Society of Nuclear Medicine Procedure Guideline for Hepatobiliary Scintigraphy

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I. Purpose

The purpose of this procedure guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of hepatobiliary scintigraphy.

II. Background Information and Definitions

Hepatobiliary scintigraphy is a radionuclide diagnostic imaging study that evaluates hepatocellular function and patency of the biliary system by tracing the production and flow of bile from the liver through the biliary system into the small intestine. Sequential images of the liver, biliary tree and gut are obtained. Computer acquisition and analysis as well as pharmacological interventions are frequently employed.

III. Common Indications

A. Functional assessment of the hepatobiliary system
B. Integrity of the hepatobiliary tree

These broad categories include, for example:

- Evaluation of suspected acute cholecystitis
- Evaluation of suspected chronic biliary tract disorders
- Evaluation of common bile duct obstruction
- Detection of bile extravasation
- Evaluation of congenital abnormalities of the biliary tree

IV. Procedure

A. Patient Preparation

To permit gallbladder visualization, the patient must have fasted for a minimum of two, and preferably four hours prior to administration of the radiopharmaceutical. If the patient has fasted for longer than 24 hr or is on total parenteral nutrition, the gallbladder may not fill with tracer. In these cases the patient may be pretreated with sincalide, see IV.F.1 below.

B. Information Pertinent to Performing the Procedure

The physician should review all available pertinent clinical/laboratory/radiographic information about the patient prior to the study. Additional information specifically related to hepatobiliary scintigraphy includes:

1. History of previous surgeries, especially biliary and gastrointestinal.
2. Time of most recent meal.
3. Current medications, including the time of their most recent administration (with particular attention to opioid compounds).
4. Results of bilirubin and liver enzyme levels.
5. Results of gallbladder or abdominal ultrasound.

C. Precautions

The test should be performed fasting to avoid a false-positive result. Interference by opioids can be minimized by delaying the study for 4 hours after the last dose. In some cases the effect can be reversed with Narcan. Additional details are listed in IV.A. ("Patient Preparation") and IV.K. ("Sources of Error").

D. Radiopharmaceutical

Tc-99m labeled disofenin (DISIDA, 2,6-diisopropylacetanilido iminodiacetic acid) or mebrofenin (BRIDA, bromo-2, 4,6-trimethylacetanilido iminodiacetic acid) is administered intravenously in activities of 50–200 MBq (1.5–5 mCi) for adults; higher dosages may be needed in hyperbilirubinemia, 100–370 MBq (3–10 mCi). Mebrofenin may be selected instead of disofenin in moderate to severe hyperbilirubinemia due to its somewhat higher hepatic extraction. For infants and children the administered activity is 2–7 MBq/kg (0.05–0.2 mCi/kg) with a minimum of 15–20 MBq (0.4–0.5 mCi).

Radiation Dosimetry for Adults

Radiopharmaceuticals	Administered Activity MBq (mCi)	Organ Receiving the Largest Radiation Dose* mGy/MBq (rad/mCi)	Effective Dose* mSv/MBq (rem/mCi)
Tc-99m Disofenin Tc-99m Mebrofenin	50 – 200 i.v. (1.5 – 5.0)	0.11 Gallbladder Wall (0.41)	0.024 (0.089)

* ICRP 53, page 203, normal liver function

E. Image Acquisition

A large field of view gamma camera equipped with a low energy all-purpose or high-resolution collimator is usually used. For a smaller field of view gamma camera a diverging collimator may be needed. Whenever possible, continuous computer acquisition (usually in the anterior view) should be performed (1 frame / min for 30–60 min). Imaging should start at injection and continue serially for 60 min or until activity is seen in both the gallbladder (which confirms patency of the cystic duct) and the small bowel (which confirms patency of the common bile duct). Additional views (e.g., right lateral, left or right anterior oblique) may be obtained as needed to clarify anatomy.

