

Nuclear Medicine Tests for Acute Gastrointestinal Conditions

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Acute cholecystitis (AC) and lower-gastrointestinal (GI) bleeding are 2 emergencies commonly encountered in nuclear medicine. Evidence of AC on hepatobiliary scintigraphy (HBS) allows for confident diagnosis and provides support for definitive surgical treatment. Proper patient preparation is essential for HBS including fasting and the use of pharmacologic adjuncts is sometimes required. Pharmacologic adjuncts may also be administered during HBS to shorten the length of the examination and increase its specificity. In the interpretation of HBS, there are several sources of false-positive results to be aware of, most commonly chronic cholecystitis. False-negative results on HBS are usually the result of mistaking another structure, such as a dilated cystic duct, for the gallbladder. Abdominal ultrasound is the appropriate initial test in patients with suspected AC, but HBS is an excellent second tier test for the diagnosis of AC in the work-up of indeterminate cases by sonography.

GI bleeding scintigraphy plays an important role in the evaluation and management of patients with acute lower-GI bleeding. Scintigraphy serves to localize sites of active GI bleeding and stratify those patients who would benefit from aggressive treatment (surgery or arteriography) vs those who can be managed medically. Pretest involvement of respective services is critical for successful bleeding site confirmation and therapy by interventional radiology or surgery or both. Single photon emission computed tomography/computed tomography erythrocyte scintigraphy has demonstrated superior accuracy and precision over planar scintigraphy in the diagnosis of acute GI bleeding. Additionally, single photon emission computed tomography/computed tomography scintigraphy of GI bleeding provides useful supplemental anatomical information that benefits patient management.

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The 2 most common acute gastrointestinal (GI) conditions addressed by nuclear medicine include acute cholecystitis (AC) and GI bleeding. There is urgency for the diagnosis in both conditions and patient management critically depends on the study results. In patients with suspected AC the presenting complaint is often the ambiguous abdominal pain, which can be caused by a number of other diseases. Showing evidence of AC on hepatobiliary scintigraphy (HBS) allows for confident diagnosis and provides support for definitive surgical treatment. This high level of confidence in diagnosis is particularly important in severely ill patients who have an inherently high risk of surgical mortality and morbidity. On

the one hand, given that the best outcome in AC is afforded by a prompt laparoscopic cholecystectomy (LC),¹⁻³ high accuracy and expedience of some HBS protocols could improve those patients' outcome. On the other hand, for those who believe in the effectiveness of conservative treatment,⁴ the high specificity of HBS would be reassuring that the other more ominous causes of abdominal pain have not been overlooked. A comprehensive review of HBS in AC was recently published⁵; therefore, this article focuses on the practical aspects and nuances that aim at further enhancing interpretational accuracy as well as improving the clinical applicability.

For more than 30 years, the GI bleeding scan has played an important role in the evaluation and management of patients with acute GI bleeding. The purpose of the GI bleeding scan is to locate the site of active GI bleeding and also to identify those patients who would benefit from aggressive treatment (surgery or arteriography) vs those who can be managed

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medically. Once the upper GI source of bleeding has been excluded, typically by negative nasogastric aspirate or endoscopy or both, the GI bleeding scan is typically performed as the next step in the evaluation of acute GI hemorrhage which is non-life threatening. Life-threatening GI hemorrhage is treated surgically. Due to the technique's superior sensitivity for detecting small amounts of active GI hemorrhage, a positive result on a GI bleeding scan generates enough confidence to proceed with the next step in the diagnostic evaluation (eg arteriography and endoscopy) or even surgical intervention.

AC: Pathophysiology and Clinical Presentation

AC is typically an acute inflammation of the gallbladder (GB) that results from obstructing gallstone, acute calculous cholecystitis (ACC), which occurs in over 90% of all AC cases.⁶ The obvious result is that obstruction does not allow for the radioactively marked bile to enter the GB on HBS. The pathophysiology of acute acalculous cholecystitis (AAC) is not as well understood. Chemical injury from bile stasis with added insult from microvascular ischemia⁷ is implicated as the central catalyst of mucosal injury in AAC, leading to inflammation and necrosis. It is most likely that the inflammatory material fills the GB, increasing its pressure to the level that does not allow for newly produced bile to enter.

The pathologic changes in AC evolve from mild sterile inflammation to subserosal hemorrhage and GB wall swelling. Although no histologic characteristic distinguishes AAC from ACC, there are major differences in clinical characteristics and prognostic implications. The predisposing factors for ACC include gender (females), pregnancy, obesity, hemolytic process, and many others. Stone dislodgement occurs in about 70% of the cases with gradual resolution of the acute inflammatory reaction. About 30% of the patients showed no improvement without surgical intervention and could progress to complications.⁴ In 5%-10% of all the cases, ischemia and necrosis extend to include the entire thickness of the GB wall, creating a fertile ground for secondary bacterial infection that is found in 20%-75% of the bile from ACC LC specimens.⁸⁻¹⁰ The overall mortality rate of ACC is about 1%.¹¹ The incidence of ACC has declined following popularization of elective LC in chronically symptomatic patients with cholelithiasis, which prevents their progression to ACC.¹²

AAC is rare (5%-10%) among AC patients undergoing LC. It is reasonable to presume that most, if not all of the patients with AAC would progress if left untreated. Infection is thought to be a secondary event.⁹ It facilitates the development of gangrene, which can progress to abscess or empyema in AAC, as well as in ACC. The most serious complication of AC is when the pus traverses the GB wall and finds its way into the peritoneum or forms a fistulous tract that may lead into neighboring organs. All the complications are much more common in AAC compared with ACC.¹³ The

population at risk for AAC includes both extremes of age (especially older males), critically ill (burn, trauma, diabetic, and immunosuppressed patients), those on total parenteral nutrition, patients with vasculopathy, and women shortly after childbirth.¹³ Therefore, it is not surprising that mortality rates reported in AAC patients have been high, averaging about 30% with a range from 10% (when diagnosis is made early) to 90% (when diagnosis is delayed).¹³ Male patients comprise a higher proportion of the AAC population.¹³

The prevalence of cholelithiasis is approximately 10% among adults in the United States, most of whom are asymptomatic.¹⁴ Hence, a stone discovered on any imaging test is not a specific finding for any associated symptoms. Annual development of intermittent, biliary-type abdominal pain (colic) is 1%-4%.^{15,16} There is often a history of periodic episodes of colicky pain, usually lasting less than 6 hours. The clinical presentation of ACC is typically an attack of biliary colic that worsens with time. When symptoms and signs progress to generalized pain over the right upper quadrant, a palpable and painful GB that is commonly made worse with inspiration or cough to the point that it interrupts an inspiratory effort (clinical Murphy's sign), diagnosis of AC would be suspected. There is usually a low-grade fever, leukocytosis, mild hyperbilirubinemia, and a modest elevation of serum aminotransferases. However, it is widely recognized that none of these clinical manifestations, individually or in combination, provide sufficient diagnostic certainty for proceeding with management decisions.^{17,18} Diagnoses of AC that are based on clinical and laboratory findings result in 16%-20% error rates.^{19,20}

