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MEDICINE

Pediatric Gastrointestinal Nuclear Medicine

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General localization of gastrointestinal bleeding through the use of labeled red blood cells may be performed in children, or ^{99m}Tc-pertechnetate may be used if a Meckel's diverticulum is suspected. As in adults, cholecystitis and biliary leak may be assessed in children via ^{99m}Tc-IDA derivatives. Gastroesophageal reflux can be evaluated by oral consumption of the child's usual diet labeled with ^{99m}Tc sulfur colloid. For the scintigraphic determination of pulmonary aspiration, a relatively high concentration of tracer within a drop of liquid is placed beneath the child's tongue followed by dynamic imaging of the respiratory tract. Colonic transit scintigraphy can aid in the identification and therapeutic decision-making in patients with functional fecal retention, the most common cause of chronic constipation in children. ^{18}F-DOPA positron emission tomography is useful for classifying pancreatic involvement in infantile hyperinsulinism as focal or diffuse, thereby differentiating between patients who should receive curative focal pancreatic resection versus those who should receive medical management. Assessment of protein-losing enteropathy can be conducted scintigraphically and, compared with fecal alpha-1 antitrypsin collection, the scintigraphic method can detect esophageal and gastric protein loss. Also, scintigraphic quantification of protein loss can be performed without the requirement for fecal collection. Intestinal inflammation in children with inflammatory bowel disease can be evaluated using ^{99m}Tc white blood cells. The scintigraphic method is safe, accurate, well-tolerated by children and complementary to endoscopy in most patients.
Semin Nucl Med 37:269-285

This review describes both established examinations in pediatric gastrointestinal nuclear medicine as well as scintigraphic pediatric procedures that are either new or are less commonly used. The article covers facets of gastrointestinal (GI) bleeding, hepatobiliary scintigraphy, and splenic scintigraphy. Pediatric gastrointestinal transit is reviewed, including discussions of the scintigraphic assessment of gastroesophageal reflux, esophageal transit, gastric emptying, pulmonary aspiration, and colonic transit in children. An emphasis is placed on the use of labeled white blood cells for the detection and assessment of inflammatory bowel disease (IBD) in children. Methodology for acquiring ^{99m}Tc-labeled white blood cells images in IBD is described as well as advantages and disadvantages of the procedure compared with other diagnostic modalities. ^{18}FDOPA positron emission tomography (PET) in the assessment of patients with congenital hyperinsulinism of infancy is discussed. Scintigraphy in the assessment of protein losing enteropathy is also reviewed.

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Meckel's Scan

Pediatric patients presenting with GI bleeding may be suspected of having a Meckel's diverticulum as the underlying cause. A Meckel's diverticulum is an outgrowth on the antimesenteric side of the ileum and represents incomplete closure of the omphalomesenteric duct. It is usually located approximately 100 cm proximal to the ileocecal valve, occurs in 1% to 3% of the population, and is 3 times more common in male patients. The most common complication is intermittent and painless bleeding per rectum, which may occur at any age but is more likely to occur in childhood, often when the child is younger than 2 years of age. The cause of bleeding is mucosal ulceration of the Meckel's diverticulum or adjacent ileum as ectopic gastric mucosa within the Meckel's diverticulum produces hydrochloric acid. Approximately 60% of cases of symptomatic Meckel's diverticula contain ectopic gastric mucosa. Other potential complications of Meckel's diverticula are partial or complete small bowel obstruction and Meckel's diverticulitis (which tends to mimic appendicitis). Symptomatic Meckel's diverticula should be surgically resected.

^{99m}Tc pertechnetate localizes to gastric mucosa as well as to ectopic gastric mucosa in the intestinal tract. A dose of 3.7 MBq/kg of body weight is given intravenously, with minimal and maximal doses of 7.5 MBq and 370 MBq, respectively. A

0001-2998/07/$-see front matter
doi:10.1053/j.semnuclmed.2007.02.005

positive study demonstrates near-simultaneous visualization of gastric uptake and a focus of ectopic gastric mucosa during the study, usually by 30 minutes after tracer injection. The activity within both ectopic gastric mucosa and stomach should concurrently intensify over time. The sensitivity and specificity of scintigraphic detection of a Meckel's diverticular bleeding site are approximately 85% and 95%, respectively.[1] Both ectopic gastric mucosa and gastric duplication typically demonstrate simultaneous visualization with the stomach, whereas, intestinal duplications can be visualized dynamically before the stomach is seen. Intrathoracic foregut duplication cysts with functioning gastric mucosa may be visualized on delayed images (up to 24 hours) after gastric uptake occurs. Initially, a photopenic area in the thorax corresponding to the duplication cyst may be visualized.[2]

Certain pharmacologic maneuvers have been reported to improve the detection of Meckel's diverticulum. Pentagastrin (6 mg/kg) given subcutaneously just before imaging can increase acid production and tracer uptake. Cimetidine (20 mg/d) may be given orally for 2 days before imaging. It inhibits intraluminal secretion of tracer but does not block uptake. Glucagon (50 mg/kg IV) given 10 minutes after the ^{99m}Tc pertechnetate administration has an antiperistaltic effect on the smooth muscles of the gastrointestinal tract.[1]

GI Bleeding

^{99m}Tc red blood cell (RBC) scintigraphy generally is useful for assessing GI bleeding in patients. Meckle's diverticula also may be identified through this technique, although other causes of bleeding may include intussusception, IBD, Henoch-Schonlein purpura, gastritis, duodenitis, Mallory-Weiss tear, infectious enterocolitis, allergic enterocolitis, midgut volvulus, polyps, tumors, vascular malformations, enteric duplication cysts, nodular lymphoid hyperplasia, hemolytic uremic syndrome, and foreign body and trauma.[3] The main advantage of using ^{99m}Tc-RBCs is that doing so permits visualization of GI bleeding over the course of several hours. Bleeding rates as low as 0.1 mL/min to 0.4 mL/min may be detected. Large bowel endoscopy of actively bleeding patients has a low diagnostic yield, is potentially harmful to the patient, and the small bowel is not successfully visualized endoscopically. Angiography typically localizes bleeding when the rate is greater than 1 mL/min. However, for bleeding to be identified, it should occur during the 20- to 30-s time interval during which contrast is administered. Scintigraphy permits visualization of the entire GI tract.

Labeling of RBCs is most efficient by the in vitro method (98%) as compared with the in vivo (70%) and modified in vivo (90-95%) methods. The disadvantage of lower labeling efficiencies is the possibility of secretion of free pertechnetate within gastric mucosa into the duodenum and also excretion of free pertechnetate into the urinary collecting system increasing the likelihood of false positive studies.

Positive studies demonstrate tracer activity outside of normal vascular structures with antegrade or retrograde motion of tracer through bowel. The motion is best detected on cinematic display and may occur very rapidly. Small bowel bleeding may be distinguished from a colonic source by the demonstration of rapid distal progression through a series of multiple small, centrally located, curvilinear segments on cinematic display of the abdomen. Large bowel bleeding has a more elongated pattern with peripheral location within the abdomen compared with bleeding within small bowel. Stationary activity is more likely to represent a vascular abnormality, urinary or penile activity. In rare cases, a stationary site may represent adherent blood clot to the bowel wall.

^{99m}Tc sulfur colloid also has been used in the assessment of GI bleeding. It has the advantage of detecting rates as low as 0.05 to 0.1 mL/min through achievement of a high bleeding to background ratio. Its disadvantages include a short duration of imaging time to localize bleeding of approximately 20 min and limited interpretation of potential bleeding sites in proximity to the liver and spleen as the liver and spleen accumulate ^{99m}Tc sulfur colloid during the test.

The utility of ^{99m}Tc RBC scintigraphy is its ability to localize the site of GI bleeding before angiography and its ability to detect intermittent bleeding. Angiography is approximately 10-fold less sensitive for the detection of GI bleeding than scintigraphy. Both ^{99m}Tc RBC scintigraphy and ^{99m}Tc sulfur colloid scintigraphy detect sources of venous and arterial GI bleeding, whereas contrast angiography only detects arterial sources. ^{99m}Tc RBC scintigraphy for GI bleeding has prognostic value and is predictive of transfusion requirements and the need for angiography and surgery.[1,4-7]

Hepatobiliary Scintigraphy

Biliary Atresia Versus Hepatitis

Biliary atresia and hepatitis in the neonate have similar clinical features. Biliary atresia has a slight female preponderance and occurs in approximately 1 in 10,000 live births. Neonatal hepatitis more commonly affects male patients and is associated with infection (CMV, rubella, toxoplasmosis, HSV, and viral hepatitis), alpha-1-antitrypsin deficiency, and idiopathic onset. Identification of patients with biliary atresia before 2 to 3 months of age is important to prevent irreversible liver damage and complete deterioration of the extrahepatic biliary tree. The Kasai procedure (choledochojejunal anastamosis) is often corrective of biliary atresia.

