

Cholecystectomy

Cholecystectomy has been the definitive therapy for acute cholecystitis for over a century. In recent years, laparoscopic cholecystectomy has become the treatment of choice for patients with symptomatic gallstone disease, acute cholecystitis, and more complicated problems, including common bile duct stone disease.[2] Although delayed surgery is considered safer, increased adhesions make the gallbladder more difficult to remove laparoscopically. With early surgery, hospital stay is shorter and the return to productivity earlier. Mortality rates are equal, and there is a similar frequency of postoperative complications. The open approach is still often used for patients with gallbladder perforation, pericholecystic abscess, or empyemia.

Noninvasive Imaging

Early diagnosis of acute cholecystitis is essential for prompt, therapeutic decisions and prevention of complications. Although steady colicky pain, fever, and leukocytosis are the typical triad of symptoms, a 20% diagnostic error rate occurs when cholecystectomy is based solely on clinical findings. When the etiology of abdominal pain is uncertain, ultrasonography is often performed first because nonbiliary disease and bile duct dilatation can be detected. Computerized tomography (CT) is used as an alternative to ultrasonography in the setting of an acute abdomen, or when gastrointestinal symptoms predominate over signs or symptoms of biliary disease. When the clinical index of suspicion for acute cholecystitis is high, cholescintigraphy should be the initial imaging study.

Ultrasonography

Ultrasonography sensitivity for detection of gallstones is high. Although 90% of patients with acute cholecyctitis have cholelithiasis, so do 20% of asymptomatic patients older than age 55, making this a very nonspecific sign. Other findings of acute cholecystitis include gallbladder distension, wall thickening, intramural sonolucency, sludge, and maximum tenderness over the gallbladder ("sonographic Murphy's sign"). Increased blood flow seen on power Doppler is the hyperemia of acute inflammation. However, to make with high accuracy the diagnosis of acute cholecystitis, the composite findings of stones, intramural sonolucency, and the ultrasonographic Murphy sign are required. A single finding or several nonspecific findings are unreliable.[3] Sludge in the gallbladder is a common ultrasonographic finding in patients with chronic understimulation of the gallbladder (eg, sick, fasting patients on TPN). Sludge is lithogenic bile and does not have the same significance as discrete gallbladder calculi. However, if not treated with cholecystokinin (CCK) to empty the gallbladder, sludge can progress to stones.

The ultrasonographic finding of focal or circumferential intramural lucency (hypoechoicity) is caused by subserosal edema. However, diffuse edema and wall thickening can be seen with ascites, hepatitis, hypoalbuminemia, etc. A focal or striated (striped) appearance is more specific for acute inflammation. The ultrasonographic Murphy's sign has a reported accuracy as high as 88%.[3] However, a cooperative patient not receiving analgesia is required. Differentiation of focal from diffuse pain is not always easy, and there is considerable interobserver variation.

Cholescintigraphy

Cholescintigraphy has proven to be the best, single noninvasive test for the diagnosis of acute cholecysititis, directly showing cystic duct obstruction. Failure of gallbladder filling in the presence of normal hepatic uptake and biliary excretion reliably indicates acute cholecystitis (Fig. 1), while normal gallbladder visualization excludes the diagnosis. Cholescintigraphy can also diagnose low-grade or early biliary obstruction before ultrasonography shows biliary dilatation.

Various Tc-99m labeled hepatobiliary radiopharmaceuticals have been used over the years. Two radiopharmaceuticals are Food and Drug Administration approved and in common use, Tc-99m disofenin (DISIDA, Hepatolite, CIS-US, Inc, Bedford, MA) and Tc-99m mebrofenin (Choletec, Bromo-triethyl IDA, Bracco Diagnostics, New Brunswick, NJ). Both are iminodiacetic acid (IDA) derivatives with high hepatic extraction and clearance.

Diagnostic accuracy of cholescintigraphy. Investigations published between 1975 and 1980 initially showed the clinical use of cholescintigraphy to diagnosis acute cholecystitis.[4-10] A large patient series published from 1980 to 1982 reported a high accuracy. In the largest series, Weissmann et al showed a 95% sensitivity and 99% specificity.[11] Freitas et al found a sensitivity of 98% and specificity of 90%.[12] Other studies published between 1978 and 1983 confirmed high accuracy (Table 1).[13-16] In 2 of these 3 investigations, sensitivity was $\geq$97%. Specificity has been more variable. The false-positive rate is as low as 0.6% and as high as 27%.[11,17,18] However, in 9 of 12 studies, specificity was higher than 90%. Although reports have claimed high accuracy for ultrasonography,[3] cholescintigraphy has consistent, superior accuracy in direct comparison studies (Table 1).[12,13,15-17,19]

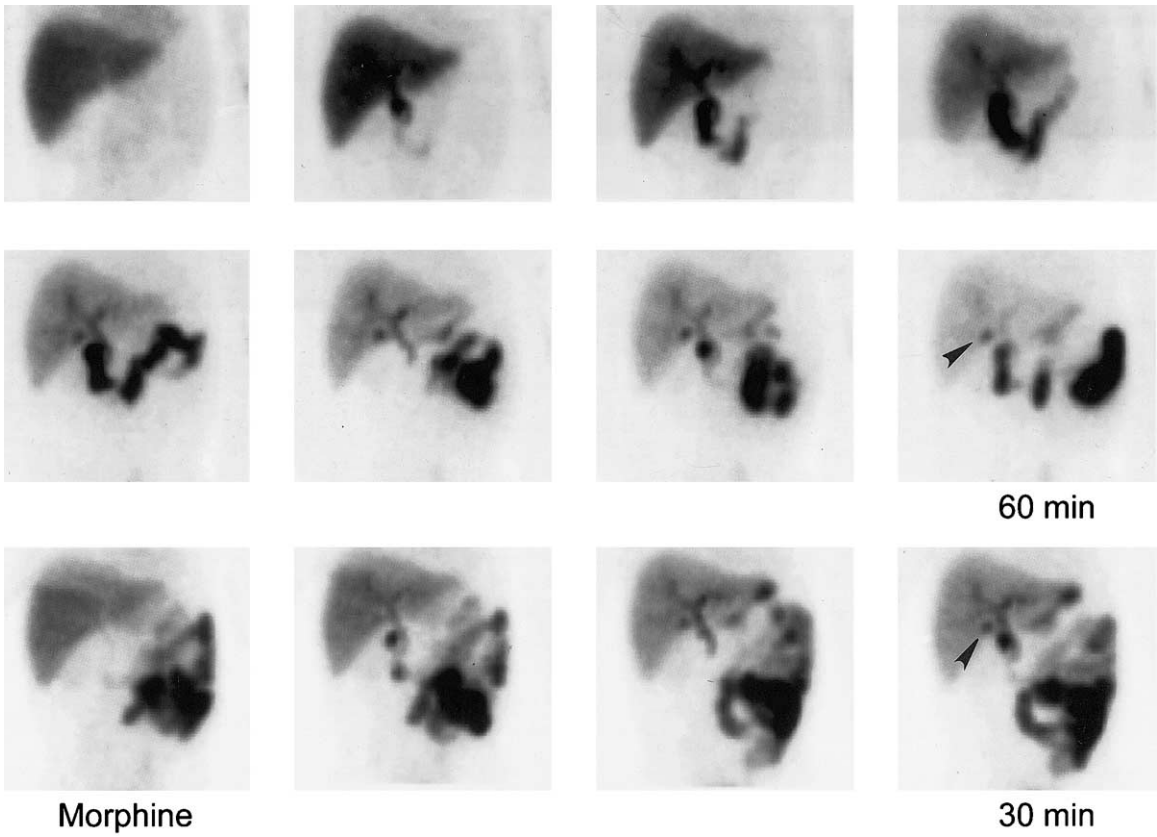

Fig 1. Cystic duct sign. Forty-five-year-old female with acute right upper quadrant pain. Top two rows: 60-minute HIDA study shows small focal accumulation in the medial aspect of the gallbladder fossa initially at 30 minutes and persisting until 60 minutes. Common duct and duodenal activity clears medial to this. The common duct appears displaced medially. Bottom row: Morphine is given at 70 minutes and imaging continued for 30 more minutes. The focal accumulation is not initially seen after morphine but recurs, and persists between 15 and 30 minutes. The patient had acute cholecystitis with a stone impacted in the cystic duct.

Freitas et al have explained some of the variability in sensitivity and specificity reported for cholescintigraphy and ultrasonography.[20] They emphasized that the histopathologic criteria used in investigations significantly affect the study results. They distinguished strict criteria (ie, acute inflammatory cells in the gallbladder wall) and

Table 1. Acute Cholecystitis: Accuracy of Cholescintigraphy and Ultrasonography

Investigator	Publication Date	No. Pts	Cholescintigraphy Sensitivity/Specificity (%)		Ultrasonography Sensitivity/Specificity (%)	
Stadalnik et al[6]	1978	120	100	100	70	93
Weissmann et al[7]	1979	90	98	100		
Freitas et al[10]	1980	186	97	87		
Suarez et al[8]	1980	62	98	100		
Szlabick et al[9]	1980	271	100	98		
Weissmann et al[11]	1981	296	95	99		
Zeman et al[13]	1981	200	98	82	67	82
Worthen et al[17]	1981	113	95	100	67	100
Mauro et al[14]	1982	95	100	94		
Ralls et al[16]	1982	59	86	84	86	90
Freitas et al[12]	1982	195	98	90	60	81
Samuels et al[15]	1983	194	97	93	97	64
Chatziioannou et al[19]	2000	107	92	89	40	89

liberal criteria (ie, hemorrhagic necrosis, cystic duct obstruction, gallbladder wall edema). In 211 patients, strict criteria resulted in a 100% sensitivity/85% specificity, while liberal criteria produced a 95% sensitivity/99% specificity. They emphasized that the fibrotic reparative process of prior acute episodes may prevent the development of acute, transmural inflammatory changes. Cases of acute cholecysitits superimposed on chronic cholecysititis are often mislabeled as chronic cholecysitis. The criterion of complete cystic duct obstruction and/or gallbladder wall edema is most appropriate because it recognizes the natural history of acute cholecystitis.

False-Positive Cholescintigraphy for Acute Cholecystitis

False-positive cholescintigraphy can be minimized by an awareness of its common causes and by using optimal methodology.

Nonfasting

Fasting for 3 to 4 hours before cholescintigraphy has become standard protocol. Half the normal subjects who eat within 1 hour of cholescintigraphy will have gallbladder nonvisualization.[21,22] Postprandially, the gallbladder is contracted due to endogenous stimulation of CCK.

Prolonged Fasting

Gallbladder nonvisualization often occurs in patients fasting for more than 24 hours.[23,24] Without stimulus to contraction, the gallbladder fills to capacity, but water reabsorption allows further inflow of bile. The increasingly concentrated viscous bile may prevent Tc-IDA entry into the gallbladder. Although this process occurs most frequently with ill, hospitalized patients, outpatients should be carefully questioned regarding recent dietary history. A meal containing 10 fat is required to contract the gallbladder.[25] CCK is recommended before cholescintigraphy for patients fasting more than 24 hours.[26,27] Tc-IDA should not be administered until at least 30 minutes after CCK infusion to allow time for gallbladder relaxation.

Total Parenteral Nutrition

TPN is associated with a high incidence of hepatobiliary disease; 40% of patients require emergency cholecystectomy.[28,29] Biliary ultrasonographic studies have detected sludge in 6% of patients during the first 3 weeks of TPN, 50% during the fourth through sixth weeks, and 100% after 6 weeks.[30] Patients with TPN have a 30% to 40% false-positive (nonvisualization) rate for cholescintigraphy.[24,31-33] The explanation is likely similar to that of prolonged fasting. Pretreatment with CCK is recommended.