Acute phase LC is preferred over LC that follows a cooling-off period of 6-10 weeks because of reduction in morbidity, hospital stay, and time off work.^{21,22} The preponderance of evidence indicates that LC is the optimal treatment for AC and has a lower conversion rate to open LC when done within the first 2 days of clinical presentation, as compared with longer delays.²³ In most studies, the perioperative mortality of LC approaches 0%.²³ Therefore, clinicians have a 2-day window after initiation of symptoms to make the diagnosis of AC before referring these patients to surgery. Accepting that there is always a trade-off between sensitivity and specificity, the most sensitive AC imaging test that would offer the best chance for early detection may be preferred. However, it is also important to select an imaging test that can be performed in the shortest time, with the least expense and radiation exposure.

The most common AC complication is development of gangrene (20%-30% of AC cases), which can proceed to perforation in up to 10% of the patients.²⁴⁻²⁶ The clinical picture is indistinguishable from uncomplicated AC and the diagnosis of gangrene is seldom made preoperatively.²⁷ Preoperative identification of this complication is highly desirable as it changes the standard surgical management (open cholecystectomy would be preferred to LC). Making the clinical diagnosis of AAC is even more challenging than ACC because it occurs in a population of severely ill patients who have a complex clinical picture and greater comorbidity.

Physical examination of severely ill AAC patients is also problematic—many of them are on ventilators or under heavy sedation and unable to communicate complaints. The key to timely diagnosis of AAC is maintaining a high index of suspicion in these patients at high risk.

AC: HBS

The published clinical research on modalities, including the HBS, has been recently reviewed in this journal.⁵ The same article detailed approach to the description of findings and their interpretation. HBS is the second line test for AC and should be preceded by the abdominal ultrasound (AUS) examination.⁵ This review expands discussion on variety of approaches to HBS and clinical factors that influence the test sensitivity and specificity.

The diagnostic finding on HBS that signals AC is the inability of radiolabeled bile to enter the GB, which is described as GB nonvisualization (non-viz). In ACC this is due to the blocking stone, whereas in AAC it is due to maximally filled GB with viscous inflammatory fluid or frank pus. If the GB is visualized, the study is called negative for AC. In patients with poor or absent radiotracer excretion into the biliary tree, no comment about AC is possible (indeterminate). It is also indeterminate when biliary excretion is absent secondary to common bile duct (CBD) obstruction or severe nonobstructive (intrahepatic) cholestasis.^{28,29} AC diagnosis can be pursued by other means (CT or magnetic resonance imaging (MRI)) in these patients.

There are 2 main approaches used for AC evaluation—unaided HBS (UA-HBS) and morphine-augmented HBS (MA-HBS). The UA-HBS uses the advantage of time to allow the patent cystic duct to fill the GB with radioactive bile. MA-HBS uses the ability of morphine to more expeditiously force the radioactive bile through the patent cystic duct, as explained further in this article. The accuracy and utility of either HBS approach depends greatly on proper preparation.

Preparation for HBS

The patient should be fasting for 4 hours or longer to avoid inability of GB to fill with radioactive bile simply because it is contracted (stimulated).³⁰⁻³² One study showed GB non-viz on HBS in 53%-64% of the normal volunteers 1 hour after a meal vs 0% (all visualized the GB) after 4-6 hours of fasting.^{33,34} However, prolonged fasting (greater than 24 hours) may result in a GB that is maximally filled with bile, causing false-positive results in some studies.³⁵ The same mechanism is probably responsible for false-positive HBS cases in patients on total parenteral nutrition.³⁶ Patients with prolonged fasting should be pretreated with sincalide (synthetic cholecystikinin) that contracts and empties the GB. Visualization of the GB is optimized by timing the radioactive bile excretion to occur during GB relaxation and refilling (the “turkey baster phenomenon”).^{5,37} One study demonstrated that 50 minutes after 0.02 mcg/kg of sincalide administration,

GB refilling was observed in all normal adults.³⁸ Sincalide was infused over 3 minutes in that study, which we now recognize as too fast for consistent, optimal stimulation and emptying of the GB.³⁹ A reasonable modification would be to infuse 0.02 mcg/kg of sincalide over 15, 30, or 60 minutes (depending on logistics dictated by local and individual patient factors), realizing that longer infusion empties GB best with the least side effects.⁴⁰ The administration of the radiopharmaceutical and imaging can be started 30 minutes after sincalide infusion ends.⁵ However, Flancbaum et al. published evidence challenging false-positive results for MA-HBS in patients with prolonged fasting and total parenteral nutrition.^{41,42}

Ideally, patients should have had no narcotics prior to the study because those drugs have a profound influence on the biliary tract. They constrict the sphincter of Oddi, which raises the pressure in the biliary tract, driving the bile to the low-pressure reservoir—the GB. This is true in the presence of patent cystic duct and healthy GB that is at the time in the basal (nonstimulated) state. The healthy GB can continue receiving the incoming bile by dilating and concentrating (dehydrating) it. This mechanism allows the GB to accommodate excess bile in a totally obstructed system at the level of the CBD for 24-48 hours. At the point of saturation, the GB pressure equilibrates with the high pressure of the obstructed biliary tree and inflow of bile into the GB ceases. At this point the HBS can be false positive for AC even if the cystic duct is patent. But prior to this point, increased biliary pressure would only expedite radiolabeled bile appearance in the GB, which is the basis of MA-HBS. Therefore, if a patient receives narcotics for clinical indications, such as severe abdominal pain, it is reasonable to start HBS as long as the first dose was no longer than 24 hours ago. It would be reasonable to give additional morphine, as per standard MA-HBS protocol, if the most recent dose would not amount to the same effect in your best clinical estimation. In cases without AC (patent cystic duct) there would be rapid tracer appearance in the GB (Fig. 1). If a patient has been receiving narcotics for over 48 hours, it is reasonable to stop them for 4 half-lives of the drug and conduct MA-HBS after sincalide pretreatment. The 24-48 hours interval is a gray zone and should be handled by clinicians individually, depending on circumstances.