^{99m}Tc IDA derivatives are used in hepatobiliary scintigraphy for the differentiation of biliary atresia and neonatal hepatitis. ^{99m}Tc DISIDA or ^{99m}Tc mebrofenin are often the radiopharmaceuticals chosen for hepatobiliary scintigraphy. Premedication with phenobarbital (5 mg/kg/d divided bid for 3 to 5 days before scintigraphy) increases bile secretion and improves the diagnostic differentiation between biliary atresia and neonatal hepatitis. Ursodeoxycholic acid has also been included in the pretreatment regimen to stimulate bile secretion.

At most institutions, dynamic abdominal images are acquired for 1 h; however, at some centers, including our own, only 15 min of dynamic imaging is acquired. Excretion into the bowel excludes the presence of biliary atresia. If no bowel activity is detected after 1 h of imaging, delayed images up to 24 h are recommended to diagnose biliary atresia. However,

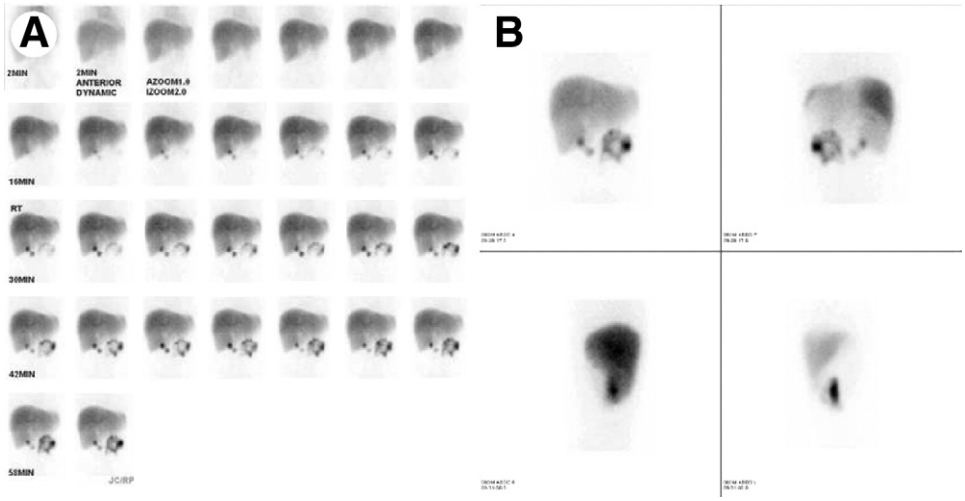

Figure 1 Hepatobiliary imaging demonstrating acute cholecystitis in a 16-year-old girl with sickle cell disease. Dynamic (A) and delayed (B) images demonstrate nonvisualization of the gallbladder. Gallbladder activity was not seen on 3-h delayed views (not shown).

normal liver uptake of tracer with no excretion up to 24 h can occur in severe cases of neonatal hepatitis, Alagille syndrome, dehydration, sepsis, TPN cholestasis, and bile plug syndrome in cystic fibrosis, thereby giving a similar scintigraphic appearance as biliary atresia. Neonatal hepatitis typically demonstrates poor hepatocyte uptake and poor hepatobiliary transit with passage of tracer into the bowel.

Cases in which hepatocellular uptake is severely impaired and bowel is not visualized are indeterminate. A repeat examination with phenobarbital (if not already performed) may prove useful. Conceivably, a single-proton emission computed tomography–computed tomography (SPECT/CT) scan could improve the accuracy of the examination by localizing questionable activity to bowel lumen versus liver, spleen, genitourinary tract, or elsewhere in equivocal cases.[8,9]

Biliary Obstruction and Cholecystitis

Hepatobiliary scintigraphy is useful in the assessment of patients with right upper-quadrant pain (Figs. 1 and 2). Cholecystis is presumed to occur less frequently in children than in adults, but its incidence in children has probably been underestimated.[10] Cholecystitis with underlying cholelithiasis is more common in children with hemolytic anemias. Acute calculous cholecystitis

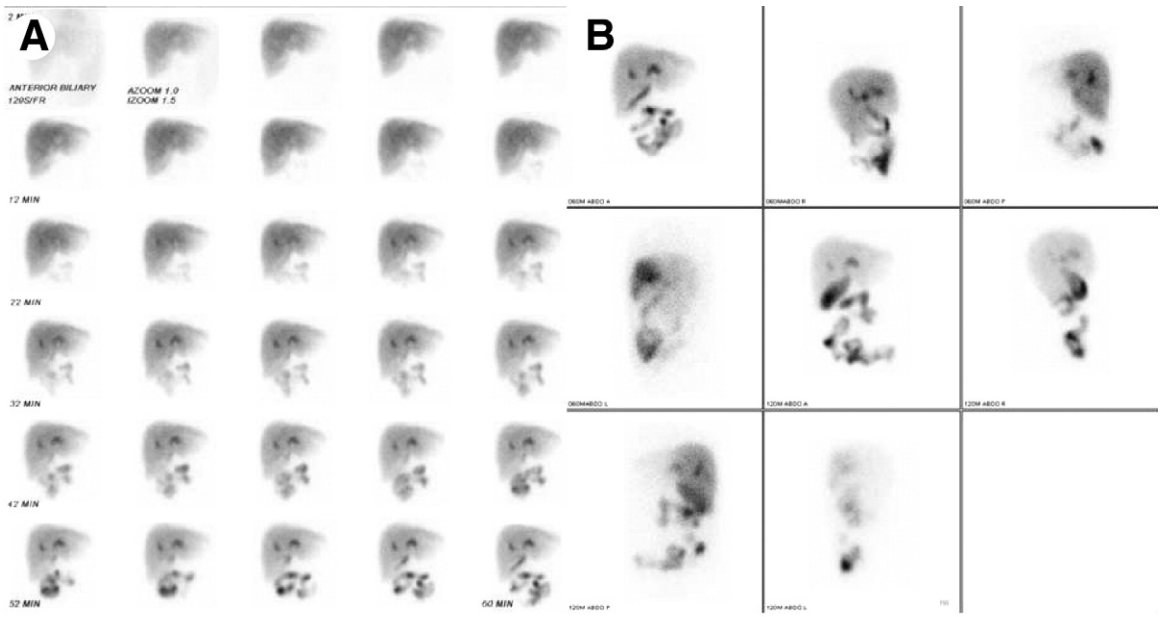

Figure 2 Hepatobiliary scintigraphy showing dilation of the intrahepatic bile ducts on dynamic (A) and delayed images (B) representing Caroli's disease.

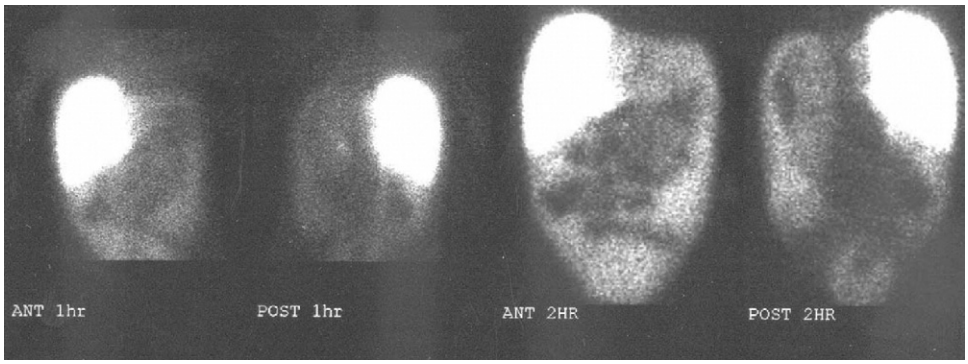

Figure 3 Hepatobiliary scintigraphy demonstrating intense perihepatic tracer accumulation resulting from a biliary leak. Note photopenia representing loops of bowel made apparent by tracer activity within the peritoneal space seen most prominently on 2-h delayed images.

occurs when the cystic duct becomes obstructed by gallstones leading to gallbladder distension and edema. Bile stasis may then lead to bacterial overgrowth. Acalculous cholecystitis occurs infrequently in the adult population, but proportionately, is a more common cause of cholecystitis in children. Acalculous cholecystitis can occur in prolonged illness, sepsis, or trauma. These conditions (and their treatment) predispose increasing cholesterol saturation, biliary stasis, and cholestatic hypofunction. Biliary sludge may then form with resultant cystic duct obstruction. The associated inflammation and edema may compromise blood flow and promote bacterial infection. Infections such as scarlet fever and other streptococcal infections as well as vasculitis from Kawasaki's disease and polyarteritis nodosa can lead to acalculous cholecystitis in children. Chronic cholecystitis most often is related to gallstone formation; however, cases of chronic acalculous cholecystitis (biliary dyskinesia) are believed to be related to gallbladder dysfunction causing chronic bile stasis and sphincter of Oddi dysfunction.[11]