Hepatocellular Disease

Hepatocellular disease is seen on cholescintigraphy as delayed uptake and excretion of Tc-IDA. The altered pharmacokinetics may result in nonvisualization of the gallbladder at the expected intervals. A 40% to 60% false-positive rate was reported in early studies.[32,34,35] However, with delayed imaging, 83% of patients have gallbladder visualization.[33] The negative predictive value (NPV) in this study was 100%. One study found alcoholism as a cause for false-positive cholescintigraphy.[32] However, all patients in that study also had hepatocellular disease.

Severe Intercurrent Illness

Severe intercurrent illness (eg, massive trauma, sepsis, life-threatening postoperative complications, acute respiratory diseases has been associated with false-positive cholescintigraphy.[27,33,36] One report found a 30% false-positive rate.[33] Of the 70% of patients with gallbladder visualization, a third were visualized only on delayed imaging, half between 4 and 24 hours.[33] A negative study (gallbladder visualization) is quite useful to exclude acute cholecystitis due to its high NPV.[27]

Acute Pancreatitis

It is another reported cause for false-positive cholescintigraphy. Zeman et al reported 4 of 7 false-positive studies in patients with acute pancreatitis.[13] However, another study showed gallbladder visualization in 87% (13 of 15) of patients.[37] Two had delayed visualization at 2 hours, and both had chronic cholecystitis by ultrasonography. One patient, when pretreated with CCK on repeat study, visualized by 1 hour. Two other investigations may help clarify the conflicting data. One found that most patients with nonbiliary pancreatitis have normal cholescintigraphy, compared with 50% of patients with biliary pancreatitis,[38] although gallbladder visualization was often delayed. Another report found normal scans in 95% of patients with nonbiliary pancreatitis but in only 23% with biliary pancreatitis.[39] Common causes for acute pancreatitis are alchoholism and biliary tract disease. The pathophysiology of biliary pancreatitis is uncertain, but precipitating factors include pancreatic duct obstruction by an impacted stone in the ampulla of Vater or by inflammatory spasm of the ampullary sphincter. The mortality rate of pancreatitis associated with gallstone disease is high (20% to 50%), compared with that associated with alcoholism with a low mortality rate (2% to 5%).

Chronic Cholecystitis

Chronic cholecystitis is a frequent cause for false-positive cholescintigraphy. More than 90% of patients

with chronic cholecysititis have normal 60-minute cholescintigraphy.[10] However, of those patients with delayed gallbladder filling, more than 70% have chronic cholecystitis.[40] The more delayed the filling, the more likely that it is chronic cholecysitis. Most visualize by 2 to 4 hours. Delayed filling is caused by a functional resistence to flow through the cystic duct caused by viscous bile, sludge, and stones within the gallbladder, or by chronic mucosal thickening and, rarely, fibrosis. Evidence for a functional mechanism is seen in patients with delayed visualization if they are pretreated with CCK on a repeat study; the gallbladder often visualizes within the first hour.[4,41,42] Emptying of the gallbladder decreases resistence to Tc-IDA entry. Some patients have continued nonvisualization at 4 hours. CCK pretreatment does not ensure gallbladder emptying because it is dependent on normal contractile ability, often diminished with chronic disease. The most common cause of false-positive morphine cholescintigraphy is also chronic cholecystitis.

METHODS TO MINIMIZE FALSE-POSITIVE CHOLESCINTIGRAPHY

Optimal Methodology

Attention to technique and methodology maximizes the accuracy of cholescintigraphy. The radiopharmaceutical dose can be increased in patients with hepatic insufficiency.[40] Although the larger dose will increase the count rate, it will not improve the target-to-background ratio. At times, there is diagnostic uncertainty caused by the overlap of anatomy and biliary flow of the gallbladder, biliary ducts, and small bowel in the anterior view. Right lateral and left anterior oblique views are often helpful for clarifying structures and confirming or excluding gallbladder filling. Standing and ingestion of water help move duodenal activity distally.[43] Viewing the study on a computer in a dynamic cinematic display is often helpful for viewing the course of bile flow.[44] A dilated cystic duct must not be misinterpreted as gallbladder visualization (Fig. 1).[45]

In 143 cases of proven acute cholecystitis, Weissmann et al reported nonvisualization of the gallbladder in 83%.[11] The gallbladder visualized in 4% of cases (false-negatives). An obstructive pattern (ie, nonvisualization of the gallbladder and common duct) was seen in 13% of cases. This pattern should be included as evidence of acute cholecystitis. Not all series have done this when calculating accuracies. The obstructive pattern may be caused by contiguous inflammation of the adjacent hepatic bile duct (Mirizzi syndrome) or to a concomitant, common duct stone.

Delayed Imaging

Weissmann et al found that patients with nonvisualization of the gallbladder at 1 hour should have delayed imaging for up to 4 hours. This procedure decreased the false-positive rate from 10% to 0.6%.[11] Imaging for 24 hours has been suggested for patients with intercurrent disease, hepatic insufficiency, and prolonged fasting.[13,27,33]

CCK

CCK has been used for many years in conjunction with cholescintigraphy to empty concentrated bile from the gallbladder, to shorten the length of the procedure, and to reduce the number of false-positive studies for acute cholecystitis. In 1975, Eikman et al routinely administered CCK 30 minutes before cholescintigraphy because animal studies had suggested that this was necessary to ensure normal gallbladder filling.[4] Preliminary results were encouraging, although this never became standard. In 1978, Pare et al administered CCK to patients who had nonvisualization of the gallbladder at 2 hours and then readministered the radiopharmaceutical.[41] In patients with acute cholecystitis, nonvisualization persisted. In 8 of 16 patients with chronic cholecystitis, the gallbladder did not initially visualize. A repeat study with CCK pretreatment resulted in gallbladder visualization in 2.[41]

In 1981, Freeman et al studied 10 patients with gallbladder visualization between 1.5 and 4 hours.[42] A repeat study 24 to 48 hours later was preceded by sincalide. All patients had visualization within 1 hour.[42] Of 10 patients with persistent nonvisualization on delayed images, preadministration of CCK had no effect in 9. The one patient had only 90-minute imaging on the initial study. The investigators emphasized that pretreatment with CCK should not become routine because this would preclude differentiating normals from patients with chronic cholecystitis. Also, because more than 90% of patients with chronic cholecystitis have gallbladder visualization by 60 minutes, CCK would be given unnecessarily to a large percentage of them.

Shuman et al gave sincalide before cholescintigraphy to 22 of 58 patients with alcoholism, hepatocellular disease, and TPN.[32] The 60% false-positive rate was similar in those who did and did not receive sincalide. In a retrospective review, gallbladder visualization was initially seen in 13 of 15 patients with acute pancreatitis.[37] Of the 2 patients whose gallbladders did not visualize, a repeat study was performed with CCK. The gallbladder visualized in 1 of 2 patients.

Delayed biliary-to-bowel transit occurs in half the patients given sincalide before cholescintigraphy.[46] Delayed biliary-to-bowel transit raises the question of partial common duct obstruction. Delayed imaging or repeat sincalide administration can differentiate obstruction from functional causes. Sincalide pretreatment does not preclude good gallbladder contraction with repeat administration at 60 minutes because the serum half-life of CCK is 2.5 minutes.[47]

Proper methodology is critical when administering

Table 2. Accuracy of Morphine-Augmented Cholescintigraphy

Investigator	Publication Date	Cholescintigraphy	
		Sensitivity (%) No. Pts/Total No. Pts	Specificity (%) No. Pts/Total No. Pts
Choy et al[56]	1984	23/24 (96)	35/35 (100)
Keslar and Turbiner[59]	1987	19/19 (100)	10/12 (83)
Vasquez et al[60]	1988	10/10 (100)	22/26 (85)
Flancbaum et al[61]	1989	12/12 (100)	29/33 (88)
Fig et al[64]	1990	15/16 (94)	22/32 (69)
Fink-Bennett et al[62]	1991	35/35 (95)	23/24 (96)
Kistler et al[63]	1991	13/14 (93)	14/18 (78)
Kim et al[67]	1993	24/26 (92)	15/19 (79)
Totals		151/156 (97)	170/199 (85)

sincalide to ensure adequate gallbladder contraction. A third of normal subjects receiving a short, 3-minute sincalide infusion (ie, 0.02 μgm/kg) had poor gallbladder contraction. With a 30 to 60-minute infusion (same total dose), the subjects had good gallbladder contraction.[48,49] The shorter sincalide infusion produces a supraphysiologic serum level that causes gallbladder dysfunction. Sincalide infusion does not guarantee gallbladder contraction. Patients with chronic cholecysitis, diabetes, or who are on therapeutic drugs known to inhibit gallbladder contraction (eg, narcotics, octreotide, calcium blockers, progesterone)[50] may not respond to CCK. Ultrasonographic confirmation of gallbladder contraction in response to CCK would be useful if available. No contraction on ultrasonography would indicate the possibility of a possible false-positive study (ie, gallbladder nonvisualization).

Morphine sulfate has a 4 to 6-hour physiologic half-life. Recent administration can inhibit the effect of CCK on gallbladder contraction. One study of 24 patients who had morphine-augmented cholescintigraphy received sincalide 30 to 120 minutes after the morphine. Gallbladder contraction occurred in 14.[51] A negative study (ie, good gallbladder contraction) is more useful in this setting than a positive one (ie, poor contraction) because the latter may be caused by either gallbladder disease or the residual effect of morphine. Nalorphine (Narcan, Endo Pharmaceuticals, Chadds Ford, PA) could be used to reverse the morphine effect.[52]

Morphine Sulfate

Subanalgesic doses of intravenous morphine contract the sphincter of Oddi.[53] With 2.5 mg of morphine sulfate, biliary flow resistence doubles, and intraductal pressure increases 60%.[54,55] Peak effect occurs at 5 minutes. A 3-fold higher dose has no added effect. In 1984, Choy et al reported on the use of morphine sulfate as an alternative to delayed imaging.[56] They postulated that morphine would increase bile duct pressure enough to overcome a partial or functional cystic obstruction and, thus, reduce the incidence of false-positive studies and the length of the study. In 60 patients, the sensitivity for acute cholecystitis was 96% and specificity 100%. Six patients converted from gallbladder nonvisualization to visualization within 20 minutes of morphine injection and were proven true negatives. Subsequent studies have confirmed a high accuracy of morphine-augmented cholescintigraphy (Table 2).[57-66]

The sensitivitity of morphine augmented-cholescintigraphy for the diagnosis of acute cholecystitis has been uniformly high, 92% to 100% (mean 97%) (Table 2). False-negative studies are uncommon. Specificity has had a wider range, 69% to 100% (mean 85%). The lowest specificities have been 69%, 78%, and 79%.[63-65] Fig et al found a false-positive rate of 40%, which was attributed to the large number of patients with severe intercurrent illness, a problem similarly seen with delayed imaging.[64] Another report of patients in intensive care units (ICU) had a lower false-positive rate, 25% (88% specificity).[61] Kim et al compared a morphine-augmented study with historical controls using delayed imaging.[67] The positive predictive value (PPV) was considerably better with morphine-augmentation, 86% versus 59%, respectively, although the delayed imaging controls had a curiously low specificity, 35%.[67] Considering all the studies, morphine-augmentation has had similar accuracy as the delayed imaging method, while shortening the study from 3 to 4 hours to 90 minutes (Fig 1). Similar to the delayed imaging method, an increased false-positive rate occurs in patients with prolonged fasting, TPN, severe intercurrent illness, chronic cholecysitis, and hepatic insufficiency. Delayed imaging beyond the 30 minutes after morphine occasionally converts a false-positive to a true negative.[59,64]