The digital data can be reformatted to 5–15 min images for filming. Cinematic display of the data may reveal additional information not readily apparent on the film.

When acute cholecystitis is suspected and the gallbladder is not seen within 40–60 min, 3–4 hr-delayed images should be obtained, or morphine augmentation (see IV.F.2.) may be employed in lieu of delayed imaging. Delayed imaging at 18–24 hr may be necessary in some cases (e.g., severely ill patient, severe hepatocellular dysfunction, suspected common bile duct obstruction, suspected biliary atresia).

If the patient is being studied for a biliary leak, 2–4 hr delayed imaging and patient-positioning maneuvers (e.g., decubitus views) may be helpful. Any drainage bags should by included in the field of view if the biliary origin of a leak or fistula is in question.

F. Interventions

A variety of pharmacologic or physiologic interventions may enhance the diagnostic value of the examination. Appropriate precautions should be taken to promptly detect and treat any adverse reactions caused by these interventions.

1. Sincalide pretreatment: Sincalide, a synthetic C-terminal octapeptide of cholecystokinin (CCK), in doses of 0.01–0.02 µg / kg, may be given intravenously, 30–60 min prior to the hepatobiliary tracer injection to minimize the potential for a false-positive study (e.g., in patients who have fasted longer than 24 hr, are

Radiation Dosimetry for Children (5 year old)

Radiopharmaceuticals	Administered Activity MBq (mCi)	Organ Receiving the Largest Radiation Dose* mGy/MBq (rad/mCi)	Effective Dose* mSv/MBq (rem/mCi)
Tc-99m Disofenin Tc-99m Mebrofenin	50 – 200 i.v. (1.5 – 5.0)	0.11 Gallbladder Wall (0.41)	0.024 (0.089)

* ICRP 53, page 203, normal liver function

on parenteral hyperalimentation, or have a severe intercurrent illness). Sincalide should be administered slowly (over a 3–5 min duration) to prevent biliary spasm and abdominal cramps. A slower infusion (30–45 min) may also be used (see IV.F.3.).

2. Morphine Sulfate: When acute cholecystitis is suspected and the gallbladder is not seen by 40-60 min, morphine sulfate, 0.04–0.1 mg/kg, may be administered intravenously over 2-3 min. If the cystic duct is patent, flow of bile into the gallbladder will be facilitated by morphine-induced temporary spasm of the sphincter of Oddi. The intrahepatic biliary tree and common bile duct (CBD) must contain radioactive bile, and tracer activity should be present in the small bowel at the time of morphine injection. A second injection of radiopharmaceutical (booster dose of approximately 1 mCi) may be necessary prior to morphine if the remaining liver/biliary tree activity appears insufficient to permit gallbladder filling. Shielding the bowel activity with lead may also be helpful. Imaging is usually continued for another 30 min following morphine administration but may be extended if desired. Contraindications to the use of morphine include respiratory depression in non-ventilated patients (absolute), morphine allergy (absolute) and acute pancreatitis (relative).
3. Sincalide stimulation: Gallbladder contractility may be evaluated by determining the gallbladder ejection fraction (GBEF) response to sincalide. The study involves an intravenous injection over a minimum of 3 min or a 30-45 min infusion of 0.01- 0.02 µg/kg sincalide after the gallbladder is maximally filled with radiopharmaceutical (usually 60 min after the injection) and there is minimal activity in the liver. Computer acquisition (1-2 frames/min) then continues for 30 min. Various protocols can be employed. When performing and interpreting this procedure, the physician must adhere to a specific technique (i.e., total dose of sincalide, dose rate and duration of infusion) and normal values validated for that technique.
4. Fatty meal stimulation: Gallbladder ejection fraction measurement using a fatty meal challenge instead of sincalide has also been described. If visual assessment of gallbladder emptying is sufficient, a fatty snack may be used.
5. Phenobarbital: In jaundiced infants in whom biliary atresia is suspected, pretreatment with phenobarbital, 5 mg/kg/day, may be given orally in two divided doses daily for a minimum of 3–5 days prior to the hepatobiliary imaging study to enhance the biliary excretion of the radiotracer and increase the specificity of the test. Mebrofenin may be preferred over Disofenin in suspected biliary atresia.