Acute cholecystitis is associated with nonvisualization of the gallbladder on hepatobiliary scintigraphy with a diagnostic accuracy of 98%, and a specificity of 100% in adults.[12] However, in children, visualization of the gallbladder does not exclude cholecystitis as gallbladder visualization, though infrequent, is possible in acalculous cholecystitis. In acalculous cholecystitis, the cystic duct may be partially obstructed and associated edema of the cystic duct may result in gallbladder nonvisualization. If the gallbladder is visualized, infusion of 0.02 mg/kg sincalide permits further assessment. Poor contraction of the gallbladder following sincalide may occur in partial cystic duct obstruction, acalculous cholecystitis or chronic cholecystitis. Chronic cholecystitis is associated with a gallbladder ejection fraction of approximately less than 35%. No normal values for gallbladder ejection fraction have been established in children, and it is expected that there is significant overlap between the normal and abnormal range. Additionally, chronic cholecystitis may be accompanied by a delay in gallbladder filling in the absence of hepatic dysfunction. As in adults, morphine augmentation of hepatobiliary scintigraphy of acute cholecystitis may help reduce the number of false positive studies in children and reduce scanning time, however, in acute acalculous cholecystitis, it may overcome functional obstruction of the cystic duct resulting in a false negative examination.[8,11,13-15]

Biliary Leak

A biliary leak may occur as a complication of trauma or surgery. In the case of surgery, 70 to 75% of bile leaks occur at the cystic duct. Hepatobiliary scintigraphy demonstrates activity within the peritoneal cavity, usually within the hepatic capsule or adjacent to the liver (Fig. 3). Rarely, free bile ascites may occur. Through the use of scintigraphy, the presence of a hepatobiliary leak and hepatic capsule integrity can be determined and a qualitative assessment of the severity of the leak can be made. Large biliary leaks require intervention, whereas small biliary leaks are allowed to heal spontaneously.

Scintigraphy is more sensitive than CT or ultrasound for the detection of biliary leaks. CT and ultrasound may demonstrate the presence of a fluid collection; however, scintigraphy is better able to establish an active hepatobiliary component associated with the fluid collection. In the setting of a clinically high suspicion of biliary leak, endoscopic retrograde cholangiopancreatography is often performed to identify the leak and in some cases to also repair the leak. If the clinical suspicion for an active biliary leak is low, then scintigraphy is preferred as it is a sensitive, noninvasive and inexpensive test.[8,14,16]

Gastroesophageal Reflux

Gastroesophageal reflux has been described as the presence of gastric contents within the esophagus. Infants with severe reflux typically present by 2 months of age. Sixty percent of patients will have symptom resolution by 18 months of age, and 30% of patients will have symptoms until 4 years of age. Ten percent of infants with reflux may develop severe complications, including strictures and possible death as a result pneumonia or failure to thrive if left untreated.

^{99m}Tc sulfur colloid in milk or formula is often used for the assessment of GI reflux in children. The examination should be performed at the time of the child's scheduled feeding, and a feeding volume typical for the individual patient should be used. 0.2 mCi to 1 mCi of radioisotope may be given orally in two thirds of the expected feeding volume. The remaining unlabeled

one third of the feeding volume is then swallowed to clear any residual activity within the oropharynx and esophagus. The patient is burped and placed above a gamma camera. Anterior 5-s images are acquired for 60 min. The acquisition of short-lasting 5-s images increases the sensitivity for the detection of short lived episodes of gastroesophageal reflux. Anterior acquisition has the advantages of minimizing the patient to camera distance and preventing the thoracic spine from attenuating possible activity within the esophagus. The stomach and thorax are positioned within the field of view of the camera. At 60 min, anterior and posterior static images of the thorax can be acquired to look for evidence of aspiration.

The dynamic images should be reviewed with high-contrast settings to best visualize any episodes of reflux. The results may be represented graphically by placing regions of interest around the entire esophagus and around the upper esophagus only to aid in the analysis of data. The number of episodes of reflux, level reached within the esophagus, and the clearance rate of reflux episodes may then be determined.

A pH probe also can be used for the detection of gastroesophageal reflux. This method allows detection of reflux events as decreased pH during a period of 24 h. A decrease of pH less than 4 is often used to define an acid reflux event. The main advantage of a pH probe over scintigraphy is its ability to detect nocturnal episodes of reflux. However, 60-min scintigraphic assessment has been shown to compare well with 24-h pH-metry. Although considered the gold standard for assessment of gastroesophageal reflux, disadvantages include possible adherence of refluxed gastric juice to the pH probe, resulting in the false appearance of a sustained reflux episode, and the increase of pH by neutral feeds during the procedure (eg, milk), causing false-negative findings and invasiveness of the test. The scintigraphic method includes additional information such as gastric emptying data, aspiration, and abnormal esophageal contraction. Nonacid reflux does not affect the diagnostic accuracy of the test. It has been noted that 16% of children had predominantly alkaline reflux.[17-23]

Several studies have demonstrated the relationship between the scintigraphic assessment of gastroesophageal reflux and patient symptomatic and pathologic states, suggesting further potential clinical utility for the study. In one series, 67 patients between 1 and 5 years of age with symptoms of gastroesophageal reflux were assessed through upper GI studies, scintigraphy and pH monitoring.[24] Fifty-five percent of patients had intestinal malrotation and 83% had gastroesophageal reflux disease (GERD). The mean nuclear gastric emptying time was 52 ± 8 min in patients with primary GERD and 97 ± 21 min in children with intestinal malrotation and GERD. Malrotation was shown to be an important factor for delayed gastric emptying in GERD, and it was suggested that all children and infants with GERD and delayed gastric emptying be assessed for intestinal malrotation. In a different study of 126 asthmatic children not responding to routine antiasthmatic medications, 23% of patients without symptoms of GERD demonstrated gastroesophageal reflux on scintigraphy, whereas 39% with symptoms of GERD demonstrated gastroesophageal reflux on scintigraphy.[25]

Delayed gastric emptying time is believed to contribute to the occurrence of gastroesophageal reflux in children with cerebral palsy. Seventy-six children with cerebral palsy were assessed for both gastric emptying time and gastroesophageal reflux.[26] Twenty-eight children with medication-resistant asthma assessed for pulmonary aspiration formed the control group. Fifty-one percent of patients with cerebral palsy demonstrated gastroesophageal reflux. Gastric emptying time in cerebral palsy patients with reflux was no different from gastric emptying time in the asthmatic control group. Scintigraphy has been employed in the detection of gastroesphageal reflux in patients who have experienced caustic esophageal injury. Such injury to the esophagus causes luminal narrowing and longitudinal contraction resulting in gastroesophageal reflux. Scintigraphy was shown to be useful for the detection of gastroesophageal reflux in seventeen children with caustic esophageal injury, and in the assessment of the outcome of antireflux surgery.[27,28]

Esophageal Transit

Esophageal transit scintigraphy may be used in the evaluation of patients with esophageal motility disorders such as achalasia, diffuse esophageal spasm, nutcracker esophagus, tracheoesophageal fistula, Down syndrome, esophagitis, systemic sclerosis, and diabetes mellitus. Before the examination, the patient should fast for at least 3 h. The test may be performed with the patient in the supine position and having him or her swallow a 10-mL bolus of water or milk labeled with 150 μCi (5.55 MBq) of ^{99m}Tc sulfur colloid. A small radioactive marker may be placed over the cricoid cartilage for an anatomic reference. Posterior images are acquired, including the mouth and stomach, in the camera field of view. A practice swallow with unlabeled liquid is first performed. Images are acquired at 0.4-s intervals for 150 frames. A radioactive bolus is placed in the mouth and swallowed on command followed by a dry swallow 30 s later. Abnormal studies may be repeated in the upright position to determine the effect of gravity.

Image analysis involves drawing regions of interest around the upper, middle, and lower thirds of the esophagus and the stomach. Time activity curves derived from these regions of interest may demonstrate abnormal esophageal transit in pathologic states. Condensed dynamic images may also be used to visualize esophageal transit. A condensed dynamic image is acquired from a sequence of frames representing images of esophageal transit taken from the time of swallowing to the end of the study. The esophagus, being a linear structure oriented cranially to caudally, is digitized into one vertical activity profile with intensity variation representing activity distribution for each acquired frame. These linear profiles are sequentially placed side by side over time to generate a condensed image of esophageal transit.