Morphine should not be given if there is suggestion of partial biliary obstruction (eg, delayed common duct or biliary-to-bowel clearance). Morphine would make it impossible to differentiate a partial biliary obstruction from a functional obstruction secondary to the drug. There are no absolute contraindications to morphine administration. Relative contraindications might include hyperamylasemia and narcotic addiction. Reinjection of

Table 3. Rim Sign: Incidence in Acute Cholecystitis and Association with Gallbladder Perforation, Gangrene, and Complicated vs. Uncomplicated

Investigator	Publication Date	Rim Sign No. Pts/ Total No. Pts (%)	% Complicated Cholecystitis	% Noncomplicated Cholecystitis	% Perforation	% Gangrene
Smith et al[70]	1985	5/24 (21)			39	31
Bushnell et al[74]	1986	17/28 (61)			44	
Meekin et al[72]	1987	9/27 (35)	45	0	0	0
Swayne and Ginsberg[71]	1989	48/141 (34)			31	57
Greer et al[73]	1992	7/38 (18)				
Bohdiewicz[78]	1993	31/65 (47)	59	19		
Oates et al[75]	1996	43/170 (25)	44			

the radiopharmaceutical (ie, booster dose) has been recommended at morphine administration if Tc-IDA has cleared from the liver.[62] Careful shielding of bowel activity, use of cinematic display, and adjustment of image intensity usually make it unnecessary to reinject the radiopharmaceutical for the short, additional 30-minute morphine study.[64]

Investigators have infused morphine at different times after radiopharmaceutical administration: 30, 40, 50, and 60 minutes.[58,59,62,63] The exact timing is not critical for diagnostic purposes. The advantage of earlier administration is to shorten further the study. Given at 30 minutes, the study can be complete by 60 minutes.[56,63] The argument against giving morphine before 60 minutes is that one then cannot differentiate normal cases from those of chronic cholecysititis. Patients who visualize after morphine are assumed to be the same ones who have gallbladder filling at 2 to 4 hours on the delayed imaging method.

Most investigators have used a morphine dose of 0.04 mg/kg. A few have given a standard dose of 2 mg,[63,64,67] and one investigation used a variable dose ranging from 0.05 to 0.2 mg/kg.[61] The dose is infused over 1 to 3 minutes. After morphine, gallbladder filling begins within 5 to 10 minutes and is diagnostic by 20 to 30 minutes. A few studies have looked at imaging beyond 30 minutes. Choy et al found no patients who had further gallbladder filling.[56] Two studies reported some improvement in specificity with delayed imaging.[59,64] Fig et al had 2 cases of chronic cholecystitis that filled at 5.5 and 22 hours and 1 normal case that filled the gallbladder at 40 minutes after morphine.[64] However, one patient with acute cholecystitis had gallbladder visualization at 85 minutes (false-negative).

Choy et al showed that the second portion of the duodenum cleared within 5 to 10 minutes after morphine administration, accompanied by a slight widening of the common bile duct, presumably caused by cessation of bile flow caused by contraction of the sphincter of Oddi.[56] Kim et al, using quantitative analysis, also noted a transient decrease in bile flow in half the patients.[68] Bile flow reappears in the duodenum by 25 to 50 minutes. Enterogastric reflux is common and probably caused by relaxation of the pyloric sphincter. Choy et al reported abdominal cramping in 15 of 36 patients.[56] However, no other investigations have noted any adverse effects.

It has been suggested that pretreating all patients with CCK before radiopharmaceutical injection could shorten the study and make delayed imaging unnecessary.[4,42] A retrospective review investigated 155 patients pretreated with sincalide.[69] If there was gallbladder nonvisualization at 90 minutes, morphine was administered. Morphine decreased nonvisualization from 28% to 12%, with a concomittant decrease in the false-positive rate and increase in the PPV.

Rim Sign

The cholescintigraphic pattern of increased, pericholecystic hepatic activity in patients with acute cholecystitis has been variously named: pericholecystic hepatic activity,[70] pericholecystic hepatic uptake,[71] rim of increased hepatic activity,[72] and the rim sign.[73-78] In 1984, the first cases were reported by Brachman[79] et al (5 cases) and Cawthon et al.[80] (1 case) All had nonvisualization and gangrenous gallbladders; 5 had perforation. The rim sign has been variously reported to occur in 18% to 61% of patients with acute cholescystitis (Table 3).[70-75,78] All are retrospective studies. Several also found that the rim sign had a strong association with gangrene (range, 31% to 44%) and perforation (range, 31% to 57%).[70,71,74] Other studies have reported a high incidence (45% to 47%) of "complicated" cholecystitis, defined by the histopathology of ulceration, necrosis, fibrous exudation, empyemia, gangrene, and perforation.[72,75,78] "Uncomplicated cholecystitis" had edema, dilatation, and cellular infiltration. The rim sign was seen in 0% to 19%.[72,78] Although the overall sensitivity of the rim sign for acute cholecysititis is not high, it has a high PPV for complicated acute cholecysitis. False-positive studies are extremely rare.[81] It has been suggested that nonvisualization of the gallbladder with a rim sign at 60 minutes might not require delayed imaging or morphine to confirm the diagnosis of acute cholecystitis. However, one report found that morphine decreased the false-

positive rate in patients with a rim sign and improved their PPV from 72% to 86%.[75]

The rim sign is seen as mild-to-intense increased parenchymal liver uptake as a thin band adjacent to the gallbladder fossa or extending into much of the lower portion of the right lobe. It is seen within the first hour of imaging, better seen as the liver clears, and is persistent on delayed images.[70,72,82] A marked rim sign has a higher incidence of complicated cholecystitis than a mild rim sign (83% versus 32%).[75] Most studies have used Tc-99m disofenin. However, the sign is also seen with Tc-99m PIPIDA (paraisopropylacetanilide) and Tc-99m mebrofenin.[75,83]

Possible pathophysiologic mechanisms have been postulated for the the rim sign: (1) inflammation and edema of hepatic parenchyma adjacent to the inflamed gallbladder, causing obstruction and impaired drainage of bile canaliculi; (2) injury of local hepatocytes in the inflamed region, resulting in reduced ability to excrete the tracer; (3) increased blood flow to the region surrounding the gallbladder due to inflammatory hyperemia; (4) extravasation of a small amount of tracer into the gallbladder fossa via a gangrenous, perforated gallbladder; and (5) incomplete obstruction with faint gallbladder visualization.[79]

Data support the hypothesis that the gallbladder inflammatory process spreads to the adjacent hepatic parenchyma.[72] In one study, 8 of 9 patients with the rim sign had dilated gallbladders. The close proximity of the gallbladder allows the inflammatory process to spread to the adjacent liver. Liver tissue was attached by fibrous adhesions to the gallbladder specimen in 5 cases. Two patients with a rim sign had inflammatory changes in the adjacent liver.

Increased Blood Flow

Increased blood flow to the gallbladder fossa is another secondary sign of acute cholecystitis. In a small study, the PPV of cholescintigraphy increased from 71% to 90% when gallbladder nonvisualization was associated with either a rim sign or increased flow to the gallbladder fossa.[84] In another study of 25 patients with acute cholecystitis, 23 had increased flow; increased flow had a sensitivity of 72%, specificity 95%, and PPV 92.[85] Abscess or gangrene occurred in 36% of patients with increased blood flow. Three patients with positive flow had negative cholescintigraphy (gallbladder visualization); all had pericholecystic abscess. In a follow-up prospective study by the same investigators, similar results were found.[86] All patients with a rim sign had increased flow, although only 46% with increased flow had a rim sign. Other investigators reported that increased flow was seen in 53% of patients with acute cholecystitis, and 47% had a rim sign.[78] Only one had hyperperfusion without a rim sign. All but one patient with marked hyperperfusion and a rim sign had complicated cholecystitis.

Gangrene and Perforation of the Gallbladder

Scintigraphic evidence for perforation is present in approximately only half the cases. The rim sign and increased flow are indirect, insensitive, and nonspecific cholescintigraphic findings of gangrene and perforation.[87] Other scintigraphic findings have been described. In a retrospective review of 9 surgically proven cases of gangrenous cholecystitis, 3 had only gallbladder nonvisualization, 2 had nonvisualization plus a rim sign, and 4 had nonvisualization plus an enlarged photon deficient area in the region of the gallbladder fossa caused by a very dilated gallbladder.[88] Some reported findings are moderately specific and are described later.[70,83]

The various cholescintigraphic findings have been correlated with the type of perforation[83] according to the Niemeier classification:[89]

- Type 1 acute free perforation with peritonitis is not commonly diagnosed by cholescintigrapy because an obstructed cystic duct prevents Tc-IDA flow to the perforation site. However, if an obstructing cystic duct stone becomes dislodged and passes distally or, in acalculous disease without cystic duct obstruction, gallbladder perforation with biliary leak may be seen directly.[83,88,90] Acute acalculous cholecystitis has a high incidence of type 1 perforation. Examples of perforation without and, less commonly, with gallbladder visualization have been published.[71,83,91-96] Swayne and Filippone reported an overall 44% scintigraphic detection rate for type 1 free spills.[83] A rim sign was seen in only 1 of 8 cases.
- Type 2 subacute localized perforations with pericholecystic abscess are most commonly found at surgery,[97] but rarely seen on cholescintigraphy. A study investigating the accuracy of cholescintigraphy to diagnose acute cholecysititis found an 11% false-negative rate; all the false-negative studies were with type 2 perforations.[83] In another series of 29 patients with perforation, type 2 perforations were detected by cholescintigraphy in only 11%.[83] Gallbladder nonvisualization is the most common scintigraphic pattern, likely caused by inflammatory adhesions resealing the perforation.[70,83] The fistulous tracts are rarely seen.[98-100] A specific but infrequent finding is the direct showing of the cholecystoenteric fistula.[83] A more common finding is that of a well-demarcated photopenic region in the gallbladder fossa, with this mass effect on the right inferior hepatic lobe and medial displacement of the common bile duct. Confined Tc-IDA extravasation in the gallbladder fossa may be seen and should not be confused with gallbladder visualiza-

Table 4. Acute Acalculous Cholecystitis: Accuracy of Cholescintigraphy

Investigator	Publication Date	Miscellaneous	Cholescintigraphy Sensitivity (%) No. Pts/Total No. Pts	Cholescintigraphy Specificity (%) No. Pts/Total No. Pts
Weissmann et al[106]	1983		14/15 (93)	
Shuman et al[104]	1984		14/19 (73)	
Ramanna et al[108]	1984		11/11 (100)	
Mirvis[107]	1986	ICU	9/10 (90)	21/34 (61)
Swayne[109]	1986		37/49 (93)	
Flancbaum and Choban[110]	1995	ICU MS	12/16 (75)	29/29 (100)
Kalliafas et al[111]	1998	MS	9/10 (90)	
Prevot et al[112]	1999	P ICU MS	9/14 (64)	18/18 (100)
Mariat et al[113]	2000	P ICU MS	8/12 (67)	16/16 (100)
Totals			123/156 (79)	84/97 (87)

Abbreviations: ICU, intensive care unit; P, prospective study; MS, morphine sulfate.

tion.[101] A rim sign occurs in approximately 25%.[83]

- Type 3 chronic perforation with cholecystenteric perforation has an uncommon but characteristic cholescintigraphic pattern in gallstone ileus: (1) gallbladder nonvisualization, (2) dilated proximal duodenum, and (3) gastric reflux.[99,102,103] Gallbladder nonvisualization and, secondly, the rim sign are the most common cholescintigraphic findings.