G. Processing
   1. Gallbladder ejection fraction (GBEF): Using the immediate pre-sincalide and the post-sincalide data, regions of interest (ROI) are drawn around the gallbladder (taking into account patient motion) and adjacent liver (background) using any standard nuclear medicine software package. The liver background ROI is selected taking care to exclude ductal activity. GBEF is calculated from the gallbladder time-activity curve as:

$$\text{GBEF (\%)} = \frac{(\text{net GB cts}_{max}) - (\text{net GB cts}_{min})}{\text{Net GB cts}_{max}} \chi\ 100$$

   2. Hepatocellular function may be assessed by deconvolution analysis from ROI over the liver and heart (hepatic extraction fraction) or by analysis of a heart ROI for tracer clearance from the blood pool.

H. Interpretation Criteria
   1. Normal: A normal hepatobiliary scan is characterized by immediate demonstration of hepatic parenchyma, followed sequentially by activity in the intra- and extrahepatic biliary ductal system, gallbladder and upper small bowel. All these structures should be seen within one hour. Gallbladder filling implies a patent cystic duct and excludes acute cholecystitis with a high degree of certainty.
   2. Acute cholecystitis: The hallmark of acute cholecystitis (acalculous as well as calculous) is persistent gallbladder non-visualization 30 min post morphine or on the 3–4 hr delayed image.

      A pericholecystic hepatic band of increased activity (rim sign) is often associated with severe phlegmonous/gangrenous acute cholecystitis, a surgical emergency.
   3. Chronic cholecystitis and clinical settings associated with physiologicfailure of the gallbladder to fill with radiotracer (e.g., prolonged fasting for >24–48 hr, severely ill or post-operative hospitalized patients) may result in gallbladder non-filling within the first hour, but may be separated from acute cholecystitis using low dose intravenous morphine (see above) or delayed imaging. In chronic cholecystitis the gallbladder will usually be seen within 30 min of morphine administra-

tion or on 3–4 hr delayed images, while true cystic duct obstruction (acute cholecystitis) will result in persistent gallbladder non-visualization. Appearance of the gallbladder after the bowel has a significant correlation with chronic cholecystitis. In severely ill patients and in those on total parenteral nutrition, frequently the gallbladder will not be seen even after morphine despite a patent cystic duct, and a larger dose of morphine (0.1 mg/kg) may be necessary to decrease the false positive rate of the study.