Pharyngeal bolus transit is quite rapid and usually requires less than 1 s. The normal transit time through the esophagus is typically less than 10 s. Esophageal transit ranges from 3.4 ± 1 s for infants to 4.6 ± 1.9 s for patients 8 to 16 years of age. Gastroesophageal reflux or esophagitis are associated with prolonged transit times.[29]

Esophageal manometry may also be used to assess esophageal peristalsis and pressure behavior of the upper esophageal

sphincter and lower esophageal sphincter. Contrast radiography can be used to assess anatomical lesions of the esophagus, and mucosal lesions such as those resulting from esophagitis and gastroesophageal reflux. Endoscopy permits direct visualization of the esophagus and biopsy when required. Advantages of esophageal scintigraphy include its noninvasive nature, quantifiability and low radiation burden. Its clinical utility is not well-defined. It has been suggested that esophageal transit scintigraphy may be useful when esophageal manometry is unavailable or not tolerated by the patient, or when the results of manometry are equivocal, when the results of manometry are negative but clinical concern for esophageal dysmotility is high and to monitor disease and/or its response to therapy.[21,30-35]

Gastric Emptying

Patients with rapid or delayed gastric emptying may present with nausea, vomiting, epigastric fullness, and early satiety. There is often a poor correlation between severity of symptoms and the degree of abnormal gastric emptying; however, assessment of gastric emptying helps to guide treatment decisions. Neurologically impaired children frequently demonstrate symptomatic delayed gastrointestinal motility and determination of gastric emptying rate can aid in assessing therapeutic interventions. Gastric emptying may provide an objective assessment of the transit abnormality pre or postoperatively to help guide treatment decisions, an example being that scintigraphic determination of prolonged or rapid gastric emptying assessed preoperatively predicts postoperative retching following antireflux surgery.[36] Also, 289 children were assessed scintigraphically before undergoing antireflux surgery.[37] Those with postoperative paraesopheal hernia were more likely to have had delayed gastric emptying preoperatively compared with those who did not develop postoperative paraesopheal hernia. In another study, children with scintigraphic evidence of delayed gastric emptying refractory to medical therapy underwent balloon pyloroplasty.[38] Scintigraphic normalization of gastric emptying was seen in all patients reassessed postoperatively. In a different assessment, 27 children had double-isotope scintigraphic evaluation of gastric emptying before and after gastric fundoplication.[39] Prediction of postfundoplication delayed gastric emptying was found to be accurate for solids but not for liquids by the double-isotope method employed.

Another study used scintigraphic determination of solid gastric emptying in 10 children with repaired esophageal atresia and in 11 healthy control children (ages 5 to 11 years of age).[40] Gastric emptying half-time, lag phase values, and 60- and 90-min retention values were greater in the patient group compared with the healthy control group. Values for gastric emptying of solids in healthy children corresponded well to gastric emptying values reported in healthy adults. In a different study, 15 children with gastroesophageal reflux and scintigraphically demonstrated delayed gastric emptying underwent repeat gastric emptying scintigraphy 3.6 years after fundoplication and antroplasty.[41] The mean 90-min gastric retention improved from 72% to 40% postoperatively, and improvement was seen in three-quarters of patients. Fundoplication with antroplasty was recommended for symptomatic children with documented gastroesophageal reflux and delayed gastric emptying. Also with regard to gastric emptying, it has been shown that children with diabetes have a high incidence of abnormal gastric emptying after 1 year of disease history, but the correlation between symptoms, risk factors, and gastric emptying becomes weaker after a longer period of disease history.[36]

Rapid gastric emptying may accompany partial gastric resection. A proximal gastric resection may cause loss of accommodation of food contents within the stomach inducing rapid gastric emptying. A distal gastric resection may result in loss of antropyloric resistance and result in rapid gastric emptying. Damage to the vagus nerve may occur during esophageal surgery, and consequently increase gastric emptying.[42] Nonsurgical causes of rapid gastric emptying include Zollinger-Ellison syndrome, carcinoid syndrome, duodenal ulcer, and medications such as cisapride, metoclopramide, erythromycin and ondansetron.[30] It was shown that the presence of *Helicobacter pylori* infection correlated with accelerated gastric emptying in forty-seven children with nonulcer dyspepsia.[43]

Delayed gastric emptying may be secondary to pyloric stenosis, duodenal stenosis, duodenal web, hypokalemia, acidosis, hypothyroidism, autonomic neuropathy associated with diabetes mellitus, opioid or anticholinergic medications, central nervous system disease, vagotomy, systemic lupus erythematosus, dermatomyositis/polymyositis, myotonic dystrophy, infection, or gastric arrhythmia.

The rate of gastric emptying assessed scintigraphically, has been shown to be dependent on the test meal used. Liquids, solids and indigestible solids have different rates of emptying, with liquids typically emptying faster than solids. Liquids generally follow an exponential clearance of activity, whereas solids demonstrate a lag-period followed by near linear disappearance. Solid particles must be reduced to 1 mm before passing through the pylorus.[30] Caloric content delays gastric emptying and the effect is separate from that of size of the meal.[44] Increased osmolality also delays gastric emptying. Cow's milk has been demonstrated to empty at a slower rate than human milk. Whey-based formulae empty more rapidly than casein-based formulae perhaps due to effects of variable precipitation and formation of solid materials within the stomach which may affect tracer binding and apparent clearance pattern.[45]

Milk or formula is used to assess gastric emptying in infants. The child's usual feeds generally are given. A region of interest is drawn around the stomach. Activity from the bowel should not be included in the region of interest. Correction for radioactive tracer decay and background subtraction should be performed. The rate of gastric emptying was determined in 28 normal newborns and young infants with a mean age of 25 days.[46] The babies were given 15 μCi of ^{113m}In-microcolloid in 50 mL of milk. The half-time for emptying was demonstrated to be 87 $\pm$ 29 min. Extrapolation of this data gives a range of normal gastric emptying range of 48% to 70% at 60 min, and 24% to 48% at 120 min.[21] In another study, the normal range for gastric emptying was assessed in a group of infants and children who were being evaluated for gastrointestinal reflux and who were in retrospect determined to be within normal limits. The normal range for gastric emptying in 41 infants (mean age, 5.7 months)

at 1 hour was 32% to 64%. The normal range for gastric emptying in 8 children (mean age, 9.1 years) at 1 h was 44% to 58%.[47]

In older children, solid or combined solid and liquid emptying can be assessed. Solid gastric emptying may be performed by having the patient eat an egg sandwich containing ^{99m}Tc sulfur colloid (250 to 300 μCi). When combined solid and liquid gastric emptying is to be assessed, the liquid phase may include 50 μCi of ^{111}In DTPA in water. A ratio of ^{99m}Tc to ^{111}In counts of at least 6:1 should be used to minimize the effects of downscatter of ^{111}In photons into the ^{99m}Tc energy window. The meal should be scaled according to patient size (where adults are given 4 eggs and 50 mL of water). Thirty second anterior images are acquired every 10 min. Between images the patient should sit upright. Images are acquired until 120 min.

Simultaneous anterior and posterior acquisition allows calculation of a geometric mean that corrects for the posteroanterior migration of tracer through the stomach giving an artifactually delayed appearance of gastric emptying when anterior views only are acquired. This correction is more useful in older children or obese children, in whom attenuation effects play a greater role in count detection. Other potential sources of error are including added counts in the gastric region of interest from overlying duodenal activity and scatter from adjacent bowel into the gastric region of interest. Correction for downscatter into the lower isotope energy window should be performed when two isotopes are used.[19-21]

One study demonstrated good correlation between gastric emptying and epigastric impedance measurements in seven infants.[48] Epigastric impedance was found to be sensitive to spontaneous patient movement, which creates artifacts resulting in nonvalid measurements.[49] It was determined that epigastric impedance measurement of gastric emptying requires that the patient fall asleep to acquire meaningful results.[48,50,51]

Pulmonary Aspiration

Chronic pulmonary aspiration in the neurologically impaired child or in children after upper airway surgery can be the source of frequent episodes of pneumonia. Two scintigraphic studies can identify pulmonary aspiration: the salivagram and the milk scan. The salivagram primarily detects aspiration during swallowing (antegrade events) and the milk scan is more likely to detect events related to gastroesophageal reflux (retrograde events).

The milk scan is typically not very sensitive for detecting gastroesophageal reflux causing aspiration, in part, perhaps because the frequency of retrograde reflux events as a cause of aspiration may be less than that of antegrade reflux events particularly in the neurologically impaired in whom these tests are more likely to be performed. It has been noted that increasing the concentration of tracer during swallowing (2.5mCi in 20 mL of ^{99m}Tc sulfur colloid in water) in adults increased the sensitivity of detection of antegrade aspiration compared with videofluoroscopy. The salivagram, uses a small amount of total fluid, and therefore does not stress the swallowing mechanism; however, a higher concentration of radiotracer is used compared with the milk scan (approximately 300 times greater), thereby increasing the sensitivity of the method for demonstrating pulmonary aspiration of salivary secretions.