Acute Acalculous Cholescystitis

Concern has been expressed since the early years of cholescintigraphy about its potential ability to diagnose acute acalculous cholecysititis. The high accuracyate for acute calculous cholecystitis is due to detection of the pathophysiologic abnormality, cystic duct obstruction, seen as nonfilling of the gallbladder. However, with the acalculous form of the disease, patients may not have cystic duct obstruction. The cystic duct may be partially obstructed by edema, cellular debris, or inspissated (thick) bile, and other patients may have direct inflammation of the gallbladder wall from sepsis, toxemia, or ischemia, without cystic duct obstruction.

In 1984, an investigation showed a low sensitivity (68%) for cholescintigraphic detection of acute acalculous cholecysititis.[104] A published critical review of that study suggested that the sensitivity was higher than reported, 73% to 89%, depending on how the data were reanalyzed.[105] Subsequently, 5 publications reported sensitivities higher than 90%. However, of 9 published reports (Table 4), there is a wide variation in the results, with sensitivity ranging from 64% to 100%.[104-113] There are major differences in these studies. Only 2 are prospective.[112,113] Studies that do not report specificity have retrospectively investigated the role of cholescintigraphy in patients found pathologically to have acute acalculous cholecysitis. Specificity (ie, TN/TN + FP) could not be calculated because all patients had the disease by study criteria. The investigations with reported specificity values selected patients based on a clinical suspicion of the disease in those who had cholescintgraphy as part of the work-up. Only studies from 1995 to 2000 performed morphine-augmented cholescintigraphy.

It would not be surprising to discover that cholescintigraphy has a high false-positive rate for acute acalculous cholecystitis. These patients are often in ICU with serious illnesses, fasting for a prolonged period, and are on TPN. There are 4 reported studies with calculated specificities, all involving ICU patients in Surprisingly, 3 of 4 studies showed 100% specificity (Table 4).[107,110,112,113] All 3 used morphine. The study that used the delayed imaging method reported the lowest specificity (61%).[107] More data would be useful. However, with the available data, accuracy is good but not as high as with the calculous form of the disease. Morphine-augmented cholescintigraphy should be routinely performed.

In 1984, Weissmann et al recommended that CCK be given to patients with clinically suspected, acute acalculous cholecystitis, but who had gallbladder visualization.[106] If the gallbladder contracts normally with CCK, acute acalculous cholecystitis could be excluded because diseased gallbladders do not contract. Of 10 patients, all with pathologically proven acute acalculous cholecystitis, one had gallbladder filling but no gallbladder contraction with CCK. However, poor contraction can be caused by either acute or chronic cholecystitis. A radiolabeled leukocyte study may be useful in this situation. CCK administered after morphine is problematic. The long, 4 to 6-hour physiologic effect of morphine may interfere with the effectiveness of CCK. Intravenous naloxone could be be used to reverse the morphine effect.[52]

BILIARY OBSTRUCTION

Common causes for biliary obstruction include malignancy, choledocholithiasis, and inflammatory stricture. Much less common causes are sclerosing cholangitis, choledochal cyst, hemobilia, duodenal diverticulum, echinococcus, and ascariasis. Stone formation is related to the secretion of lithogenic bile. Approximately 90% of calculi form in the gallbladder and pass into the biliary

duct via the cyst duct. A minority of calculi form de novo outside the gallbladder in the intrahepatic or extrahepatic ducts.

Clinical Presentation

The clinical presentation of biliary obstruction varies, depending upon the duration, the degree, and the site of obstruction. Painless jaundice, a common presentation, is gradual in onset and is usually caused by malignancy. Sudden, severe abdominal pain occurs with acute, complete biliary obstruction, usually due to cholelithiasis. Persistence of obstruction beyond 2 to 3 days may result in cholangitis, with symptoms of biliary colic and fever, chills, and jaundice (ie, Charcot triad). Intermittent colicky pain is most commonly due to benign etiologies of partial obstruction (eg, stones or biliary stricture). Stones often incompletely obstruct, producing fluctuating symptoms and often normal or low levels of hyperbilirubinemia. Small stones may pass into the duodenum with transient symptoms. The serum alkaline phosphatase increases early in the natural history of obstruction. Released from the biliary ductal epithelium, it is the most sensitive indicator. Liver enzymes (serum glutamatic-oxaloacctic transaminase, serum glutamate pyruvate transaminase), released from injured hepatocytes, are normal in uncomplicated choledocholithiasis but increase with cholangitis and hepatic dysfunction. Jaundice is a late occurring manifestation of obstruction. Biliary cirrhosis is the end result if left untreated.

Hepatic Bile Secretion and Biliary Flow

They occur at a constant rate during fasting, determined by relative intrabiliary pressures. The normal hepatocyte secretory pressure is approximately 35 cm water, resting gallbladder pressure 10 cm, common bile duct 12 cm, and sphincter of Oddi 15 cm. The tone of the sphincter is normally the determining factor. Approximately 70% of bile enters the gallbladder, and 30% transits through the common duct to the duodenum.

After complete biliary obstruction, hepatic bile secretion decreases as biliary pressure increases. Secretion ceases when the back pressure equals or exceeds the secretory pressure of hepatocytes, usually after 1 to 2 days. By 24 to 48 hours, bile duct dilatation of extrahepatic and intrahepatic ducts occurs proximal to the site that obstruction occurs. The degree of dilatation varies depending on the duration, grade, and etiology of the obstruction. Liver function deteriorates after a week of complete obstruction and the bilirubin increases. Function recovers rapidly after relief of obstruction. With partial obstruction, hepatic function is maintained, but bile flow is delayed and retained above the obstruction site. The presence or absence of a gallbladder affects the presentation, course of symptoms, and findings because it normally acts as a low-pressure release reservoir. Although liver function tests may not become abnormal for 2 to 3 days after complete obstruction with an intact gallbladder, in the absence of a gallbladder, similar abnormalities can be seen within 4 to 6 hours. If the obstruction is proximal to the juncture of the hepatic and cystic ducts, symptoms present earlier than with a more distal obstruction and intact gallbladder.

Noninvasive Imaging

It is critical for the prompt work-up and diagnosis of patients with suspected biliary obstruction, whether presenting as painless jaundice or abdominal pain.

Real-Time Ultrasonography

It is commonly used to screen patients with suspected biliary obstruction. Detection of extrahepatic and intrahepatic biliary dilatation is often diagnostic. In early obstruction, ducts may not be dilated. Dilatation is most prevalent in high-grade obstruction of several days duration and in those patients with malignant etiologies. Benign causes of low-grade obstruction often do not result in significant biliary dilatation. Reported sensitivity for the diagnosis of biliary obstruction is reported to range from 80% to 99%, and the results are very dependent on patient selection.[114] Sensitivity for detection of stones in the common bile duct, cystic duct, or gallbladder neck is as low as 15%.[115] The type of pathology causing obstruction influences the accuracy. A large pancreatic mass is easier to see than a small, intraluminal common duct stone. Ultrasonography can indicate the level and nature of an obstructing process. Many of the concepts regarding ultrasonography apply to CT, which has similar sensitivity and specificity.

Magnetic Resonance Cholangiopancreatography (MRCP)

MRCP has been a major advance in the noninvasive diagnosis of biliary obstruction. It is viewed in a coronal plane to mimic the appearance of contrast cholangiogram. Dilated ducts appear as tubular structures with high T-2 weighted signal. Two-dimensional or 3-dimensional fast spin-echo sequence allows for data acquisition during a single breath hold. Its accuracy for detecting obstruction is high, with reported sensitivities of 89% to 93% and specificities of 90% to 99%. Diagnosis of the presence and level of biliary ductal obstruction in patients with malignant disease is comparable with endoscopic retrograde cholangiopancreatography (ERCP).

Cholescintigraphy

Cholescintigraphy plays an important role in the differential diagnosis of biliary obstruction despite advances of other anatomic imaging modalities that rely on detecting biliary dilatation. Both bilirubin and Tc-IDA

radiopharmaceuticals share a common organic anion receptor mediated endocytosis mechanism for uptake by the heptocyte. When serum bilirubin levels are high, bilirubin occupies available receptor sites and blocks Tc-IDA uptake. Tc-IDA radiopharmaceuticals used in the early days of cholescintigraphy had only moderate sensitivity for detection of obstruction (ie, 78% to 85%), which is slightly lower than that reported for ultrasonography. However, modern day radiopharmaceutials (eg, Tc-99m disofenin and mebrofenin) have high hepatic extraction and permit visualization of bile flow at serum bilirubin levels of 20 mg/dL or higher. Here, the higher hepatic extraction of Tc-99m mebrofenin (98% versus 88%, respectively) is advantageous.

Patients with early, low-grade or intermittent biliary obstruction may not have dilated ducts. Physiologic abnormalities precede morphologically evident disease and discordance in favor of cholescintigraphy, compared with morphologic imaging modalies can be as high as 23%.[116] Cholescintigraphy can be diagnostic for patients whose symptoms are suggestive of biliary obstruction but who are not clearly jaundiced, have only mild liver function abnormalities, and have normal ultrasonography. It can also distinguish cholecystitis from biliary obstruction or suggest concomitant disease. The patient with prior bouts of obstruction and common duct exploration, in whom a dilated, atonic, but nonobstructed duct is supected, can benefit from cholescintigraphy as well. Normal scintigraphic drainage can avert needless additional evaluation.

"Retained" biliary stones are those that have been overlooked during preoperative studies, operative inspection, and intraoperative cholangiography. Some patients may have postoperative stones that formed in the biliary tree since the time of surgery. Choledocholithiasis causes serious complications of ductal stricture, cholangitis, biliary cirrhosis, biliary fistulae, and hepatic abscess. Common duct stones sometimes act in a ball valve fashion, causing mild, intermittent obstruction. When clinically it appears that a patient has "passed a stone," it may mean that the stone actually moved cephalad instead of distally through the sphincter of Oddi.

Diagnosis and therapy. The anatomy of an obstruction must be confirmed by percutaneous transheptic cholangiography (PTCA) or ERCP before surgery. Although surgery is usually indicated for malignancy, stones can often be removed during ERCP. Endoscopic sphincterotomy permits introduction of a balloon-tip catheter and wire basket into the biliary tree. Agents that dissolve stones or mechanical techniques (eg, extracorporeal shock wave lithotripsy) are used to fragment larger stones for easier extraction.

Summary of Published Cholescintigraphy Literature for Biliary Obstruction

Cholescintigraphy with Tc-IDA derivatives has been used to diagnose biliary obstruction since 1978.[117] Delayed imaging was recommended to differentiate complete from partial obstruction, although partial obstruction was defined as biliary clearance by 24 hours.[118] Morphine-like drugs may cause the scintigraphic pattern of partial obstruction.[119]

In a 1983 retrospective review of 60 patients with a cholescintigraphic pattern of total biliary duct obstruction (ie, hepatic uptake but no biliary clearance by 24 hours), total obstruction was confirmed by surgery in 41.[120] Although the sensitivity was 100% and specificity 95%, the PPV was only 68%. Fourteen patients had severe hepatocellular disease, 4 had massive liver metastases, and 1 had portal vein thrombosis. With increasing levels of serum bilirubin, the PPV decreased from 100% to 73% (Tc-99m PIPIDA). Other uncommon etiologies for the pattern of complete biliary obstruction reported include cholangitis, severe hepatitis, the Dubin-Johnson syndrome, and intrahepatic cholestasis.[121-123] Cholestasis may be due to various etiologies, including viral and alcoholic hepatitis, and numerous drugs (e.g., erythromycin).