UA (Without Augmentation)-HBS

Duration of the early UA-HBS studies was for up to 1 hour.⁴³⁻⁴⁶ It became obvious early on that extending the imaging to 4 hours or longer improves specificity of the study by allowing GB viz in cases with chronic cholecystitis (CC).⁴⁷⁻⁵⁴ The range of sensitivity and specificity of this protocol for AC is 95%-97% and 93%-99%, respectively.⁵ It is the optimal approach when time allows or when administration of morphine or both is either undesirable or contraindicated. In patients with intercurrent illness and patent cystic duct, GB non-viz can persist for longer than 4 hours for a variety of reasons (CC, slow biliary flow, etc.), but could be visualized clearly on the 18-24 hours delayed image.^{55,56}

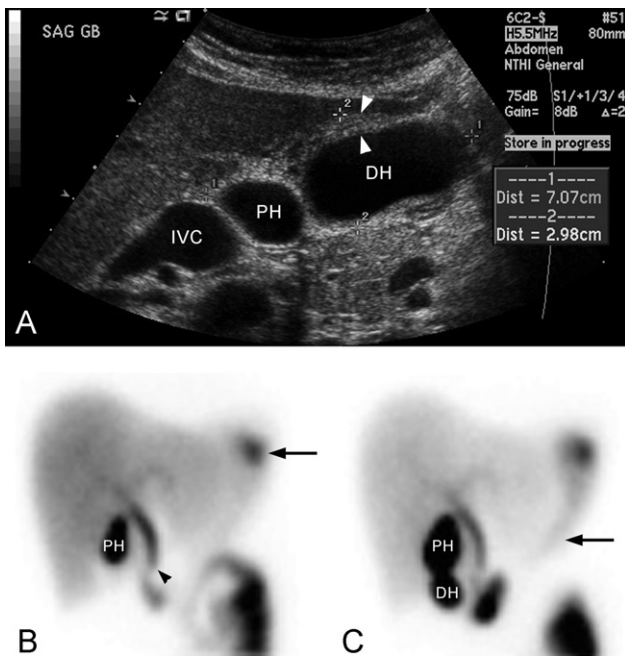


Figure 1 36-Year-old male developed severe right upper quadrant pain 2 days after hemorrhoidectomy. (A) Sagittal ultrasound section showed 7 cm long, “hourglass shaped” gallbladder (GB) with thickened wall (arrowheads) of distal half (DH) that measured 0.8 cm. Acute cholecystitis (AC) of distal half was suspected. The patient received a single 4 mg dose of morphine sulfate for pain 2 hours before hepatobiliary scan (HBS). His calculated morphine dose for the study was 2 mg and when the remaining drug from the prior injection was estimated to be equivalent or greater, the imaging was initiated. (B) Image taken between 20 and 24 minutes showed intense activity in the proximal half (PH) of the GB and in the common hepatic or bile duct to the duodenal junction (black arrowhead). There is also reflux of bile to the gastric fundus (arrow). (C) Image taken between 44 and 48 minutes showed activity progressing to the DH and AC was excluded. Significant activity was seen in the gastric body and fundus (arrow), which can be seen in bilious gastritis.

M-A HBS

MA-HBS shortens the study and improves its specificity. Choy et al. developed the method and tested it on a prospective cohort.⁵⁷ The morphine dose of 0.04 mg/kg was diluted in 10 mL of saline and given over 3 minutes to those with GB non-viz after 40 minutes of UA-HBS. They found GB visualization in 36% of those patients within 20 minutes after morphine. UA-HBS and MA-HBS had the same sensitivity of 96%, but MA-HBS outperformed UA-HBS (with 2.5 hours delay imaging) in specificity—100% vs 88.5%, respectively. Scintigraphy characteristically showed prominent CBD activity with slowed tracer passage into the duodenum, shortly after morphine infusion. Subsequent investigations have confirmed the diagnostic accuracy of MS-HBS, showing a pooled sensitivity of 96% and specificity of 89%.^{29,42,58-69} The only weakness of this approach is that diagnosis of CC cannot be made, as that would require 60 minutes of GB non-viz on UA-HBS (but eventual visualization after morphine).

There are 3 variations of MA-HBS technique based on the timing of morphine injection. The first, and the most time-consuming, variation begins with 1 hour UA-HBS. Those who demonstrate GB non-viz proceed to the second phase of imaging after morphine administration that would typically continue for 20-30 minutes,^{29,60-62,67,70,71} and in some other reports for up to 60 minutes.^{60,72} If activity appears in the GB after morphine, the diagnosis of CC can be confidently made. In cases of GB non-viz, the diagnosis is AC. The maximal imaging time is 80-120 minutes. The second variation suggested morphine administration at 40 minutes or as soon as activity is seen in the bowel during UA-HBS (first phase), which starts the morphine (second) phase that lasts from 30-40 minutes.^{57,61,64} The criterion for AC is GB non-viz after morphine injection. The maximal testing time is 60-90 minutes. The diagnosis of CC cannot be made, as already explained above. The third variation was introduced by Louridas et al. and totally omits the first phase.⁶⁰ It starts with sincalide pretreatment followed 10 minutes later by simultaneous injection of morphine and the radiotracer. The criterion for a positive study is GB non-viz at 60 minutes post-morphine injection. The whole study is done in 70 minutes or less. Because sincalide pretreatment does not improve the accuracy of MA-HBS,⁷²⁻⁷⁴ the test can be further shortened to 60 minutes by omitting it. Again, diagnosis of CC cannot be made. Although some may be concerned that morphine infusion could compound CBD obstruction,^{29,66} there is no evidence to support this concern and the experience of Louridas et al. supports the safety of morphine pretreatment.⁶⁰

There are 4 variations on morphine dosing. The original one was developed by Choy et al. and has been described already.⁵⁷ The second variation uses the same formula, but to the maximum dose limit of 2 mg.⁶² The third variation is a fixed dose of 2 mg,^{64,67} which defies the basic pharmacologic principals of adjusting a total dose to an individual's body mass. There is concern that the fixed dose of 2 mg may be ineffective in heavier patients, causing false-positive studies.^{75,76} Finally, Flancbaum et al. used 0.05-0.1 mg/kg of morphine, but offered no rationale for it or guidance on how to navigate this dose range.⁶³ At the present time, it makes the best pharmacologic sense to use the weight-adjusted 0.04 mg/kg dose of morphine.⁷⁷

Although true hypersensitivity to morphine is rare, it constitutes an absolute contraindication, if confirmed during patient interview.⁷⁸ It is important to realize that most patients with a history of “allergic reaction” to morphine are inappropriately labeled and actually experienced either a pseudoallergy (for which premedication with antihistamine would suffice) or simply had one of the mild, common morphine side effects, such as vomiting, agitation, or vision changes (in which case a single administration of a small morphine dose for HBS would be acceptable).^{79,80} Morphine is absolutely contraindicated in patients with respiratory depression or acute asthma, that is, status asthmaticus. Morphine is also contraindicated in patients with circulatory shock and in patients whose ability to maintain blood pressure has already been compromised by hypovolemia. Finally, morphine is

absolutely contraindicated in patients with paralytic ileus. Caution is advised in administering morphine for a long list of GI and other medical conditions (see the package insert), but one 0.04 mg/kg dose of morphine can be safely administered as it would be highly unlikely to compound any of them.