A salivagram is performed by placing a small drop of liquid (100 μL) containing 300 μCi ^{99m}Tc sulfur colloid on the patient's tongue. Posterior images are obtained for 60 minutes (often ends at 10-15 min) with patients in the supine position. In abnormal cases, aspiration of saliva is clearly documented by tracheobronchial activity and/or lung activity. The mouth, chest, and stomach should be included in the field of view (Fig. 4). Imaging can be continued until oral radioactivity is no longer present.[19,29,52]

The salivagram is more frequently positive than videofluoroscopy or the milk scan in the detection of pulmonary aspiration. The salivagram was positive in 56% of patients, videofluoroscopy was positive in 39% and the milk scan was positive in 6% of patients with severe cerebral palsy.[53] It was noted that each test assesses different aspects of pulmonary aspiration and there was little correlation between different methods, though, the strongest correlation between tests was for the salivagram and videofluoroscopy. The number of inpatient days for treatment of respiratory tract infection for 30 children with chronic aspiration pneumonitis who underwent laryngotracheal separation were compared with 27 children with chronic aspiration pneumonitis who did not undergo laryngotracheal separation during a 10-month period.[54] Eleven of 15 patients who underwent laryngotracheal separation had positive preoperative radionuclide salivagrams. This same group was effectively controlled by laryngotracheal separation as a significant difference in the number of inpatient days for treatment of respiratory tract infection was seen in patients with positive salivagrams referred for laryngotracheal separation compared with children who had negative salivagrams who did not undergo laryngotracheal separation. In another study, patients with chronic pulmonary congestion and persistent hypoxemia were diagnosed with chronic aspiration by use of a radionuclide salivagram.[55] These same patients were treated with constant positive airway pressure via tracheotomy which resulted in improvement in clinical symptoms and a corresponding marked decrease in saliva aspiration as documented on the radionuclide salivagram.

Colonic Transit

The incidence of constipation in the general population is high, and is the chief complaint of 3% of pediatric outpatient visits.[56] Before puberty, boys are more affected than girls, after which girls are more affected than boys. Constipation is a symptom but may be caused by a number of underlying disorders, which can be divided into organic and nonorganic causes. The majority of children with constipation have nonorganic causes such as functional fecal retention, infant dyschesia or grunting baby syndrome. Functional fecal retention is the most common chronic defecation disorder in children. It is characterized by the passage of enormous stools, with bowel movements occurring at weekly

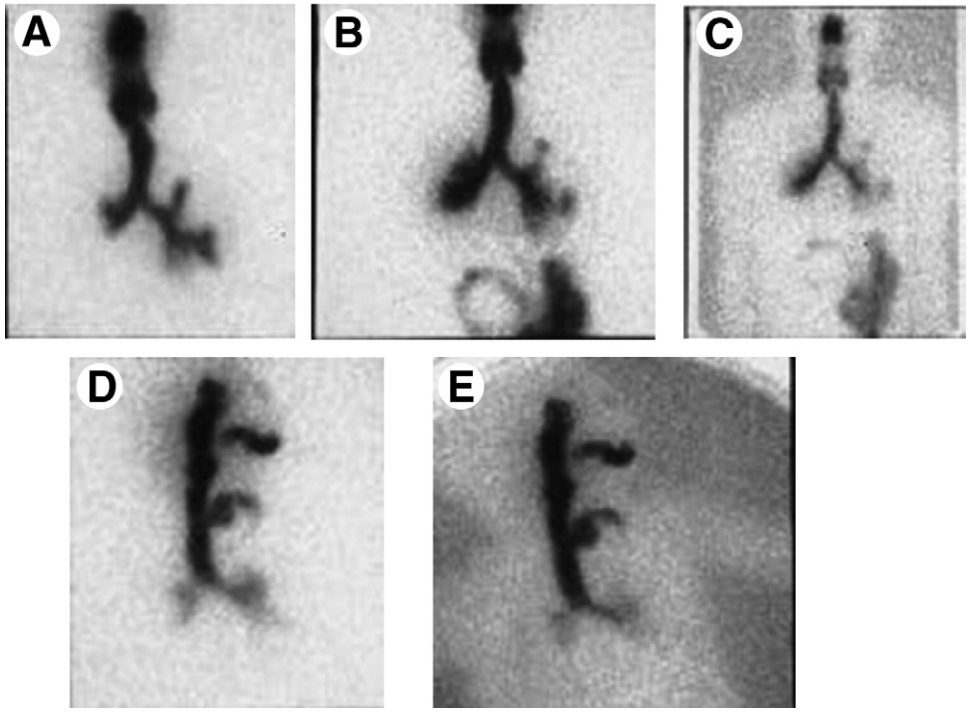

Figure 4 Radionuclide salivagrams positive for aspiration. There is intense continuous activity outlining the oropharynx, trachea and bronchi bilaterally on anterior views in (A-C). (D) and (E) demonstrate anterior thoracic views of an infant with head turned laterally to the left. There is bilateral bronchial activity. Note that (C) and (E) also include a cobalt flood source posterior to the patient, providing an outline of the form of the patient's body.

intervals with onset after 1 year of age. The child associates defecation with pain and fear.[57]

Organic causes of constipation are rare in comparison with nonorganic causes and include Hirschprung's disease (1% of children presenting with constipation), anorectal malformations, hypothyroidism, cystic fibrosis, spina bifida, Down syndrome, and medications such as opiates and anticholinergics.[57] Patients with severe chronic constipation refractory to dietary, behavioral, and medical therapy without a known underlying cause for constipation or encopresis, may benefit from colonic transit scintigraphy to establish whether the cause is attributable to slow colonic transit versus functional fecal retention.[21,58-60]

In one study, 180 children with intractable constipation were assessed scintigraphically. It was shown that the findings of either slow colonic transit, normal colonic transit and functional fecal retention determined scintigraphically divides patients into groups which respond distinctly to different therapies.[59] In another study, 101 children with chronic idiopathic constipation with soiling were assessed. The total radiation dose from the scintigraphic study was determined to be equal to that of two plain abdominal radiographs. Fifty patients demonstrated slow colonic transit, 24 patients had normal transit, 22 patients had definite functional fecal retention, and 5 patients had borderline results. Radionuclide colonic scintigraphy is an accurate method of measurement of colonic transit in children. It also has the advantage of permitting additional assessment of gastric and small bowel transit.[58] Scintigraphic screening of gastrointestinal transit up to 24 h in 109 patients presenting with nausea, vomiting, diarrhea, or constipation has demonstrated slow or normal gastric, small bowel and colonic transit in those presenting with constipation and normal or fast results in patients presenting with diarrhea.[61]

Splenic Scintigraphy

Splenic scintigraphy may be performed by intravenous administration of 1.85 MBq/kg of ^{99m}Tc sulfur colloid to a maximum of dose of 111 MBq. Imaging may be performed after 10 to 15 min after tracer delivery. The tracer clears with a half-time of 2.5 min. The particle size ranges from 0.01 to 1.0 μm.

Alternatively, ^{99m}Tc-denatured RBCs may be used. RBCs withdrawn from the patient are labeled with ^{99m}Tc. They are then denatured to improve splenic localization. Denaturation consists of incubation of the labeled blood in a constant temperature bath at 49.5°C for 12 to 15 min. The labeled, denatured RBCs are then reinjected slowly into the patient with images acquired at least fifteen minutes after tracer administration.

Increased ligamentous laxity may allow the spleen to become mobile within the abdomen giving the false appearance of an abdominal neoplasm on anatomic imaging. ^{99m}Tc sulfur colloid or heat damaged RBC scintigraphy can distinguish the "wandering spleen" from abdominal neoplasm.[62] In some cases a "wandering spleen" can undergo torsion. Twisting of

the spleen about its vascular pedicle may result in ischemia and scintigraphic nonvisualization splenic tissue.

Accessory spleens or splenules are present in as many as 40% of patients. They are most frequently situated at the splenic hilum and may represent failure of early embryologic fusion of multiple buds of splenic tissue. After splenectomy, these residual buds may hypertrophy and create or recreate an appearance of hypersplenism. Splenic scintigraphy is useful for establishing the presence of splenic tissue versus neoplastic proliferation.[26] SPECT imaging can help to better visualize the presence and distribution of splenic tissue. SPECT/CT imaging can conceivably be useful for precise correlation of splenic scintigraphic foci with uncertain anatomic findings in this clinical setting.

Splenosis occurs with fragmentation of the spleen after splenic trauma with subsequent autotransplantation of splenic tissue. Simultaneous splenic injury and diaphragmatic rupture can result in thoracic splenosis and should be considered in a patient presenting with a thoracic mass and a previous history of splenic trauma.[8,14] Splenic scintigraphy with ^{99m}Tc sulfur colloid or ^{99m}Tc heat-damaged RBCs can be utilized in making this distinction.