The sensitivity and specificity of cholescintigraphy to differentiate biliary tract obstruction from other etiologies was 97% and 90% specificity, respectively in a 1986 study of 96 jaundiced patients.[124] An uncommon "hyperacute biliary obstruction" pattern was described (i.e. rapid hepatic uptake, biliary ducts, and gallbladder visualization) but no bowel activity over 24 hours.[124,125] This pattern occurred immediately after the onset of obstruction and was thought to be caused by the gallbladder's ability to reasborb water and act as a reservoir. It was assumed that with a further increase in biliary pressure, bile flow would cease and the pattern change to nonvisualization of biliary structures and bowel. CCK was not administered. We would now call this partial obstruction.

Ten percent of patients with acute cholecystitis have concommitant common bile duct stones.[126] In 1985, Kaplun et al studied 27 patients referred for suspected acute cholecystitis, who had persistent nonvisualization of biliary tract for 2 to 4 hours or longer.[127] This pattern had a 97% PPV for common duct obstruction. Three patients had malignancy, and 22 had stones. There were 2 "false-positive" studies, one patient with ascending cholangitis and another who had recently passed a stone. Grey-scale ultrasonography showed normal size ducts in 70% of patients.

In 1986, investigators reported a 92% (23 of 35) PPV of cholescintigraphy to diagnose total biliary obstruction (ie. nonvisualization of the gallbladder, biliary tract, and intestines at 4 hours).[123] Hepatitis and sickle cell crisis

without obstruction were false-positives. Sensitivity was 100%, specificity 99.5%. Although in part of the investigation, partial obstruction was documented in 8 of 14 patients, with intestinal visualization between 2 and 4 hours.

The cholescintigraphic findings of partial biliary obstruction were described in 14 patients.[128] These findings included segmental biliary narrowing, abrupt biliary cutoff, intraluminal filling defects, and persistent pooling in major ducts following CCK administration. Serial imaging at short intervals of 2 minutes was recommended for detection of the obstruction site as radiotracer first reaches the site. Because of the high biliary back pressure, the CCK-stimulated GBEF was poor in 13 of 14 patients. An inconsistent scintigraphic finding of partial obstruction described was reflux into the right hepatic and left hepatic ducts following CCK administration.[128,129]

In 1984, Zeman et al emphasized that not all obstruction presents with jaundice or biliary dilatation.[116] Of 139 patients with suspected early or low grade, but not clinically obvious, obstruction, 64 had confirmed obstruction. Cholescintigraphy had a 98% sensitivity, Ultrasonography, 78%. specificity was similar, 85%/86%, respectively. Partial obstruction was predicted best by these cholescintigraphic findings (1) absence of intestinal activity (19 patients), (2) delayed biliary duct to bowel transit (>1 hours in 11 and >2 hours in 15 patients), and (3) a prominent ductal pattern that did not wash out by 2 hours (24 patients). Fourteen patients with obstruction had normal biliary-to-bowel-transit with pattern number 3. Failure to include this finding as a criterion of obstruction would have decreased the sensitivity to 75%. Obstruction was excluded in 3 patients without bowel visualization but a gallbladder that acted as a reservoir until stimulated by a fatty meal. Cholescintigraphy reliably confirmed or excluded obstruction in patients with bile duct dilatation and prior history of stone passage, biliary instrumentation, or surgery.

Quantitative methods have been used to improve the accuracy for cholescintigraphic diagnosis of partial biliary obstruction. Regions of interest were selected for the liver and biliary structures, and various quantitative parameters were calculated. Sensitivity/specificity were not particularly high (67%/85% and 93%/64%, respectively).[130,131] No mention was made of image analysis. A recent report combined image analysis and a semiquantitative scoring method for diagnosing partial obstruction. Grades (ie, 0 to 3) were assigned for time-to-peak biliary activity, adequacy of duct clearance, bowel clearance, biliary-to-liver ratios, etc. Partial obstruction was diagnosed with 100% accuracy in this small study of 23 patients after cholecystectomy.[132]

Comments on Diagnosis and Methodology

The pattern of high-grade biliary obstruction is an "Aunt Minnie" (ie, prompt hepatic uptake, no gallbladder or biliary duct visualization, or biliary-to-bowel transit). Rarely can cholestasis secondary to hepatitis or drug-induced causes have the same pattern. However, biliary obstruction must first be excluded, and, with this pattern, the likelihood is high that obstruction is the cause. The diagnosis can be made in most patients at 60 minutes in those with good hepatic function. Delayed imaging beyond 1 hour may detect transit into biliary ducts at 2 to 24 hours in some patients. Although they have an incomplete obstruction, it is still high-grade. The term "high-grade" for this pattern is probably more correct than "complete obstruction." The term "partial obstruction" should be reserved for the pattern of clearance into the biliary tract during the first hour but little or no clearance from biliary ducts, regardless of whether there is some biliary-to-bowel transit. CCK administration at 1 hour can obviate the need for delayed images. In the setting of hepatic insufficiency, delayed imaging is always indicated.

The pattern of delayed bile duct clearance and biliary-to-bowel transit has causes other than obstruction (eg, morphine-like drugs, CCK given before cholescintigraphy, chronic cholecystitis (Fig. 2), and normal variation (ie, "hypertonic sphincter of Oddi").[133] Morphine-like drugs should not be given for 4 to 6 hours before the study. Naloxone can reverse the drug effect and permit the study to be performed promptly, and shorten the patient time off analgesics.[52] Delayed imaging can usually differentiate functional from obstructive causes.[116] However, sincalide allows for a rapid and standardized method to differentiate the 2.[50,128] With functional causes, biliary duct clearance and biliary-to-bowel transit occurs in 30 minutes. With obstruction, the common bile duct does not clear. There may or may not be transit into the intestines. In 1978, Nielseon recommended that cholescintiraphy be performed postprandially if the clinical question was biliary obstruction because the resulting endogenous stimulation of CCK produces increased bile flow, stressing the common duct and facilitating the findings of partial obstruction.[117] Whether or not this approach is used, it should be remembered that fasting is not necessary if the question is only that of biliary duct obstruction (eg, in patients after cholecystectomy).

BILE LEAKS

Bile leaks after post-cholecystectomy are common. Small quantities of leakage after cholecystectomy do not usually lead to serious medical complications. Gilsdorf et al. performed cholescintigraphy routinely 2 to 4, hours after open cholecystectomy.[134] Bile leaks were detected in 44% of patients. Most leaks were not clinically significant. The

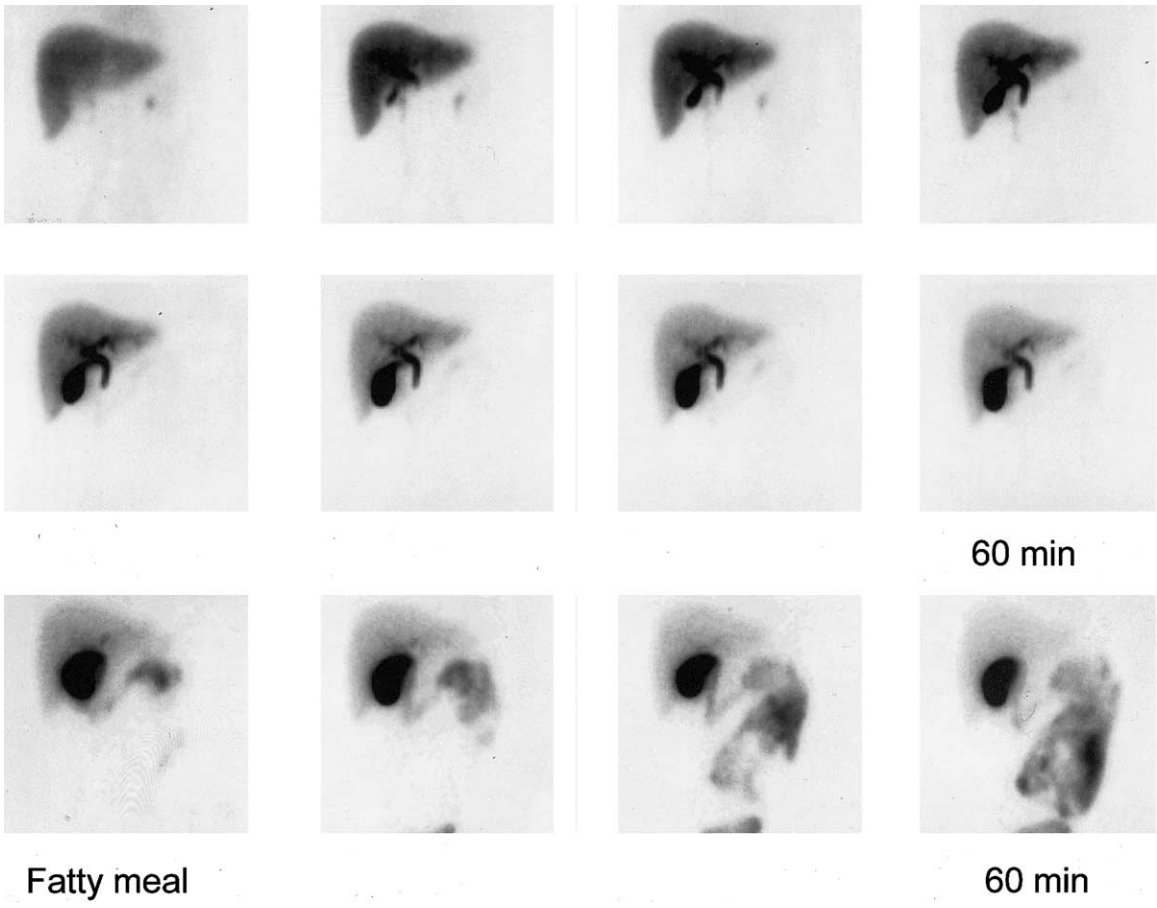

Fig 2. Delayed biliary-to-bowel transit. Acute right upper quadrant pain developed in a 50-year-old female. She had similar milder episodes in the past. Ultrasonography showed gallstones but no biliary duct stones or dilatation. Top 2 rows: Prompt gallbladder filling and common duct visualization, but no biliary duct clearance or biliary-to-bowel transit. The patient ingested a fatty meal and was imaged for another 60 minutes. The common duct rapidly cleared with simultaneous biliary-to-bowel-transit. The gallbladder contracted normally (gallbladder ejection fraction [GBEF] 45%). The patient's symptoms soon resolved. The delayed biliary-to-bowel was, likely, secondary to the patient's chronic cholecystitis, as seen on ultrasonography.

cause of bile leakage after cholecystectomy is often caused by surgical transection of small biliary radicles entering directly into the gallbladder bed (ie, bile ducts of Luschka), a normal variation in 25%, to 35% of patients. Less frequently, biliary extravasation occurs from direct injury to the biliary tree at surgery.

Laparoscopic cholecystectomy has replaced the open procedure in all but complicated cases. The procedure is associated with less discomfort, shorter postoperative recovery and hospital stay, and better cosmetic result. The incidence of bile duct injuries and bile leakage is only slightly higher than with open cholecystectomy, from 0.5% to 2.0%.[135] Injury to the biliary tree causing bile leakage or obstruction is one of the most serious and frequent complications.