4. Reduced gallbladder ejection fraction in response to sincalide occurs in calculous and acalculous biliary diseases (i.e., chronic acalculous cholecystitis, cystic duct syndrome, sphincter of Oddi spasm). It may also be associated with various non-biliary diseases and conditions, as well as caused by a variety of medications (e.g., morphine, atropine, calcium channel blockers, octreotide, progesterone, indomethacin, theophylline, benzodiazepines, histamine-2 receptor antagonists).
5. Common bile duct obstruction: Delayed biliary-to-bowel transit beyond 60 min raises the suspicion for partial common bile duct (CBD) obstruction, although this may be seen as a normal variant in up to 20% of individuals. With high grade CBD obstruction, there is usually prompt liver uptake but no secretion of the radiotracer into biliary ducts. With prolonged obstruction, concomitant hepatic dysfunction may be seen. With partial biliary obstruction, radiotracer fills the biliary system but clears poorly proximal to the obstruction by 60 min or on delayed images at 2-4 hours or with Sincalide. Clearance into the bowel may or may not be seen. Severe hepatocellular dysfunction may also demonstrate delayed biliary-to-bowel transit.
6. Biliary leak: A bile leak is present when tracer is found in a location other than the liver, gallbladder, bile ducts, bowel or urine. This may be seen more easily using a cinematic display or decubitus positioning (see above).
7. Biliary atresia: Biliary atresia can be excluded scintigraphically by demonstrating transit of radiotracer into the bowel. Failure of tracer to enter the gut is consistent with biliary atresia, but can also be caused by hepatocellular disease or immature intrahepatic transport mechanisms. Renal or urinary excretion of the tracer (especially in diaper) may be confused with bowel activity and is a potential source of erroneous interpretation.
8. Duodenogastric bile reflux: During a hepatobiliary scan, activity may reflux from the duodenum into the stomach. If the bile reflux is marked and occurs in a symptomatic patient, it may be abnormal, since it is highly correlated with bile gastritis, a cause of epigastric discomfort.
9. Post-cholecystectomy sphincter of Oddi dysfunction: Sphincter of Oddi dysfunction has the appearance of partial common bile duct obstruction. Pretreatment with sincalide or morphine may improve the sensitivity for its detection. Various visual, quantitative and semiquantitative scintigraphic parameters of bile clearance have been used in conjunction with image analysis. (e.g., a scoring system, hepatic hilum-to-duodenum transit time, % biliary emptying post-morphine provocation, etc.).

I. Reporting

Aside from patient demographics, the report should include the following information:

1. Indication for the study (e.g., suspected acute cholecystitis, suspected common bile duct obstruction, suspected bile leak, etc.).
2. Procedure
   a. Radiopharmaceutical and dose administered
   b. Other medications given and their dosage (e.g., pre-treatment with sincalide, morphine, post-treatment with sincalide)
   c. Duration of imaging, special or delayed views obtained
3. Findings
   Include the appearance of the liver, the presence and time of tracer appearance in the gallbladder, small bowel, any unusual activity (e.g., bile leak, enterogastric reflux, etc.), any quantitative data generated (e.g., GBEF)
4. Study limitations, patient reactions to drugs administered
5. Comparison/correlative imaging data
6. Impression
   This should be concise, as precise as possible, should address the clinical question, provide a differential diagnosis and make recommendations if appropriate.
7. Any urgent or unexpected findings should be directly communicated to the referring physician and this should be documented.

J. Quality Control

None

K. Sources of Error

1. The causes of a *false-positive* study (gallbladder non-visualization in the absence of acute

cholecystitis) include:

a. Insufficient fasting (<2–4 hr)
b. Prolonged fasting (>24–48 hr), especially total parenteral nutrition (despite Sincalide pre-treatment and Morphine augmentation)
c. Severe hepatocellular disease
d. High grade common bile duct obstruction
e. Severe intercurrent illness (despite sincalide pre-treatment and morphine augmentation)
f. Pancreatitis (rare)
g. Rapid biliary-to-bowel transit (insufficient tracer activity remaining in the liver for delayed imaging)
h. Severe chronic cholecystitis
i. Previous cholecystectomy

2. The causes of a *false-negative* study (gallbladder visualization in the presence of acute cholecystitis) are rare, but include:
   a. Bowel loop simulating gallbladder (drinking 100–200 ml water may remove the radiopharmaceutical from the duodenum and allow differentiation of gall bladder from bowel).
   b. Acute acalculous cholecystitis
   c. The presence of the "dilated cystic duct" sign simulating gallbladder. If this sign is present, morphine should not be given.
   d. Bile leak due to gallbladder perforation
   e. Congenital anomalies simulating gallbladder
   f. Activity in the kidneys simulating gallbladder or small bowel (may be clarified by a lateral image).

V. Issues Requiring Further Clarification

None

VI. Concise Bibliography

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VIII. Disclaimer

The Society of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high quality nuclear medicine procedures. These generic recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be quite different than the spectrum of patients seen in a more general practice setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, the resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.