Hyperinsulinism of Infancy

Congenital hyperinsulinism induces hypoglycemia in infants and treatment is required to prevent possible neurologic complications. Forty percent of cases of hyperinsulinism in children are focal resulting from pathologic adenomatous pancreatic β cells. Diffuse hyperinsulinism involves the whole pancreas with enlarged abnormal β-cell nuclei. Ten percent of cases of infantile hyperinsulinism are atypical and fit neither classification. Focal hyperinsulinism is cured by resection of the adenoma, whereas diffuse pancreatic involvement may be treated with subtotal pancreatectomy.[63]

^{18}F-DOPA PET has been used to preoperatively classify the form of infantile hyperinsulinism. Fourteen patients with congenital hyperinsulinism underwent ^{18}F-DOPA PET. Five patients were determined to have focal hyperinsulinism and were normoglycemic after the resection of the pancreatic focus. The remaining 9 patients demonstrated diffuse pancreatic disease on ^{18}F-DOPA PET. Three of these patients underwent subtotal pancreatectomy with diffuse disease confirmed histologically. Six patients with diffuse pancreatic disease identified on ^{18}F-DOPA PET were successfully conservatively treated with octreotide and/or diazoxide.[64] In another study, 7 patients with congenital hyperinsulinism underwent ^{18}F-DOPA PET. A PET diagnosis of focal hyperinsulinism was confirmed pathologically in 4 patients who received curative focal pancreatic resection. Three patients with the diagnosis of diffuse disease identified on ^{18}F-DOPA PET had subtotal pancreatectomy and pathologic confirmation of diffuse hyperinsulinism.[65]

Protein-Losing Enteropathy

Protein-losing enteropathy refers to gastrointestinal disorders associated with excessive plasma protein loss into the lumen of the gut.[66] Protein-losing enteropathy is thought to be caused by loss of integrity of the cell membranes of enterocytes joined at apical tight junctions. Mechanisms that can cause disruption of enterocyte barrier are mucosal erosion or ulceration, mucosal disease without ulceration but with increased barrier permeability, and increased intestinal lymphatic pressure, causing intestinal lymphatic villi rupture and loss of lymph containing proteins.[67]

The resulting loss of protein includes loss of albumin and decreased plasma oncotic pressure. Patients can become edematous. Also, patients may acquire infections secondary to immunoglobulin and lymphocyte loss. Malabsorption of long-chain fatty acids and a deficiency of fat-soluble vitamins may also occur. Some causes of protein-losing enteropathy as the result of lympatic obstruction are primary intestinal lymphagiectasia and secondary causes of intestinal lymphangiectasia such as cardiomyopathy, constrictive pericarditis, post-Fontan procedure, lymphoma, tuberculosis, radiation therapy, and chemotherapy. Other causes of protein-losing enteropathy caused by mucosal erosion or ulceration are often classified as infectious such as Clostridium difficile, Salmonella, Giardia, Helicobacter pylori, and cytomegalovirus or noninfectious such as Menetrier's disease, gluten-sensitive enteropathy, milk and soy-induced enteropathy, graft versus host disease, neonatal necrotizing enterocolitis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, and Henoch-Schönlein purpura.[66-68]

The diagnosis of protein losing enteropathy was first performed using ^{131}I polyvinyl pyrrolidone. It was replaced by ^{131}I albumin, which was considered to be more physiologic. This marker was limited by ^{131}I thyroid uptake and absorption of ^{131}I albumin into the intestinal tract sometimes yielding indeterminate results.[69] ^{51}Cr labeled albumin overcame difficulties associated with ^{131}I albmumin and became the radionuclide of choice for these studies.[67]

It was demonstrated that patients with protein-losing enteropathy have elevated levels of alpha-1 antitrypsin in their stool. Alpha-1 antitrypsin is an endogenous protein and is not secreted, absorbed or digested within the bowel. It is easily detected in stool, is stable within stool over several days and not excreted in urine. Alpha-1 antitrypsin levels in stool are determined by immunoassay.[67]

Radionuclide demonstration of protein losing enteropathy has been regarded as providing unnecessary radiation dose, particularly in children. Patients required hospitalization for 48- to 72-h stool collection. Urine contamination of sample had to be avoided, though the task may be difficult in children. Fecal alpha-1 antitrypsin (FA1-At) is not associated with these difficulties and has been regarded as the method of choice for diagnosing protein losing enteropathy.[67] A limitation of FA1-At is instability in acidic gastric secretions. Therefore, esophageal or gastric protein loss may go unrecognized by this method.[68]

^{99m}Tc-labeled albumin has been used for diagnosis of protein losing enteropathy, but has the added advantage of permitting imaging of the gastrointestinal tract with potential localization of a site of protein loss, thereby, assisting in the diagnosis of the underlying condition, or directing resection

for surgically correctable causes of enteric protein loss. ^{99m}Tc-HSA scans were more likely positive in patients with lower albumin and total protein levels, possibly related to higher rates of protein loss.[70-74]

^{99m}Tc-dextran was evaluated for its use in detecting protein losing enteropathy. The findings suggested improved sensitivity compared with previous documented studies using ^{99m}Tc-HSA, possibly because of faster background clearance, less electrostatic repulsion from vascular endothelium, less hepatic uptake, and better in vivo stability.[75-77]

^{111}In transferrin was evaluated for its ability to provide both imaging and detection of protein-losing enteropathy through one examination. Quantification was performed by total body imaging after 3 hours and at 5 or 6 days after tracer administration. Other possible advantages of ^{111}In transferrin imaging includes its stability with significantly less likelihood for urinary excretion compared with ^{99m}Tc HSA. The combined imaging and quantification approach has advantages over FA1-At measurements in that it obviates the requirement for accurate fecal collection and that gastric protein loss would be detectable.[78]

Miscellaneous

Twenty-one children with various causes of liver cirrhosis suspected of having hepatopulmonary syndrome underwent scintigraphic assessment of intrapulmonary arteriovenous shunting.[79] Scintigraphic evidence of arteriovenous shunting was demonstrated in 29% of patients. No correlation between the scintigraphic degree of arteriovenous shunting and the etiology or stage of underlying disease was found. However, in a study on 21 patients (19 children and 2 adults) who received a liver transplant and had intrapulmonary shunting, the shunt index determined by ^{99m}Tc MAA pulmonary scintigraphy correlated significantly with PaO_2 (on room air and 100% O_2), hematocrit and duration of dyspnea before transplantation.[80] The duration of hepatopulmonary syndrome resolution was significantly correlated with the preoperoperative scintigraphic shunt index in surviving patients.

In another study, 15 patients with cirrhosis of the liver with underlying viral infection had hepatic and portal blood flow measurement through $H_2{}^{15}O$ PET.[81] Portal blood flow measurement correlated with patient Child-Turcotte classification score, portal shunt index (assessed by per rectal administration of ^{99m}Tc pertechnetate) and receptor index (assessed by intravenous ^{99m}Tc galactosyl human serum albumin). $H_2{}^{15}O$ PET assessment of hepatic and portal blood flow, therefore, correlated significantly with the degree of portal systemic shunt and hepatic functional reserve and may be useful in studies of liver disease. Though this study involved adult patients, it is likely that similar results would be observed in children. A different study demonstrated the use of ^{111}In-labeled hepatocytes in the short-term noninvasive analysis of the biodistribution of transplanted hepatocytes in a pediatric patient with ornithine transcarbamoylase deficiency.[82]

Endoscopy was performed on 1120 children with abdominal pain. Ninety-two patients showed endoscopic features of duodenogastric reflux, of which 59 demonstrated duodenogastric reflux by scintigraphy. Prokinetic agents were of benefit in treating children with inflammatory lesions of gastric mucosa with duodenal reflux.[83]

Three patients with chylothorax underwent scintigraphy for the detection of lymphatic leak after the oral administration of an ^{123}I labeled long-chain fatty acid derivative of iodophenyl pentadecanoic acid.[84] Lymphatic leakage of intestinal origin was correctly identified in all three patients and the method was used to guide surgical treatment of the leak in 2 of the patients.

Intestinal permeability was assessed by oral administration of lactulose/mannitol and ^{51}Cr-EDTA/^{14}C-mannitol followed by measurement of urinary marker excretion.[85] Seventy patients with intestinal disorders and 65 control subjects were assessed. Excretion of mannitol and ^{14}C-mannitol (small-pore permeability markers) correlated to urinary volume, whereas the correlation was weak for lactulose and absent for ^{51}Cr-EDTA (larger-pore permeability markers). The excretion of large-pore markers was higher for the patient group than the control group. The excretion of small-pore markers was less for the patient group than the control group, and the large-pore to small-pore marker excretion ratio was higher for the patient group compared with the control group.