Symptoms of bile leakage are often mild and nonspecific in the early postoperative period. Most perihepatic, postoperative fluid collections are small, asymptomatic, and resolve spontaneously. Symptomatic leakage is usually caused by local inflammatory or compressive effects of bile collection or infection. Large leaks with bile ascites are indicative of significant biliary tract or small intestine injury and require prompt repair. Bile enters the abdomen after duct injury through a fistulous tract undetected during surgery. Bile salts are the toxic component of bile, and produce a chemical peritonitis and associated cytokine release resulting in serious alterations in fluid transport across peritoneal membranes. Patients in whom abdominal pain, fever, jaundice, or bilous drainage from a surgical drain develops have a clinically significant leak and require intervention. Morbidity is lowest when complications are recognized and treated early.

Noninvasive Imaging

CT and ultrasonography have high sensitivities for detection of perihepatic fluid collections and free peri-

toneal fluid. However, they often cannot determine the type of fluid present. Postoperative collections other than bile include seroma, hematoma, lymphocele, and abscess. Cholescintigraphy can confirm that a fluid collection is derived from the biliary system, identify active biliary leakage, and estimate the rate of leakage. Negative cholescintigraphy should lead to a search for other causes of the patient's symptoms. Even if a leak is confirmed by paracentesis, negative cholescintigraphy indicates that the leak has either ceased or is slow enough that it will likely resolve spontaneously, and aggressive therapy is not warranted.

Published reports of the use of cholescintigraphy for diagnosis of biliary leakage date back to 1974, using I-131 rose bengal.[136,137] Since 1978, Tc-IDA radiotracers have been used.[138-140] Numerous publications have defined the clinical role for cholescintigraphy for detection of different presentations of bile leakage (eg, spontaneous, after blunt and penetrating trauma, after abdominal surgery, after cholecystectomy, after biliary-enteric anastomoses, and after liver transplant surgery).[118,138-150] Publications describe detection of biliary leaks following laparoscopic cholecystectomy.[151-156] Reports have emphasized its use for detection of various manifestations of biliary leakage, including intrahepatic leaks[142,157]; active extravasation[140]; bile ascites[158,159]; bilomas[156,160]; fistula to gastrointestinal organs (eg, the stomach and colon,[161,162] skin,[139] and bronchi)[163]; and leakage from a perforated duodenal ulcer.[159]

Cholescintigraphic Methodology and Findings for Biliary Leaks

Rapid leaks can often be detected and localized during the first 30 to 60 minutes after radiopharmaceutical injection. This process is seen as rapidly increasing activity outside the normal hepatobiliary structures. After cholecystectomy, biliary leakage often collects in the gallbladder fossa, and then extravasates either down the right parcolic gutter, spreads over the dome of the liver, and/or localizes to the left upper quadrant. Biliary leaks may accumulate in a loculated collection, or biloma or diffusely throughout the abdomen (ie, bile ascites). With peritoneal free leakage, the intestines will often be outlined with small bowel loops, giving a cold stepladder appearance. Leakage exits via a fistula to another organ (eg, bronchi, stomach, bowel, or skin). Activity exiting a surgical drain may be the only evidence of a leak. Careful attention to drains, tubing, and collection bags is critical for proper diagnosis. It is common for patients to have multiple drains, some placed free within the peritoneum and others placed within a biliary structure. Knowledge of which tubing and collection bag is draining from which abdominal area is critical for proper diagnosis. The specific anatomy of biliary-enteric hookups is also essential to understand the biliary and bowel drainage pattern.

Delayed imaging and multiple views are often helpful for detection and correct localization of biliary leakage. This process is particularly useful when the diagnosis is suspected, but initial images appear normal. Delayed imaging can often confirm slow extravasation and/or small collections. The decreasing adjacent liver activity and progress of bowel clearance can facilitate diagnosis. Lateral decubitus images can sometimes confirm fluid collections.

ERCP or PTCA is required for anatomic determination of the bile leak site. ERCP has the advantage of possible therapeutic intervention, permitting prompt repair. Although bile leaks may be caused by abdominal trauma or spontaneous rupture caused by acute infection, most are iatrogenic, occur postoperatively, and after cholecystectomy, bile duct stone removal, biliary-enteric anastomoses, and liver transplants.

REFERENCES

1. Gracie WA, Ransohoff DF: The natural history of silent gallstones: The innocent gallstone is not a myth. N Engl J Med 307:798-800, 1982

2. Meyers WC, Branum GD, Farouk M, et al: A prospective analysis of 1518 laparoscopic cholecystectomies. N Eng J Med 324:1075-1078, 1991

3. Laing FC, Federle MP, Jeffery RB, et al: Ultrasonic evaluation of patients with acute right upper quadrant pain. Radiology 140:449-455, 1981

4. Eikman EA, Cameron JL, Colman M, et al: A test for patency of the cystic duct in acute cholecysitis. Ann of Int Med 82:318-322, 1975

5. Rosenthall L, Shaffer EA, Lisbona R, et al: Diagnosis of hepatobiliary disease by 99m Tc-HIDA cholescintigraphy. Radiology 126:467-474, 1975

6. Stadalnik RC, Kraus JF, Matolo NM, et al: The validity of 99mTc-pyridoxylidene glutamate cholescintigraphy as a diagnostic test for cholecystitis. Clin Nucl Med 2:142-146, 1978

7. Weissmann HS, Frank MS, Bernstein LH, et al: Rapid and accurate diagnosis of acute cholecysitis with 99m Tc-IDA cholescinigraphy. AJR Am J Roentgenol 132:523-528, 1979

8. Suarez CA, Block F, Bernstein D, et al: The role of HIDA/PIPIDA scanning in diagnosing cystic duct obstruction. Ann Surg 191:391-396, 1980

9. Szlabick RE, Catto JA, fink-Bennett D, et al: Hepatobiliary scanning in the diagnosis of acute cholecysitis. Arch Surg 115:540-543, 1980

10. Freitas JE, Gulati RM: Rapid evaluation of acute abdominal pain by hepatobiliary scanning. JAMA 244:1585-1587, 1980

11. Weissmann HS, Badia J, Sugarman LA, et al: Spectrum of 99mTc-IDA cholescintigraphic patterns in acute cholecystitis. Radiology 138:167-175, 1981

12. Freitas JE, Mirkes SH, Fink-Bennett DM, et al: Suspected acute cholecystitis. Comparison of hepatobiliary scintigraphy versus ultrasonography. Clin Nucl Med 8:364-367, 1982

13. Zeman RK, Burrell MI, Cahow CE, et al: Diagnostic utility of cholescintgiraphy and ultrasonography in acute cholecystitis. Am J Surg 141:446-451, 1981

14. Mauro MA, McCartney WH, Melmed JR: Hepatobiliary scanning with 99mTcPIPIDA in acute cholecystitis. Radiology 142:193-197, 1982

15. Samuels BI, Freitas JE, Bree RL, et al: A comparison of radionuclide hepatobiliary imaging and real-time ultrasonography for detection of acute cholecystitis. Radiology 147:2017-2020, 1983

16. Ralls PW, Colletti PM, Halls JM, et al: Prospective evaluation of 99mTc-IDA cholescintigraphy and gray-scale ultrasound in the diagnosis of acute cholecystitis. Radiology 144:369-371, 1982

17. Worthen NJ, Usler JM, Funamura JL: Cholecystitis. Prospective evaluation of sonography and 99mTc-HIDA cholescintigraphy. AJR Am J Roentgenol 137:973-978, 1981

18. Shuman WP, Mack LA, Rudd TG, et al: Evaluation of acute right upper quadrant pain: Sonography and 99mTc-PIPIDA cholescintigraphy. AJR Am J Roentgenol 139:61-64, 1982

19. Chatziioannou, Moore WH, Ford PV, et al: Hepatobiliary scintigraphy is superior to abdominal ultrasonography in suspected acute cholecystitis. Surgery 127:6-9, 2000

20. Freitas JE, Coleman RE, Nagle CE, et al: Influence of scan and pathologic criteria on the specificity of cholescintigraphy: Concise communication. J Nucl Med 24:876-879, 1983

21. Klingensmith WC, Spitzer VM, Fritzberg, et al: The normal fasting and postprandial diisopropyl-IDA Tc-99m hepatobiliary study. Radiology 14:771-776, 1981

22. Baker RJ, Marion MA: Biliary scanning with Tc-99, pyridoxylideneglutamate—the effect of food in normal subjects: Concise communication. J Nucl Med 18:793-795, 1977

23. Larson MJ, Klingensmith WC, Kuni CC: Radionuclide hepatobiliary imaging: Non-visualization of the gallbladder secondary to prolonged fasting. J Nucl Med 23:1003-1005, 1982

24. Warner BW, Hamilton FN, Silberstein EB, et al: The value of hepatobiliary scans in fasted patients receiving total parenteral nutrition. Surgery 102:595-599, 1987

25. Stone G, Ansel HJ, Peterson FJ, et al: Gallbladder emptying stimuli in obese and normal-weight subjects. Hepatology 15:L795-798, 1992

26. Freeman LM, Sugarman LA, Weissmann HS: Role of cholecystokinetic agents in 99mTc-IDA cholescintigraphy. Semin Nucl Med 11:186-193, 1981

27. Kalf V, Froelich JW, Lloyd R, et al: Predictive value of an abnormal hepatobiliary scan in patients with severe intercurrent illness. Radiology 146:191-194, 1983

28. Roslyn JJ, Berquist WE, Pitt HA, et al: Increased risk of gallstones in children receiving total parenteral nutrition. Pediatrics 71:784-789, 1983

29. Pitt HA, King W III, Man LL, et al: Increased risk of cholelithiasis with prolonged total parenteral nutrition. Am J Surg 146:106-112, 1983

30. Messing B, Bories C, Kunstlinger F, et al: Does total parenteral nutrition induce gallbladder sludge formation and lithiasis. Gastroenterology 82:1012-1019, 1983

31. Potter T, McClain CJ, Shafer RB: Effect of fasting and parenteral alimentation on PIPIDA scintigraphy. Dig Dis Sci 28:687-691, 1983

32. Shuman WP, Gibbs P, Rudd TG, et al: PIPIDA scintigraphy for cholecysitis: False positive in alcholism and total parenteral nutrition. AJR Am J Roentgenol 138:1-5, 1982

33. Drane WE, Nelp WB, Rudd TG: The need for routine delayed radionuclide hepatobiliary imaging in patients with intercurrent disease. Radiology 151:763-769, 1984

34. Nicholson RW, Hastings DL, Testa HF, et al: HIDA scanning in gallbladder diseae. Br J Radiol 53:878-882, 1980

35. Fonseca C, Rosenthal L, Greenberg D, et al: Differential diagnosis of jaundice by Tc-99m IDA hepatobilary imaging. Clin Nucl Med 4:135-142, 1979

36. Garner WL, Marx V, Fabri PJ: Cholescintigraphy in the critically ill. Am J Surg 155:727-729, 1988

37. Fonseca C, Greenberg D, Rosenthall L, et al: Tc-99m IDA imaging in the differential diagnosis of acute cholecystitis and acute pancreatitis. Radiology 130:525-527, 1979

38. Frank MS, Weissman HS, Chunk J: Visualization of the biliary tract with Tc-99m HIDA in acute pancreatitis. Gastroenterology 78:1167-1170, 1980