False-Positive and False-Negative Tests

Most false-positive results for AC are secondary to CC.^{31,46,48,52,81} Freitas and Gulati make a sound argument that CC patients should undergo LC anyway and differentiation from AC may be a moot point.⁴⁶ Rare cases with potential for false-positive interpretations include surgical or congenital GB absence,^{82,83} choledochal cysts,⁸⁴ cystic fibrosis,⁸⁵ inflammation within the immediate proximity of the GB fossa,^{86,87} rupture of a hydatid cyst into biliary tree,⁸⁸ unusually elongated GB that is mistaken for the bowel,⁸⁹ primary or secondary GB neoplasms,⁹⁰⁻⁹² severe intercurrent illness,^{62,93} ceftriaxone therapy,⁹⁴ and sphincterotomy.⁹⁵⁻⁹⁸ False-positive results can be avoided by correlating with other available anatomical imaging tests and thorough clinical history. Pancreatitis may predispose to a false-positive HBS,^{99,100} but there is also evidence to the contrary,¹⁰⁰ which leaves this question unresolved.

A false-negative test can occur in situations where the interpreter mistakes another structure for a GB. An example is a dilated cystic duct leading to the obstruction point, especially if the obstruction occurs in a portion more proximal to the GB body (such as Hartmann's pouch). This results in a tracer filling of a cystic duct segment that can create a false appearance of a small GB ("cystic duct sign").^{101,102} When a small focus of activity is seen in the GB fossa on HBS, correlation with anatomical imaging can prevent such misinterpretation. If prior anatomical imaging is unavailable, single photon emission computed tomography/computed tomography (SPECT/CT) may be helpful. Another example of mistaken identity is when activity in the duodenum or a duodenal diverticulum mimics the GB.¹⁰³⁻¹⁰⁵ Enterogastric reflux can also sometimes be mistaken for a GB.¹⁰⁶ The right lateral and left anterior oblique views should clarify most cases, but SPECT/CT should be employed if any doubt persists. An intense "rim sign" can also be mistaken for a GB.¹⁰⁷ This error occurs when prominent activity associated with a right biliary radical is mistaken for the "rim sign." This mistake can be prevented by an awareness of the distinguishing temporal changes of activity—a "rim sign" is rarely seen on the immediate image and develops within 20-40 minutes postinjection, growing in intensity progressively as compared with the washing out of activity from general liver parenchyma. The biliary radicals have growing activity starting in the first 10-15 minutes, but subsequently diminish as the bile drains from the liver over time. The pattern of increased pericholecystic hepatic uptake—the "rim sign" (Fig. 2)—is important to recognize because it signals gangrenous cholecystitis.¹⁰⁸ The open cholecystectomy is favored in these patients over routine LC.¹⁰⁹ There is increased frequency of adhesions between the GB and liver in those with the "rim sign," which could complicate laparoscopic surgery.¹¹⁰

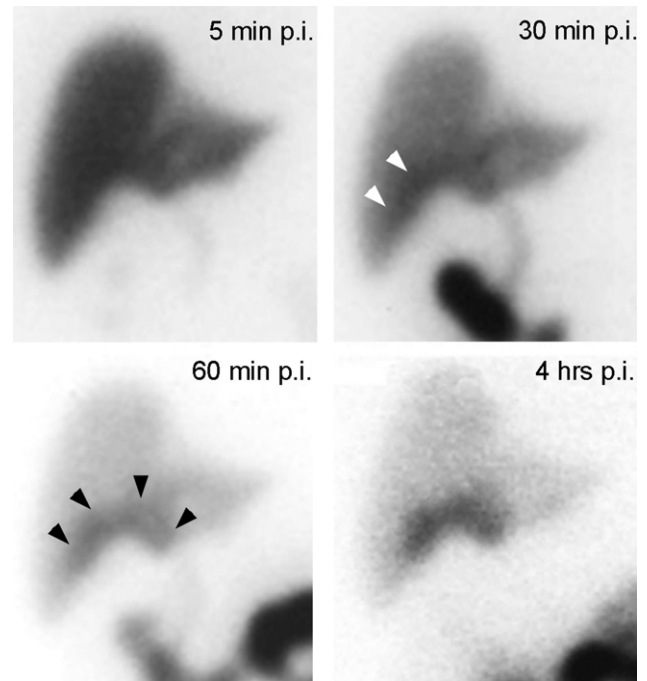


Figure 2 Patient referred for evaluation of acute cholecystitis showed excellent and homogeneous hepatobiliary extraction 5 minutes postinjection (p.i.) of disofenin. On 30 minutes p.i. images there is a subtle curvilinear band of retained activity around the gallbladder (GB) fossa (arrowheads) while the tracer has begun to clear from the rest of the liver parenchyma. On the 60 minutes p.i. image, the band was much more clearly appreciated (arrowheads), reaching an even higher contrast on the 4 hours p.i. image. The pattern of evolution was typical of the "rim sign," which is rather obvious. Most "rim signs" in practice are subtler.

Circumstances responsible for re-establishing cystic duct flow to the GB affected by AC form another group of false-negative HBS. This can occur when the obstructing gallstone is dislodged or passed into the bowel. It also happens when the GB involved in AC gets decompressed. The latter can be seen in patients treated with cholecystostomy, which usually converts GB non-viz to visualized GB on HBS within a few days postprocedure.¹¹¹ A similar mechanism probably explains cases of GB perforation^{112,113} and formation of GB to bowel fistula where abnormal passage of bile can be visualized because the flow through cystic duct resumes.¹¹⁴

AAC warrants particular consideration as a cause of a false-negative test, as pointed out in the early experience with UA-HBS.¹¹⁵ Two prospective studies with MA-HBS confirmed the same, which resulted in lower sensitivities of 67% and 70%^{71,116}; however, the specificity was 100% in both studies. The authors suggested that compared with ACC the cystic duct might be less frequently obstructed in AAC. The low sensitivity of MA-HBS in AAC should be viewed in the context of other diagnostic options, such as AUS, which had a sensitivity of 36%-50% and a specificity of 89%-94% in AAC.^{71,116} Multiple retrospective studies have used UA-HBS and MA-HBS in AAC.^{41,117-122} The preponderance of opinion supports the use of MA-HBS in AAC.