^{99m}Tc-HMPAO WBCs have been used for the detection of appendicitis.[86,87] ^{99m}Tc-HMPAO WBC imaging is limited because of time delay associated with the labeling procedure, as well as concerns regarding potential administration of a blood product to the wrong patient and the possibility of exposure of nuclear medicine technologists or radiopharmacists to blood products from HIV or hepatitis-infected patients. Radiolabeled monoclonal antibodies have been utilized to overcome many of these difficulties. Forty children with suspected acute nonclassic appendicitis were assessed with ^{99m}Tc-labeled antigranulocyte murine antibody Fab' fragment (sulesomab).[88] Of the 40 patients, 21 underwent appendectomy, whereas the other 19 patients had resolution of their presenting signs and symptoms. Correlating scan findings with final diagnoses sensitivity and specificity were determined to be 95% and 90%, respectively. ^{99m}Tc anti-CD 15 monoclonal antibody (LeuTech) was used in 200 patients presenting with equivocal signs and symptoms of appendicitis. The sensitivity of the examination was determined to be 90% and the specificity was 87%.[89]

The ^{13}C-urea breath test is often described as a safe and noninvasive method for assessing the presence of H. pylori infection in children.[90-92] ^{13}C levels in exhaled air (nonradioactive) are measured by mass spectrometry, an expensive technique.[93,94] The ^{14}C-urea breath test uses a radioactive label and, consequently, has been avoided in children. The biokinetics and dosimetry of ^{14}C-urea breath testing was performed in nine adults and eight children undergoing testing for *Helicobacter pylori* infection.[95] Adults received a dose of 110 kBq of ^{14}C-urea and children received a dose of 55 kBq of ^{14}C-urea. The effective dose was was 2.1 $\pm$ 0.1 μSv in adults and 0.9 to 2.5 μSv in children. On the basis of the findings, it was determined that from a radiation protection perspective, there is no reason for restrictions on even repeated

screening investigations with ^{14}C-urea in whole families, including children.[95,96]

The intraoperative localization of tumors through the use of intraoperative probes has been reviewed in 68 surgical procedures.[97] The procedures included successful excisions of osteoid osteoma, osteoblatoma, hamartoma, Brodie's abscess, chronic bone infection, ectopic parathyroid adenoma, and metastatic neuroblastoma. Successful surgical localization of lesions by intraoperative probe was assisted by lesion localization on preoperative images of primary and metastatic lesions.

IBD

IBDs are complex diseases that frequently begin in late childhood or adolescence. For many years, barium enema was the cornerstone of diagnostic testing and, more recently, colonoscopy has been used more liberally.[98-100] Endoscopic methods are invasive and require sedation, involve some risks of instrumentation, and often can only evaluate a limited segment of the colon. There appears to be no justification for repeated routine endoscopic assessment of colonic inflammation because there is a poor correlation between clinical symptoms and endoscopic[101-103] and histological findings.[98-100] The endoscopic findings do not predict the response to treatment[99,101-103] Also, recognition of the emotional impact of intrusive routine diagnostic studies is essential.[104] It has been demonstrated that there is overall patient preference with less perceived discomfort and embarrassment associated with ^{99m}Tc-WBC imaging compared with barium enema and colonoscopy.[105] Because of these limitations of colonoscopy, there appears to be a role for a noninvasive technique such as the ^{99m}Tc-WBC scan.

Inflammatory bowel diseases include two chronic idiopathic illnesses: ulcerative colitis (UC) and Crohn's disease (CD). In most patients, UC and CD may be distinguished with clinical, radiological, endoscopic, and histologic features; the remaining 10% to 25% is designated as having "indeterminate colitis." The etiology of IBDs is unknown. Occasionally systemic and extra intestinal features are present, and consist of weight loss, arthralgia and arthritis, nutritional deficiency, mucocutaneous lesion (oral aphtoid ulcer, erythema nodosum, pyoderma gangrenosum), renal calculi, hepatobilliary disease and ocular manifestations such as uveitis, iritis, and episcleritis. IBD are characterized by unpredictable exacerbations and remissions, and variable response to therapy.

Most children are diagnosed between the age of 5 and 16 years old (less than 5% before 5 years of age). As many as 20% of patients have an affected relative. Features that distinguish IBD in children, versus the adult population, are the higher frequency of pancolonic involvement, likelihood of proximal extension of distal disease and risk of colectomy. Localization and quantification of inflammation in CD and UC are crucial to determining diagnosis, prognosis, and optimal therapy; especially because the small intestine has been particularly inaccessible to evaluation. Distinguishing the 2 diseases, monitoring their progression, and tailoring their therapy are major challenges, incompletely met by the currently available diagnostic tools.

The inflammation in UC begins in the rectum and extends proximally and continuously. Segmental disease does not occur. The mucosa in UC may reveal diffuse erythema, edema, a granular appearance, friability, and superficial ulceration that are never seen on the background of a normal mucosa. The inflammation is generally and characteristically limited to the lamina propria. Backwash ileitis consists of terminal ileal involvement in continuity with right colon inflammation. The typical clinical features of UC are a mixture of blood with stool and lower abdominal cramps during defecation. The complications of UC include rectal abscess, fistula, perforation, stricture, and rarely massive hemorrhage. Approximately 10% of patients have a single episode and 20% have persistent incapacitating disease.

In CD, the inflammation is often transmural and characterized by skip areas. The terminal ileum is frequently involved and the rectum is generally not involved. When the disease is diagnosed, the typical endoscopic findings are characterized by focal aphthoid ulcers surrounded by normal mucosa. As the disease progresses to more severe form, cobblestoning, loss of haustra, pseudopolyp, and foreshortening are seen more frequently. Complications of CD consist of obstruction, fistulas, abscesses, perianal disease and vitamin B-12 deficiency. Granulomas are present in no more than 60% of cases. Children with CD often exhibit growth difficulties preceding the diagnosis by several years. Patients with CD have greater morbidity than patients with UC. The site of disease is an important determinant of morbidity and prognosis as patients with colonic disease are more refractory to treatment.

Radiographic Evaluation

There is poor correlation between the anatomic findings depicted by CT or barium studies and the disease activity in patients with IBD.[106-108] Patients with mild-to-moderate colitis usually have normal radiological findings. Fluoroscopic methods show only indirect evidence for inflammation (edema, fibrosis, and ulceration), and entails considerable radiation exposure. ^{99m}Tc-WBC scintigraphy has been shown to be more sensitive than CT for detecting bowel wall inflammation in IBD.[109] Radiological methods tend to produce discomfort related to instrumentation or preparation for the procedure (eg, bowel cleansing). Several studies may be needed to analyze the entire bowel. Endoscopy is more sensitive than radiological studies and allows tissue to be obtained for histologic evaluation. The effective dose equivalent for a ^{99m}Tc-WBC study is approximately 3 mSv, whereas it is of the order of 6 mSv for a barium small bowel follow through or 8.5 mSv for a barium enema[110,111] Notwithstanding the numerous aforementioned disadvantages, cross sectional imaging with CT frequently is used to assess complications of IBD such as abscesses, strictures, and fistulas.

Evaluation With ^{99m}Tc-WBC

The biodistribution of ^{99m}Tc-WBC includes the presence of lung activity (partially cleared by 4 h), the excretion of ^{99m}Tc in the urine, and gallbladder visualization in about 10% of patients. The normal distribution of ^{99m}Tc-WBC is characterized by uptake in the lung, liver, spleen, bone marrow, kidney, and bladder.

Imaging Protocol

The labeling of leukocytes with ^{99m}Tc with 20 to 45 mL of venous blood has been described.[112] Imaging is performed with a large field of view gamma camera fitted with a low-energy, high-resolution collimator and images are obtained at 0.5 h and 2 to 3 h after the injection of ^{99m}Tc-WBC. If a single head camera is used, anterior 8-min and posterior 5-min images of the abdomen and pelvis are recorded in analog and digital form. For dual-head cameras, the same time may be used for both anterior and posterior images. Pelvic outlet views (tail on detector)[112] are also obtained, to distinguish bladder activity from rectal activity. Anterior views of the abdomen with the patient standing up are obtained to separate the transverse colon from the liver. The patient voids before each imaging. The lateral projection rarely confers additional information, and is, therefore, not routinely acquired. In patients suspected of having CD, anterior chest images may be performed with the upper limit of the field of view at the level of the mouth to evaluate for esophageal and gastric activity.

Two to 3 h after injection, and no later, an 8-min static-anterior supine view of the abdomen and pelvis is obtained followed by SPECT imaging. SPECT imaging provides superior localization of disease distribution with a slight increase in sensitivity for detection of inflammation.[113] Volume-rendered images using the maximum activity projection or maximum intensity projection technique also are derived from the SPECT data. The maximum activity projection images increases continuity of structures and facilitates understanding of spatial relationships.[114] This technique has advantages and limitations that have been enumerated.[113]

Timing of Imaging

The exact timing of the first and second sets of images varies from institution to institution.[115] In a series of 87 patients, Lantto[116,117] found a sensitivity of 88% for detecting IBD and abdominal infection at 30 minutes and 95% at 2 h. The temporal pattern of uptake of ^{99m}Tc-WBC suggests there is a small gain in sensitivity with images acquired at 3 to 4 h after injection of the radionuclide.[118] However, most (88%)[118] studies are positive by 30 min and the test can be terminated if needed (Fig. 5).