39. Serafini AN, Al-Sheikh W, Barkin JA, et al: Biliary scintigraphy in acute pancreatitis. Radiology 144:591-595, 1982

40. Weissmann HS, Sugarman LA, Freeman LM: The clinical role of technetium-99m iminodiacetic acid cholescingraphy, in Freeman LM, Weissmann HS (eds): Nuclear Medicine Annual 1981. New York, NY, Raven Press, 1981, pp 879-1049

41. Pare P, Shaffer EA, Rosenthall L: Nonvisualization of the gallbladder by 99mTc-HIDA cholescinitigraphy as evidence of cholecystitis. CMAJ 118:384-386, 1978

42. Freeman LM, Sugarman LA, Weissmann HS: Role of cholescystokinetic agents in 99mTc-IDA cholescintigraphy. Semin Nucl Med 11:186-193, 1981

43. Wahl RL: The “water-ida”: A simple means to separate duodenal from gallbladder activity on cholescintigraphic studies. Eur J Nucl Med 9:335-336, 1984

44. Shaffer PB, Olsen JO: Differentiation of the gallbladder from the duodenum on cholescintigrams by dynamic display. Radiology 145:217-218, 1982

45. Coleman RE, Freitas JE, Fink-Bennett D, et al: The dilated cystic duct sign: A potential cause of false-negative cholescintigraphy. Clin Nucl Med 9:134-138, 1984

46. Kim CK, Palestro CJ, Solomon RW, et al: Delayed biliary-to-bowel transit in cholescintigraphy after cholecystokinin treatment. Radiology 176:553-556, 1990

47. Sostre S, Canto MI, Kaloo AN: Gallbladder response to a second dose of cholecystokinin during the same imaging study. Eur J Nucl Med 19:964-965, 1992

48. Ziessman HA, Muenz LR, Agarwal AK, et al: Normal values for sincalide cholescintigraphy: Comparison of two methods. Radiology 221:404-410, 2001

49. Ziessman HA, Fahey FH, Hixson DJ: Calculation of a gallbladder ejection fraction: Advantage of continuous sincalide infusion over the 3-min infusion method. J Nucl Med 33:537-541, 1992

50. Ziessman HA: Cholescintigraphy: Clinical indications and proper methodology. Radiol Clin N Am 39:997-1006, 2001

51. Achong DM, Oates E: Normal gallbladder ejection fraction after morphine augmentation. Clin Nucl Med 24:837-841, 1999

52. Patch GG, Morton KA, Arias JM, et al: Naloxone reverses pattern of obstruction of the distal common bile duct

induced by analgesic narcotics in hepatobiliary imaging. J Nucl Med 32:1270-1272, 1991

53. Jaffe JH, Martin WR: Opiod analgesics and antagonists, in Gilman AG, Rall TW, Nies AS, et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics (ed 8). New York, NY, Macmillan, 1990, pp 485-521

54. Murphy P, Salomon J, Roseman D: Narcotic anesthetic drugs. Their effects on biliary dynamics. Arch Surg 115:710-711, 1980

55. Dedrick DF, Tanner WW, Bushkin FL: Common bile duct pressure during enflurane anaesthesia. Effects of morphine and subsequent naloxone. Arch Surg 115:820-822, 1980

56. Choy D, Shi EC, McLean RG, et al: Cholescintigraphy in acute cholecystitis: Use of intravenous morphine. Radiology 151:203-207, 1984

57. Grund FM, Reinke DB, Larson BW, et al: Hepatobiliary imaging: The diagnostic use of intravenous morphine in fasting patients. Am J Physiol Imag 1:26-32, 1986

58. Kim EE, Pjura G, Lowry P, et al: Morphine-augmented cholescintigraphy in the diagnosis of acute cholecystitis. Am J Radiol 147:1177-1179, 1986

59. Keslar P, Turbiner EH: Hepatobiliary imaging and the use of intravenous morphine. Clin Nucl Med 12:592-596, 1987

60. Vasquez TE, Rimkus DS, Pretorius HT, et al: Intravenous administration of morphine sulfate in hepatobiliary imaging for acute cholecystitis: A review of clinical efficacy. Nucl Med Commun 9:217-222, 1988

61. Flancbaum L, Alden SM, Trooskin SZ: Use of cholescintigraphy with morphine in critically ill patients with suspected cholecystitis. Surgery 106:668-674, 1989

62. Fink-Bennett, Balon H, Robbins T, et al: Morphine-augmented cholescintigraphy: Its efficacy in detecting acute cholecystitis. J Nucl Med 32:1231-1233, 1991

63. Kistler AM, Ziessman HA, Gooch D, et al: Morphine augmented cholescintigraphy in acute cholecysitits. A satisfactory alternative to delayed imaging. Clin Nucl Med 16:404-406, 1991

64. Fig LM, Wahl RL, Stewart RE, et al: Morphine-augmented cholescintigraphy: Its efficacy in detection of acute cholecystitis. J Nucl Med 323:1231-1233, 1991

65. Kim CK, Lim JK, Machac J: Variable retention on cholescintigraphy after morphine administration. Eur J Nucl Med 23:1464-1467, 1996

66. Flancbaum L, Choban PS: Use of morphine cholescintigraphy in the diagnosis of acute cholecystitis in critically ill patients. Intensive Care Med 21:120-124, 1995

67. Kim CK, Kevin KM, Juweid M, et al: Cholescintigraphy in the diagnosis of acute cholecystitis: Morphine augmentation is superior to delayed imaging. J Nucl Med 34:1866-1870, 1993

68. Kim CK, Lim JK, Machac J: Variable bile rention on cholescintigraphy after morphine administration. Eur J Nucl Med 23:1464-1467, 1996

69. Chen CC, Holder LE, Maunoury C, et al: Morphine-augmentation increases gallbladder visualization in patients pretreated with cholecystokinin. J Nucl Med 38:644-647, 1997

70. Smith R, Rose JM, Gallo LN, et al: Pericholecystic hepatic activity in cholescintigraphy. Radiology 156:797-800, 1985

71. Swayne LC, Ginsberg HN: Diagnosis of acute cholecystitis by cholescintigraphy: Significance of pericholcystic hepatic uptake. AJR Am Roentgenol 152:1211-1213, 1989

72. Meekin GK, Ziessman HA, Klappenbach RS: Prognostic value and pathophysiologic significance of the rim sign in cholescintigraphy. J Nucl Med 28:1679-1682, 1987

73. Greer P, Lacayo L, Reiner DK, et al: The rim sign: The ghostly portender of acute cholecysitits. Am J Gastroenterol 87:627-629, 1992

74. Bushnell DL, Perlman SB, Wilson MA, et al: The rim sign: Association with acute cholecystitis. J Nucl Med 27:353-356, 1986

75. Oates E, Selland D-LG, Chin CT, et al: Gallbladder nonvisualization with pericholecystic rim sign: Morphine augmentation optimizes diagnosis of acute cholecystitis. J Nucl Med 37:267-269, 1996

76. Arose B, Shreeve WW, Baim RS, et al: Phantom Gallbladder: A variant of the rim sign. Clin Nucl Med 6:457-458, 1987

77. Lim ST, Sohn Myung-Hee: Rim sign in acute cholecystitis. Correlative images between hepatobiliary scintigraphy and helical computed tomgraphy. Clin Nucl Med 27:67-68, 2002

78. Bohdiewicz PJ: The diagnostic value of grading hyperperfusion and the rim sign in cholescintigraphy. Clin Nucl Med 18:867-871, 1993

79. Brachman MB, Tanasescu DE, Ramanna L, et al: Acute gangrenous cholecystitis: Radionuclide diagnosis. Radiology 151:209-211, 1984

80. Cawthon MA, Brown DM, Hartshorne MF, et al: Billiary scintigraphy. The "hot rim" sign. Clin Nucl Med 9:619-621, 1984

81. Jacobson AF: False-negative morphine-augmented hepatobiliary scintigraphy with a rim sign. Clin Nucl Med 20:579-581, 1995

82. Bushnell DL, Perlman SB, Wilson MA, et al: The rim sign: Association with acute cholecystitis. J Nucl Med 27:353-356, 1986

83. Swayne LC, Filippone A: Gallbladder perforation: Correlation of cholescintigraphic and sonographic findings with the Niemeier classification. J Nucl Med 32:1915-1920, 1990

84. Aburano T, Yokoyama K, Taniguchi M, et al: Diagnostic values of gallbladder hyperperfusion and the rim sign in radionuclide angiography and hepatobiliary imaging. Gastrointest Radiol 15:229-232, 1990

85. Colletti PM, Ralls PW, Siegel ME, et al: Acute cholecystitis: Diagnosis with radionuclide angiography. Radiology 163:615, 1987

86. Colletti RM, Cirimelli KM, Radin R, et al: Radionuclide angiography in suspected cholecystitis: Further observations. Clin Nucl Med 14:867-873, 1989

87. Shih W-J, Domstad PA, Kenady D, et al: Scintigraphic findings in acute gangrenous cholecystitis. Clin Nucl Med 12:717-720, 1987

88. Wilson DG, Lieberman LM: Perforation of the gallbladder diagnosed preoperatively. Eur J Nucl Med 8:145-147, 1983

89. Niemeier OW: Acute perforation of the gallbladder. Ann Surg 99:922-924, 1934

90. Abu-Dalu J, Urca I: Acute cholecystitis with perforation into the peritoneal cavity. Arch Surg 102:108-110, 1971

91. Hawkins HB, Cinti DC, Rao H, et al: Diagnosis of spontaneous perforation of the gallbladder by Tc-99m DISIDA. Clin Nucl Med 9:708-709, 1984

92. Mesgarzadeh M, Haines JE, Bobba VR, et al: Diagnosis of clinical unsuspected allbladder perforation in an obese

patient by Tc-99m IDA cholescintigarphy. J Nucl Med 24: 1028-1029, 1983

93. Powers TA, Melton RE: Diagnosis of gallbladder perforation by Tc-99m-disofenin cholescintigraphy. Clin Nucl Med 7:201-202, 1983

94. Selby JB, Glasman AB: Cholescintigraphic diagnosis of gallbladder rupture. Clin Nucl Med 8:64-65, 1983

95. Sefczek DM, Sharma P, Isaacs GH, et al: Effect of narcotic premedication on scintigraphic evaluation of gallbladder perforation. J Nucl Med 26:51-53, 1985

96. Wilson DG, Lieberman LM: Perforation of the gallbladder diagnosed preoperatively. Eur J Nucl Med 8:145-147, 1983

97. Felice PR, Trowbridge PE, Ferrara JJ: Evolving changes in the pathogenesis and treatment of perforated gallbladder. Am J Surg 149:466-473, 1985

98. Brunetti JC, Van Heertum RL: Preoperative detection of gallbladder perforation. Clin Nucl Med 5:347-348, 1980

99. Edell SL, Milunsky C, Garren L: Cholescintigrapic diagnosis of cholecystocolic fistula. Clin Nucl Med 6:303-304, 1981

100. Rosenberg RJ, Sziklas JJ, Spencer RP, et al: Gallbladder fistula demonstrated on hepatobiliary study. Clin Nucl Med 10:726-727, 1985

101. Siskind BN, Hawkins HB, Clinti DC, et al: Gallbladder perforation: An image analysis. J Clin Gastroenterol 9:670-678, 1987

102. Elkin CM, Weissmann HS, Freeman LM: Gallstone ileus diagnosed by Technetium-99m-dimethyliminodiacetic acid cholescintigraphy: A case report. Clin Nucl Med 9:79-80, 1984