AC: Other Diagnostic Modalities

Nuclear Medicine Approaches

Inflammation imaging with labeled white blood cells can be useful in AAC where HBS has lower sensitivity.¹²³⁻¹²⁵ The long delay between injection and imaging (typically 24 hours for In-111 labeled white blood cells) is problematic given the urgency of AAC diagnosis.⁷¹Tc-99m-labeled white cell imaging is faster¹²⁶ and demonstrated promising sensitivity and specificity for AC—94% and 100%, respectively.¹²⁷ Imaging inflammation directly in ACC and particularly in AAC may be revisited when faster in vivo radiolabeling of leukocytes becomes available. There are few reports of increased GB uptake on F-18 FDG-PET/CT in cases with AC,¹²⁸⁻¹³⁰ but this approach lacks substantive literature evidence.

Non-Isotopic Approaches

AUS is the initial imaging test of choice for patients with suspected AC because of lack of radiation exposure, ability to perform the test at the bedside, expedience, and lower cost. It allows exquisite anatomical evaluation of the GB, and is capable of evaluating other abdominal organs that may be responsible for patients' pain. AUS alone is sufficient for the diagnosis of AC in 80% of the patients, leaving about 20% for HBS and other diagnostic tests to clarify.¹³¹ The positive predictive value of demonstrating stones and a positive sonographic Murphy sign (pain elicited by pressing on the GB with transducer) was 92%, and that of stones and thickening of the GB wall was 95%.¹³¹ The negative predictive value of the absence of stones combined with either a normal GB wall thickness or a negative sonographic Murphy sign was 95%. Striated GB wall edema is a rare finding, but is highly specific of gangrenous AC.^{132,133} Finding gas in the GB lumen or the wall signals emphysematous AC, which constitutes a surgical emergency.¹³⁴

MRI and magnetic resonance cholangiopancreatography can demonstrate gallstones,¹³⁵ but demonstration of cystic duct patency is very difficult. Given no radiation exposure, the technique is particularly well suited for the evaluation of acute right upper abdominal pain in a pregnant patient.¹³⁶ In general, the technique is most helpful in evaluation of CBD for stones where sensitivity and specificity exceed 90%.¹³⁷⁻¹⁴⁰ Cystic duct and common duct stones may be more easily detected with MRI as compared with ultrasound.^{141,142} The GB wall and adjacent region pericholecystic fluid and tissue irregularities are well seen with MRI.^{27,143-147} Contrast agent administration can be helpful in demonstrating pericholecystic enhancement that may be seen with complicated AC,¹⁴⁸ which is similar to the "rim sign" on HBS.

CT is commonly employed in hospitalized and emergency room patients that can show AC related findings and its complications. All of the clinical investigations are retrospective with a reported negative predictive value for AC of approximately 89%.¹⁴⁹ CT can visualize only 65%-75% of gallstones and has no advantages for primary diagnosis. CT evidence of perfusion defects in the GB wall (discontinuity or decreased enhancement of the GB wall) is highly specific for

gangrene,¹⁵⁰ whereas transmural defects suggest perforation.¹⁵¹ The combination of CT findings that include perfusion defects or pericholecystic stranding or lack of gallstones is 94% sensitive and 75% specific in predicting GB gangrene, which may be CT's key advantage over other modalities.

Conclusion

HBS is excellent for the diagnosis of AC, but the above-discussed advantages of AUS make it the most appropriate first tier test for these patients. HBS remains an excellent second tier test in the work-up of indeterminate cases by AUS, as initially suggested in the algorithm proposed by Ralls et al.¹³¹ In a pregnant patient, HBS should be substituted in this algorithm with abdominal MRI/magnetic resonance cholangiopancreatography.¹³⁶

Acute GI Bleeding: Pathophysiology and Clinical Presentation

Acute GI bleeding is a common emergency that occurs with an age-dependent incidence and results in an annual hospitalization rate of approximately 25 per 100,000 in the United States.¹⁵² The clinical presentation of acute GI bleeding is quite variable with the majority of patients, approximately 85%, recovering spontaneously without any further specific intervention. However, it is essential to identify the condition in the remaining 15% where it can be quite devastating and life threatening. In particular, GI bleeding is a major cause of morbidity, especially in the elderly and those with associated comorbidities. In hospitalized patients, the published mortality rate of acute GI bleeding is as high as 10%-14%.¹⁵²⁻¹⁵⁴

Clinical manifestations of acute GI bleeding are often unreliable in identifying the ultimate source of GI bleeding. History and physical examination findings only achieve a correct final diagnosis in less than 40% of the patients.¹⁵⁵ Because of transient pooling and retrograde peristalsis that may occur in the bowel after GI bleeding, clinically evident GI bleeding lacks the temporal resolution needed for accurate diagnosis and treatment. Furthermore, the clinical evidence of GI bleeding often does not coincide with active GI bleeding.

Acute GI bleeding is typically classified according to its site of origin as either upper GI bleeding, arising from a source proximal to the ligament of Treitz, or lower GI bleeding, arising from a source distal to the ligament of Treitz. GI bleeding may also be classified as obscure or occult if not otherwise categorized.

Causes for upper GI bleeding include esophageal varices, vascular malformations, esophagitis, Mallory-Weiss tear, gastritis, gastric and duodenal ulcers, and neoplasm. Causes for acute lower GI bleeding (ALGIB) include vascular malformations such as angiodysplasia, diverticula, adenomatous polyps and neoplasms, inflammation, and, in children, Meckel's diverticulum.

Esophagogastroduodenoscopy (EGD) is the method of choice for evaluating the upper GI tract for bleeding with an accuracy of greater than 90%. Colonoscopy of the lower GI tract only has an accuracy of about 70% in confirming or excluding a site of GI hemorrhage. Endoscopy and arteriography may be used to localize and control a lower GI bleeding site but often fail due to intermittent bleeding.¹⁵⁶ Although it has no therapeutic role, scintigraphy plays a complementary role to arteriography and endoscopy in the evaluation of lower GI bleeding.

Acute GI Bleeding: GI Bleeding Scintigraphy

Nuclear medicine techniques with varying sensitivities for the detection of acute GI bleeding have been well described in the literature,¹⁵⁷⁻¹⁶¹ and their role in GI bleeding has been comprehensively reviewed by others in this journal^{160,162} This section focuses on the preparation, interpretation, nuances, and potential pitfalls aimed at further enhancing the clinical utility of nuclear medicine evaluation of acute GI bleeding. Additionally, the novel application of hybrid SPECT/CT imaging technology to the clinical problem of acute GI bleeding has been discussed.