Delayed scans are associated with late physiologic excretion of ^{99m}Tc-WBC in the right lower quadrant. This was thought to be a shortcoming adversely affecting the accuracy of imaging the abdomen with ^{99m}Tc-WBC[116,117,119,120] These concerns have led to the suggestion by many to image patients early after injection of ^{99m}Tc-WBC to lower the number of false positives. In other reports, physiologic bowel uptake was not noted before 2 h and was rarely seen at 3 h.[112,121-125] This late accumulation (seen in 19% of controls)[126] is probably the result of the biliary excretion of noncell-bound ^{99m}Tc-labeled secondary hydrophilic complexes.[127] With time, because of bowel peristalsis, these complexes eventually accumulate and concentrate sufficiently to be visualized only on the late 4-h scans. Characterization of patterns that permit identification of this late physiologic excretion and its differentiation from active inflammation has been described.[126] One essential criterion to identify this physiologic activity is its migration with time into distal segments. Conversely, this does not apply to segments of bowel involved with acute inflammatory exacerbation of IBD. Additionally, the intensity of uptake in IBD is typically greater than this physiologic excretion of ^{99m}Tc-WBC.[126]

In most patients, at 2 to 3 h, this free activity is in the distal small bowel and migrates into the cecum at approximately 4 h. When these free complexes are in the distal small bowel one cannot identify a distinct segmental shape that would indicate a bowel segment (as seen in IBD), but rather the amalgam of many different segments.[126] In summary, physiologic late accumulation of ^{99m}Tc-WBC in the right lower quadrant is characterized by (1) accumulation at no less than

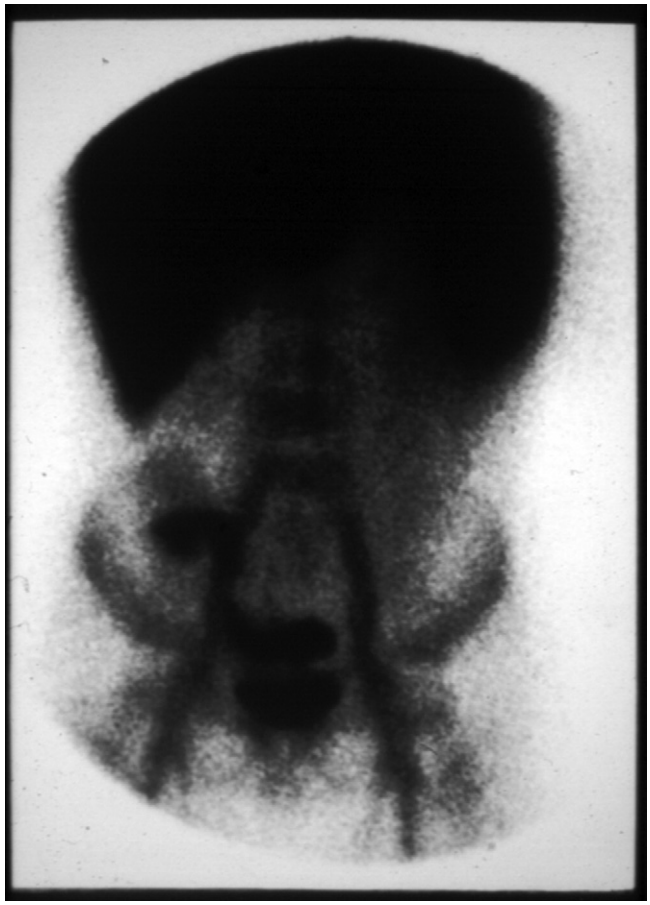

Figure 5 ^{99m}Tc-WBC anterior abdomino-pelvic image at 30 min. Intense continuous right lower-quadrant activity within the terminal ileum representing inflammation from Crohn's disease.

3 h, (2) no accumulation in other segments of the bowel, (3) faint accumulation of lesser intensity than the iliac crest, (4) a diffuse accumulation pattern, (5) migration of the ^{99m}Tc-WBC into the cecum over time. Recognition of this excretion pattern assures accurate differentiation of active CD of the small bowel from migration and accumulation of ^{99m}Tc-WBC in the right lower quadrant of the abdomen.

Interestingly, it has been shown that ^{99m}Tc-WBC activity correlates well with ESR level during inflammatory flare episodes in children with Crohn's disease. No such correlation was observed in children with UC.[128,129] Sixty-four pediatric patients were imaged using ^{99m}Tc-stannous colloid WBC imaging yielding a sensitivity of 88% and a specificity of 90%.[130] These results are comparable with those of other WBC imaging agents. Benefits of this labeling method over other WBC labeling methods were cited as lower cost, shorter preparation time, and smaller required blood volumes. Immunoscintigraphy using ^{99m}Tc-labeled antigranulocyte antibodies was performed on 66 children with histologically confirmed IBD.[131] Twenty-one children with suspected IBD subsequently not confirmed were used as controls. Immunoscintigraphy demonstrated high sensitivity for the detection of IBD in young patients compared with colonoscopy, enemas and ultrasonography, thus decreasing the rate of diagnostic delay in patients. However, the specificity of immunoscintigraphy was low, requiring histologic confirmation of positive cases. A prospective study using ^{99m}Tc-antigranulocyte monoclonal antibody imaging for the detection and assessment of inflammatory bowel disease in children showed poor sensitivity of detecting IBD per bowel segment on planar images with improved detection utilizing SPECT images.[132] ^{18}F-fluorodeoxyglucose PET imaging was performed in 25 pediatric patients with suspected IBD.[133] The overall sensitivity and specificity was determined to be 81% and 85%, respectively. In another study involving 65 children with abdominal pain, the use of ^{18}F-fluorodeoxyglucose-PET enabled researchers to correctly identify active IBD in 80% of children with IBD and showed no evidence of inflammation in children without IBD but present with recurrent abdominal pain.[134]

Advantages and Disadvantages

Scintigraphy with ^{99m}Tc-WBC has been reported to be sensitive for the detection of inflammation in adults[122,135-143] The correlation between scintigraphic and endoscopic findings is sufficiently close that scintigraphy can supplement left-sided colonoscopy in the event that total colonoscopy is technically impossible in selected cases[116,122,136,139,144-149] ^{99m}Tc-WBC scintigraphy can be used as a monitoring tool for inflammatory activity in place of colonoscopy.[150] Scintigraphy also can be used to document proximal extension of ulcerative proctosigmoiditis[151,152] or postoperative recurrence of CD.[153] The ^{99m}Tc-WBC scan is occasionally useful to assess the inflammatory component of a stricture seen on a small bowel follow-through studies. The combined use of the ^{99m}Tc-WBC scan and transabdominal bowel ultrasound has been shown to be accurate in the diagnosis of small bowel CD ([154]). The agreement between colonoscopy and ^{99m}Tc-WBC imaging for the localization and evaluation of the extent of inflammation is excellent. The ^{99m}Tc-WBC scan is superior to radiology procedures at showing the correct intensity and location of inflammation. The ^{99m}Tc-WBC scan seems ideally suited to obtain a precise temporal snapshot of the distribution[138] and intensity of inflammation in the large and small bowel while radiographic modalities of investigation tend to represent more chronic changes.[155-157] An additional advantage of the ^{99m}Tc-WBC study is high patient acceptability, especially children.[158] Three-dimensional images of ^{99m}Tc-WBC may be acquired and have the advantage of being easy to interpret, of showing the continuity of structures and allowing better differentiation of small bowel from large bowel. The ^{99m}Tc-WBC scan can be performed easily and should be readily available in any of the 5,000 facilities with nuclear medicine equipment in North America.

The ^{99m}Tc-WBC scan is noninvasive and can evaluate the entire bowel in just one study. The ^{99m}Tc-WBC scan produces less radiation exposure compared with barium radiograph studies and, thus, is quite useful when repeated evaluations are necessary.[110] The overall cost for endoscopy in children has been reported to be higher than that for ^{99m}Tc-WBC scanning ($3,500 vs $800).[155]

However, ^{99m}Tc-WBC scintigraphy has limitations. It is not useful in defining anatomic details such as prestenotic dilations, strictures or fistulas, which are best evaluated by barium radiographic studies. Occasionally, in a patient with CD when the uptake of ^{99m}Tc-WBC is focal it can be difficult to differentiate the large bowel from small bowel since landmarks are not clear. The presence of GI bleeding occurring at the same time as the ^{99m}Tc-WBC study can mimic IBD if late images are not obtained, ie, clearance of uptake from the initial site on the delayed images indicates the presence of a GI bleed.

Late accumulation of ^{99m}Tc-WBC in the right lower quadrant of the abdomen has been recognized as a potential limitation. However, criteria have been established to differentiate this late physiologic accumulation in the right lower quadrant from active IBD.[126] The scan does not allow for histologic evaluation, which may be necessary to confirm the diagnosis and exclude other entities, such as eosinophilic gastroenteritis, lymphoma, adenocarcinoma, or cytomegalovirus colitis.

Endoscopic and radiological methods of disease localization are more invasive when compared with the ^{99m}Tc-WBC scan and tend to produce more discomfort related to instrumentation and preparation for the procedure (eg, bowel cleansing). Moreover, several studies may be needed to analyze the entire bowel. The ^{99m}Tc-WBC scan is practical and safe even in acutely ill patients who may not tolerate an endoscopic or radiological study. Although the ^{99m}Tc-WBC scans cannot replace endoscopy, it is complementary in most patients. The ^{99m}Tc-WBC scans are superior to radiology procedures in depicting the intensity and location of inflammation. The ^{99m}Tc-WBC scan has a role in the initial evaluation, and follow-up of patients with IBD.

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