103. Bocobo GR, Slavin JD, Rao H, et al: Hepatobiliary imaging in gallstone ileus. Clin Nucl Med 9:4-5, 1984

104. Shuman WP, Rogers JV, Rudd TG, et al: Low sensitivity of sonography and cholescintigraphy acalculous cholecystitis. AJR Am J Roentgenol 142:531-534, 1984

105. Cornelius EA: Letter to the Editor: Sensitivity of sonography and cholescintigraphy in acalculous cholecysitis. AJR Am J Roentgenol 143:1121-1122, 1984

106. Weissmann HS, Berkowitz D, Fox MS, et al: The role of technetium-99m iminodiacetic acid (IDA) cholescintigraphy in acute acalculous cholecystitis. Radiology 146:177-180, 1983

107. Mirvis SE: The diagnosis of acute acalculous cholecystitis: A comparison of sonograpy, scintigraphy, and CT. AJR Am J Roentgenol 147:1171-1175, 1986

108. Ramanna L, Brachman MB, Tanasescu DE, et al: Cholescintigraphy in acute acalculous cholecystitis. Am J Gastroenterol 79:650-653, 1984

109. Swayne LC: Acute acalculous cholecystitis: Sensitivity in detection using technetium-99m iminodiacetic acid cholescintigrafaphy. Radiology 160:33-38, 1986

110. Flancbaum L, Choban PS: Use of morphine cholescintigraphy in the diagnosis of acute cholecystitis in critically ill patients. Intensive Care Med 21:120-124, 1995

111. Kalliafas S, Ziegler DW, Flancbaum L, et al: Acute acalculous cholecystitis: Incidence, risk factors, diagnosis and outcome. Am Surg 64:471-475, 1998

112. Prevot N, Mariat G, Mahul P, et al: Contribution of cholescintigraphy to the early diagnosis of acute acalculous cholecystitis in intensive-care-unit patients. Eur J Nucl Med 26:1317-1325, 1999

113. Mariat G, Mahul P, Prevot N, et al: Contribution of ultrasonography and cholescintigraphy to the diagnosis of acute acalculous cholecystitis in intensive care unit patients. Intensive Care Med 26:1658-1663, 2000

114. Ziessman HA, Zeman RK, Akin EA: Cholescintigraphy: Correlation with other hepatobiliary imaging modalities, in Sandler MP, Coleman RE, Patton JA, et al (eds): Diagnostic Nuclear Medicine (ed 4). Philadelphia, PA, Lippincott Williams & Wilkins, 2003, chap 25, pp 503-529

115. Laing FC, Jeffery RB: Choledocholithiasis and cystic duct obstruction: Difficult ultrasonographic diagnosis. Radiology 146:475-479, 1983

116. Zeman RK, Lee C, Jaffe MH, et al: Hepatobiliary scintigraphy and sonography in early biliary obstruction. Radiology 153:793-794, 1984

117. Nielsen SP: Hepatobiliary scintigraphy and hepatography with Tc-99m diethyl-acetanilido-iminodiacetate in obstructive jaundice. J Nucl Med 19:452-457, 1978

118. Klingensmith WC, Kuni CC, Fritzberg AR: Cholescintigraphy in extrahepatoblilary obstruction. AJR Am Roentgenol 139:65-70, 1982

119. Taylor A, Kiper MS, Witztum K, et al: Abnormal 99mTc-PIPIDA scans mistaken for common duct obstruction. Radiology 144:373-375, 1982

120. Egbert RN, Braunstein P, Lyos K, et al: Total bile duct obstruction. Arch Surg 118:709-712, 1983

121. Hughs KS, Marrangoni AG, Turbiner E: Etiology of the obstructive pattern in hepatobiliary imaging. Clin Nucl Med 9:222-226, 1984

122. Huang M-J, Liaw Y-F, Tzen K-Y: The significance of visualization of extrahepatic bile duct in intravenous radionuclide cholescintigraphy with special reference to acute suppurative cholangititis. Clin Nucl Med 9:394-396, 1984

123. Lecklitner ML, Austin AR, Benedetto AR, et al: Positive predictive value of cholescintigraphy in common bile duct obstruction. J Nucl Med 27:1403-1406, 1986

124. Lee AW, Ram MD, Shih W-J, et al: Technetium-99m BIDA biliary scintigraphy in the evaluation of the jaundiced patient. J Nucl Med 27:1407-1412, 1986

125. Blue PW: Hyperacute complete common bile duct obstruction demonstrated with 99mTc-IDA cholescintigraphy. Nuc Med Commun 6:275-277, 1985

126. Pitluk HC, Beal JM: Choledocholithiasis associated with acute choelcystitis. Arch Surg 114:887-888, 1979

127. Kaplun L, Weissmann HS, Rosenblatt RR, et al: The early diagnosis of common bile duct obstruction using cholescintigraphy. JAMA 17:2431-2434254, 1985

128. Krishnamurthy GST, Lieberman DA, Brar HS: Detection, localization, and quantitation of degree of common bile duct obstruction by scintigraphy. J Nucl Med 26:726-735, 1985

129. Itoh H, Murase K, Hamamoto K: Reflux sign in cholescintigraphy after administration of a gallbladder contracting agent. J Nucl Med 30:1192-1197, 1989

130. Darweesh RMA, Dodds WJ, Hogan WJ, et al: Efficacy of quantitative hepatobiliary scintigraphy and fatty-meal sonography for evaluating patients with suspected partial common duct obstruction. Gastroenterology 94:779-786, 1988

131. Kloiber R, AuCoin R, Hershfield NB, et al: Biliary obstruction after cholecystectomy: Diagnosis with quantitative cholescintigraphy. Radiology 169:643-647, 1988

132. Sostre S, Kaloo AN, Spiegler EJ, et al: A noninvasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: The scintigraphic score. J Nucl Med 33:1216-1222, 1992

133. Ziessman HA: Cholecystokinin cholescintigraphy. Clinical indications and proper methodology, in Ziessman HA (ed): Radiologic Clinics of North America. Philadelphia, PA, Saunders, 2001, pp 1997-1005

134. Gilsdorf JR, Phillips M, McLeod MK, et al: Radionuclide evaluation of bile leakage and the use of subhepatic drains after cholecystectomy. Am J Surg 151:259-262, 1986

135. The southern Surgeons Club: A prospective analysis of 1518 laparoscopic cholecystectomies. N Eng J Med 324:1073-1078, 1991

136. Silverberg M, Rosenthall L, Freeman LM: Rose bengal excretion studies as an aid in the differential diagnosis of neonatal jaundice. Semin Nucl Med 3:69-80, 1973

137. Wiener SN, Vyas M: The scintigraphic demonstration of bile leakage utilizing I-131 rose bengal. J Nucl Med 15:1074-1075, 1974

138. Klingensmith WC, Koep LJ, Fritzberg AR: Bile leak into hepatic abscess in a liver transplant: Demonstration with 99mTc-dietyl-iminoacetic acid. AJR Am J Roentgenol 131: 889-891, 1978

139. Rosenthall L, Fonesceca C, Arzoumanian A, et al: Tc-99m IDA hepatobiliary imaging following upper abdominal surgery. Radiology 130:735-738, 1979

140. Weissmann H, Chun K, Frank M, et al: Demonstration of traumatic bile leakage with cholescintigraphic and ultrasonography. AJR Am J Roentgenol 133:843-847, 1979

141. Esensten M, Ralls PW, Coletti P, et al: Postraumatic intrahepatic bilioma: Sonographic diagnosis. AJR Am J Roentgenol 130:303-305, 1983

142. Zeman RK, Lee CH, Stahl R, et al: Strategy for the use of biliary scintigraphy in non-iatrogenic biliary trauma. Radiology 151:771-777, 1984

143. Rozran RS, Preston DF, McMillan JH: Hepatobiliary imaging for demonstration of bile leaks. Clin Nucl Med 9:189-192, 1984

144. Weissmann HS, Gliedman MR, Wilk PJ, et al: Evaluation of the postoperative patient with Tc-99m-IDA cholescintigraphy. Semin Nucl Med 12:27-52, 1982

145. Rosenthal L: An update on radionuclide imaging in hepatobiliary disease. JAMA 245:2065-2068, 1981

146. Rienzo RJ, Tyler G, Morel DE: Sonographic and scintigraphic detection of a bile leak in a post cholecystectomy patient. Recognition of the tail sign. Clin Nucl Med 8:480-482, 1983

147. Makhija M, Schultz S, McManus KT, et al: Scintigraphy of bile leakage following cholecystectomy. Clin Nucl Med 10:848-850, 1985

148. Siddiqui AR, Ellis JH, Majdura JA: Different patterns in bile leakage following cholecystectomy demonstrated by hepatobiliary imaging. Clin Nucl Med 11:751-753, 1986

149. Zeman RK, Burrell MI, Dobbins J, et al: Postcholecystectomy syndrome: Evaluation using biliary scintigraphy and edoscopic retrograde cholangiopancreatography. Radiology 156:787-792, 1985

150. Scott-Smith W, Raftery AT, Wraight EP, et al: Tc-99m labeled HIDA imaging in suspected biliary leaks after liver transplantation. Clin Nucl Med 10:478-479, 1983

151. Estrada WN, Zanzi I, Ward R, et al: Scintigraphic evaluation of postoperative complications of laparoscopic cholecystectomy. J Nucl Med 32:1910-1911, 1991

152. Gelman R, Alexander MS, Zucker KA: Use of radionuclide imaging in the evaluation of suspected biliary damage during laparsoscopic cholecystectomy. Gastroenterol Radiol 16:201-203, 1991

153. Pasmans H, Go PM, Gouma D, et al: Scintigraphic diagnosis of bile leakage after laparoscopic cholecystectomy. A prospective study. Clin Nucl Med 17:697-700, 1992

154. Trerotola SO, Savader SJ, Lund GB, et al: Biliary tract complications following laparoscopic cholecystectomy: Imaging and intervention. Radiology 184:195-200, 1992

155. Walker AT, Shapiro AW, Brooks DC, et al: Bile duct disruption and biloma after laparoscopic cholecystectomy: Imaging evaluation. AJR Am J Roentgenol 158:785-789, 1992

157. Kuni CC, Klingensmith WC, Koep LJ, et al: Communication of intrahepatic cavities with bile ducts: Demonstration with Tc-99m diethyl IDA imaging. Clin Nucl Med 5:349-351, 1980

156. Lee CM, Stewart L, Way LW: Postcholecystectomy abdominal bile collections. Arch Surg 135:538-542, 2000

158. Nagle CE, Fink-Bennett D, Freitas JE: Bile ascites in adults. Diagnosis using hepatobiliary scintigraphy and parcentesis. Clin Nucl Med 10:403-405, 1985

159. Westley KA, Straub WH, Keyes JW: Cholescintigraphic detection of intraperitoneal bile leakage from a perforated duodenal ulcer. Clin Nucl Med 12:781-782, 1987

160. Ramachandran A, Gupta SM, Johns WD: Various presentations of postcholecystectomy bile leak diagnosed by scintigraphy. Clin Nucl Med 26:495-498, 2001

161. Edell SL, Milunsky C, Garren L: Cholescintigraphic diagnosis of cholecystocolic fistula. Clin Nucl Med 6:303-304, 1981

162. Henderson KW, Telfer N, Hallls JM: Gastrobiliary fistula: Pre and postoperative assessment with Tc99m PIPIDA. AJR Am J Roentgenol 137:163-165, 1981

163. Savitch I, Kew MC, Levin J: Demonstration of a biliary-bronchial fistual using Tc-99m p-butyl IDA imaging. Clin Nucl Med 8:139-140, 1983