Radiopharmaceuticals for GI Bleeding Scintigraphy

Historically, the 2 primary radiopharmaceuticals that have been employed for evaluation of ALGIB are ^{99m}Tc-sulfur colloid (^{99m}Tc SC) and ^{99m}Tc red blood cells (^{99m}Tc RBCs). Alavi introduced ^{99m}Tc-99m SC, an agent rapidly cleared from the vascular compartment, to investigate acute GI bleeding. In a canine experimental model, bleeding rates as low as 0.05-0.1 mL/min were detected with ^{99m}Tc-99m SC.¹⁶³ Because of the rapid extraction by the reticuloendothelial elements within the liver, spleen, and bone marrow, sulfur colloid offers a high target to background ratio between a bleeding site and the surrounding soft tissues resulting in a theoretical increase in sensitivity. The sulfur colloid technique continues to have its proponents today.¹⁶⁴ Advantages of Tc-99m SC for acute GI bleeding scintigraphy are the rapid uptake of the compound by the reticuloendothelial system with rapid blood pool clearance, which facilitates the detection of very small amounts of extravasation at a bleeding site. Disadvantages of sulfur colloid include uptake within the liver and spleen that obscures bleeding sites in the hepatic and splenic flexures of the colon, limiting visualization in the upper abdomen. Another significant limitation of this technique is rapid clearance of this tracer from the vascular compartment—less than 10% of the tracer remains in the vascular compartment at 7 minutes.¹⁶⁵ This is a significant limitation in the dynamic evaluation of intermittent acute GI bleeding.

Bunker et al. compared the performance of ^{99m}Tc SC and in-vitro labeled ^{99m}Tc RBCs with regard to their relative

sensitivities for the detection and accuracy in localizing of acute GI bleeding. In a prospective multicenter study of 100 patients, both agents were evaluated under identical clinical conditions with superior performance by the labeled RBCs. Bleeding sites were identified in 38 patients with labeled RBCs compared with detection of only 5 bleeding sites with sulfur colloid. Labeled RBCs were diagnostically superior in all cases with a sensitivity of 95%, a specificity of 93%, and an overall accuracy of 94%. The performance of ^{99m}Tc SC was inferior to labeled RBCs with a sensitivity of 12%, a specificity of 100%, and an overall accuracy of 62%.¹⁶⁶

The lowest detectable bleeding rate for ^{99m}Tc RBCs is 0.04 mL/min in an anesthetized animal model¹⁶⁷ and is 0.1 mL/min in a clinical study.¹⁶⁸ The SNM procedure guideline for GI bleeding indicates that labeled RBCs can detect bleeding at rates as low as 0.1-0.35 mL/min.¹⁵⁹ Although the subject of a vigorous and interesting debate during the development of GI bleeding scintigraphic techniques, the preferred radiopharmaceutical for GI bleeding scans is *in vitro* labeled RBCs. Labeled RBCs remain intravascular for hours providing the ability to image dynamically for up to 90 minutes and then reimage out to 24 hours after administration. This is significant because of the intermittent nature of most acute GI bleeding that is evaluated in the nuclear medicine department.¹⁵⁶

Preparation for GI Bleeding Scintigraphy

Patients who present with acute GI bleeding should undergo initial triage and resuscitation, a complete history and physical examination, appropriate laboratory testing, and nasogastric lavage. The nasogastric lavage results are used to stratify the bleeding into either a suspected upper or lower GI source. If an upper GI source is suspected, then EGD is performed and therapy is initiated based on positive EGD results. If a lower GI bleeding source is suspected or if an upper GI source has been excluded, then erythrocyte scintigraphy should be performed as the next step in the evaluation.¹⁶⁹

Prior to a patient's arrival in the nuclear medicine laboratory for erythrocyte scintigraphy, it is essential for the referring physician to have a follow-up management plan in place and be prepared for implementation. Because of its intermittent nature, the majority of GI bleeding that is referred to nuclear medicine for evaluation ceases spontaneously.¹⁵⁶ Temporal delays caused by a lack of prior communication between clinical services may contribute to discordance between a positive RBC bleeding scan and a subsequent negative arteriogram. Pretest involvement of respective services is critical for successful bleeding site confirmation and therapy by interventional radiology or surgery or both.

Interpretation Criteria for GI Bleeding Scintigraphy

Requisite interpretation criteria for a positive GI bleeding study include: (1) extravasation of radiotracer from the

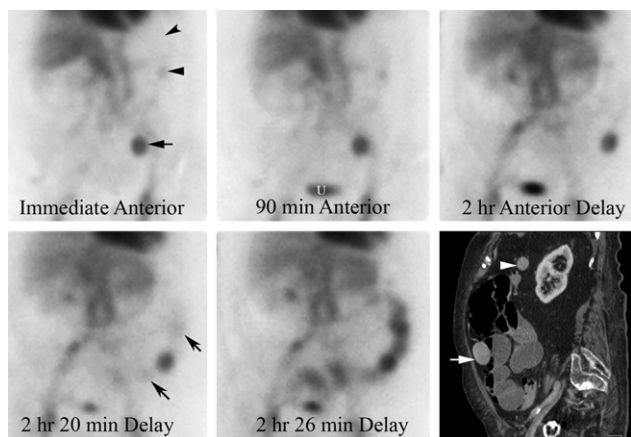


Figure 3 91-Year-old female presented with bright red blood per rectum to the hospital. The immediate image of the bleeding scan showed moderately intense focal tracer activity in the left lower abdominal quadrant (black arrow). There was another subtle round focus of activity in the left superior abdomen (straight-base arrowhead). Splenic activity was absent (concave-base arrowhead). The same image at 90 minutes after tracer injection showed the unchanged findings and tracer excretion in the urinary bladder (B). There was no active bleeding during the 90 minutes of imaging because the focal activity has not changed shape, intensity, or configuration. CT of the abdomen (shown in sagittal plane) demonstrated findings of splenectomy (not shown) and 2 splenules that corresponded to the 2 focal findings on the bleeding scan with the lower one (white arrow) more anterior and larger than the upper (white arrowhead), which explains its greater intensity on the bleeding scan.

vascular compartment and (2) movement of the extravasated blood which act as a cathartic within an identifiable bowel segment, either an antegrade or retrograde direction. Once a GI bleeding site is identified on scintigraphy, it is essential to continue the examination for sufficient time to definitively identify the bleeding bowel segment. Large bowel bleeding typically drapes around the periphery of the abdomen and has an elongated trajectory (Fig. 3). Whereas, small bowel activity is centrally located in the abdomen, propagates in curvilinear loops, and may lessen in intensity over time as the radiotracer becomes diluted in the fluid containing small bowel (Fig. 4).

Several studies have demonstrated that computerized cinematic acquisition and cinematic display of scintigraphic images results in improved detection and localization for acute GI bleeding.¹⁷⁰ O'Neill et al. demonstrated cinematic erythrocyte scintigraphy to be a sensitive and noninvasive alternative to mesenteric angiography that was accurate enough to direct selective surgical intervention.¹⁶⁹

False-Positive Tests and Pitfalls

Static areas of extravascular radiotracer accumulation on RBC bleeding scans rarely represent acute GI hemorrhage but are more commonly due to aneurysms, varices, inflammation, or

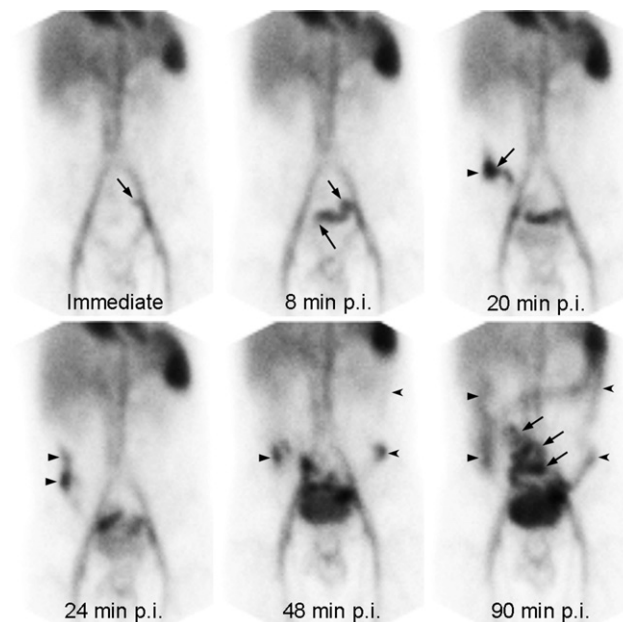


Figure 4 Red blood cell (RBC) bleeding scan showed curvilinear area of increased activity over the left common iliac vessel. Eight minutes later the focus extended to the right in a loopy shape across the middle of the pelvis. By 20 minutes, the activity reached (arrow) and accumulated in a larger bulbous structure in the right pelvis (arrowhead), which is typical of the cecum. On the 24-minute image, it extended cranially in a linear fashion (arrowheads), typical of large bowel pattern, consistent with ascending colon. At 48 minutes, some of the right colon activity briskly moved antegrade to the left colon (arrowheads with concave base). By 90 minutes the small bowel activity in the mid-lower pelvis appears in typical loopy pattern (arrows). Activity moved antegrade to visualize the right (arrowheads with straight base) and left (arrowheads with concave base) colon that is connected by a slightly redundant transverse colon. The source of bleeding was correctly diagnosed in the distal ileum and angiography identified bleeding vessel branch of ileocolic artery that was successfully embolized.

tumors. Heyman et al. reported a patient who, on sulfur colloid abdominal scan performed to evaluate abdominal bleeding, had a focal abnormality in the upper abdomen that was interpreted as consistent with a small bowel bleeding source; however, an accessory spleen was discovered to be the source of uptake at surgery.¹⁷¹ Others have detected an unsuspected splenic rupture with ongoing intraperitoneal hemorrhage on erythrocyte scintigraphy performed on a patient with suspected GI bleeding.¹⁷² A splenule can appear as a fixed focus of RBC accumulation on erythrocyte scintigraphy (Fig. 3) and cause a false-positive interpretation. Other sources of false-positive results include use of cathartics, bowel irritation or inflammation, or a recent endoscopy procedure. Fundamental to avoiding misinterpretation is investigating nonbleeding causes (by correlation with CT or performing SPECT/CT) when there is lack of movement on dynamic images (Fig. 3).

False-positive interpretations on erythrocyte scintigraphy may also result from misinterpretation of excreted free pertechnetate that accumulates within the renal upper tracts.

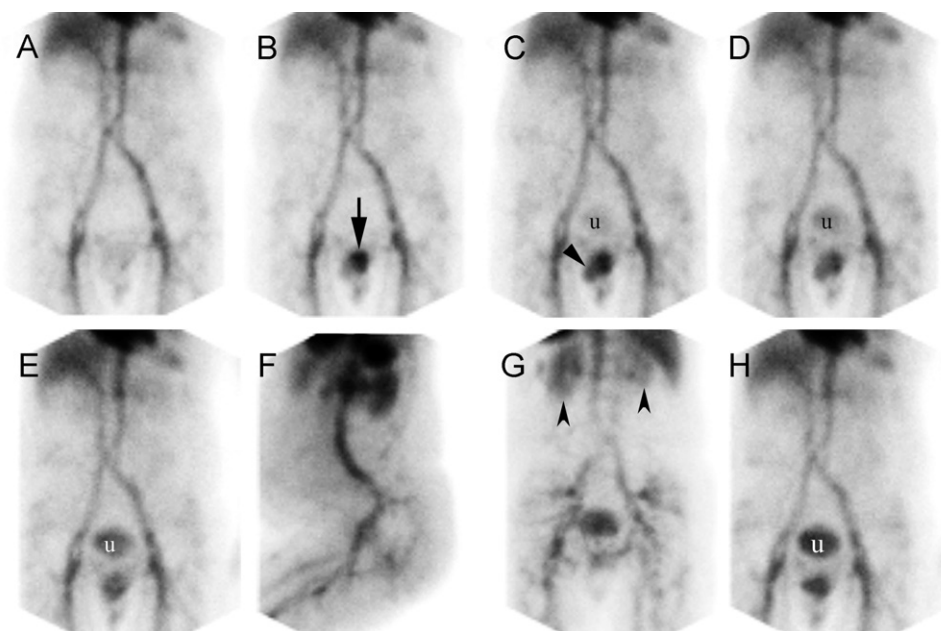


Figure 5 A young male patient with rectal bleeding was studied. (A) There is physiological activity on the immediate red blood cell (RBC) bleeding scan. (B) At 16 minutes postinjection (p.i.) there is intense rounded uptake in the lower midpelvis (arrow) that can represent either the penis base or rectal bleeding. (C) It changed to elongated structure (arrowhead) with intense activity by 24 minutes. There is expected subtle accumulation in the urinary bladder (u). (D) It decreased in intensity by 40 minutes. (E) At 90 minutes p.i., it was rounded and low in intensity. (F) Left lateral image at that time was not helpful to differentiate penile from rectal activity. (G) Posterior image showed intense uptake in the kidneys that were poorly seen on anterior images, but no rectal activity to suggest bleeding. Penile activity was suspected with changing intensity due to intermittent erection. (H) Patient was asked to position the penis pointing horizontally to the right and the anterior image was repeated, confirming that it was the source of the finding, and active rectal bleeding was excluded.

The most common false positive results from mistaking penile activity for rectal bleeding (Fig. 5). Obtaining various spot pelvic views and positional manipulations are simple yet effective methods to facilitate accurate diagnosis (Fig. 5). Those views can also occasionally disclose a rectal bleed that is being obscured by the bladder.

Application of New Technology to Acute GI Bleeding: SPECT/CT

It is intuitive that the advent of hybrid SPECT/CT fusion imaging provides an opportunity to increase the sensitivity and accuracy of erythrocyte scintigraphy for the detection and localization of GI bleeding. SPECT is well known to increase contrast resolution over conventional planar imaging by as much as 10%-15%, augmenting the ability to detect low-volume sites of GI bleeding. Investigators have found that hybrid SPECT/CT functional anatomical imaging provides a high degree of specific anatomic information when planar scintigraphy is positive for GI bleeding.¹⁷³ The supplemental anatomical information obtained by SPECT/CT can precisely localize a source of abdominal bleeding. SPECT/CT helps to avoid the common pitfalls seen in erythrocyte scintigraphy (Fig. 6).

Yama et al. reported the first case of localization of small intestinal bleeding using the fusion of separate erythrocyte

scintigraphy SPECT images and X-ray CT images.¹⁷⁴ In a study of 81 consecutive patients with various clinical conditions and radiopharmaceuticals, Schiilli and colleagues found that functional anatomical mapping with SPECT/CT allowed a more precise interpretation compared with SPECT and that fused SPECT/CT images improved the diagnostic accuracy of SPECT imaging in several clinical situations; this included 2 patients in this series with GI bleeding.¹⁷³ In a subsequent prospective investigation, Schillaci and colleagues demonstrated the feasibility and accuracy of SPECT/CT imaging in acute lower GI erythrocyte scintigraphy.¹⁷⁵ In this study, erythrocyte scintigraphy with SPECT/CT had a significant positive impact on 7 of 19 patients (36.8%) by precisely localizing the site of hemorrhage in 6 patients whose bleeding sites could not be identified on conventional planar erythrocyte scintigraphy. In 1 patient from this series, a site of suspected active bleeding identified on planar imaging was successfully excluded. Overall, this study showed erythrocyte scintigraphy with SPECT/CT to be a feasible, more precise, and accurate method of diagnosing ALGIB compared with planar erythrocyte scintigraphy. Furthermore, SPECT/CT augmented erythrocyte scintigraphy in this series provided supplemental anatomical information that was useful in subsequent patient treatment. Turgeon et al. also have reported the use SPECT/CT to successfully identify the cause of abdominal pain and obscure overt GI bleeding in a patient with a Meckel's diverticulum.¹⁷⁶

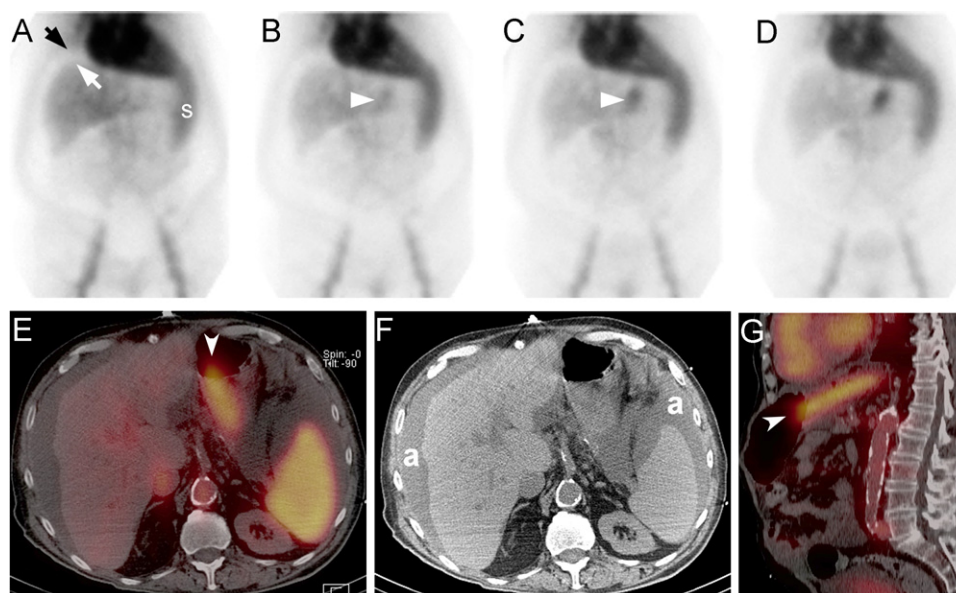


Figure 6 A patient with liver cirrhosis developed melena. Nasogastric tube aspirate was negative. (A) The red blood cell (RBC) bleeding scan immediately postinjection (p.i.) showed photopenic rim from the right heart border where it is clearly seen between the liver edge (white arrow) and warm activity along the parietal peritoneum (black arrow). This photopenic rim descends to the pelvis and from there it ascends along the left paracolic gutter to the splenic(s) border. This is typical appearance of peritoneal effusion. (B) At 24 minutes p.i. there is subtle new activity along the left medial liver edge (white arrowhead). (C) It becomes clearly defined at 54 minutes p.i., but without significant progression. (D) On 90 minutes p.i. image, the same finding is even more distinct, but stable in configuration. Differential diagnosis included gastric fundus hyperemia vs slow bleeding. (E) SPECT/CT fusion image showed the activity in the gastric fundus lumen with some exiting into the gas-distended, more distal portion (arrowhead with concave base), favoring slow bleeding. (F) CT showed ascites (A) in the same areas as on the immediate RBC bleeding scan. The liver edges are nodular, consistent with cirrhosis. (G) Sagittal SPECT/CT confirms activity in the fundus lumen that extends into the gas-filled part of the gastric body (arrowhead with concave base). Endoscopy discovered a blood-oozing polyp that was removed and showed benign features.

Conclusion

Erythrocyte scintigraphy has an important role in the evaluation and management of patients with acute lower GI hemorrhage. It helps to localize sites of active GI bleeding and stratify those patients who would benefit from aggressive treatment (surgery or arteriography) vs those who can be managed medically. Pretest involvement of respective services is critical for successful bleeding site confirmation and therapy by interventional radiology or surgery, or both. Erythrocyte scintigraphy with SPECT/CT has superior accuracy and precision over planar erythrocyte scintigraphy in the diagnosis of acute GI bleeding. Additionally, erythrocyte scintigraphy with SPECT/CT can provide useful supplemental anatomical information that benefits patient management.

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