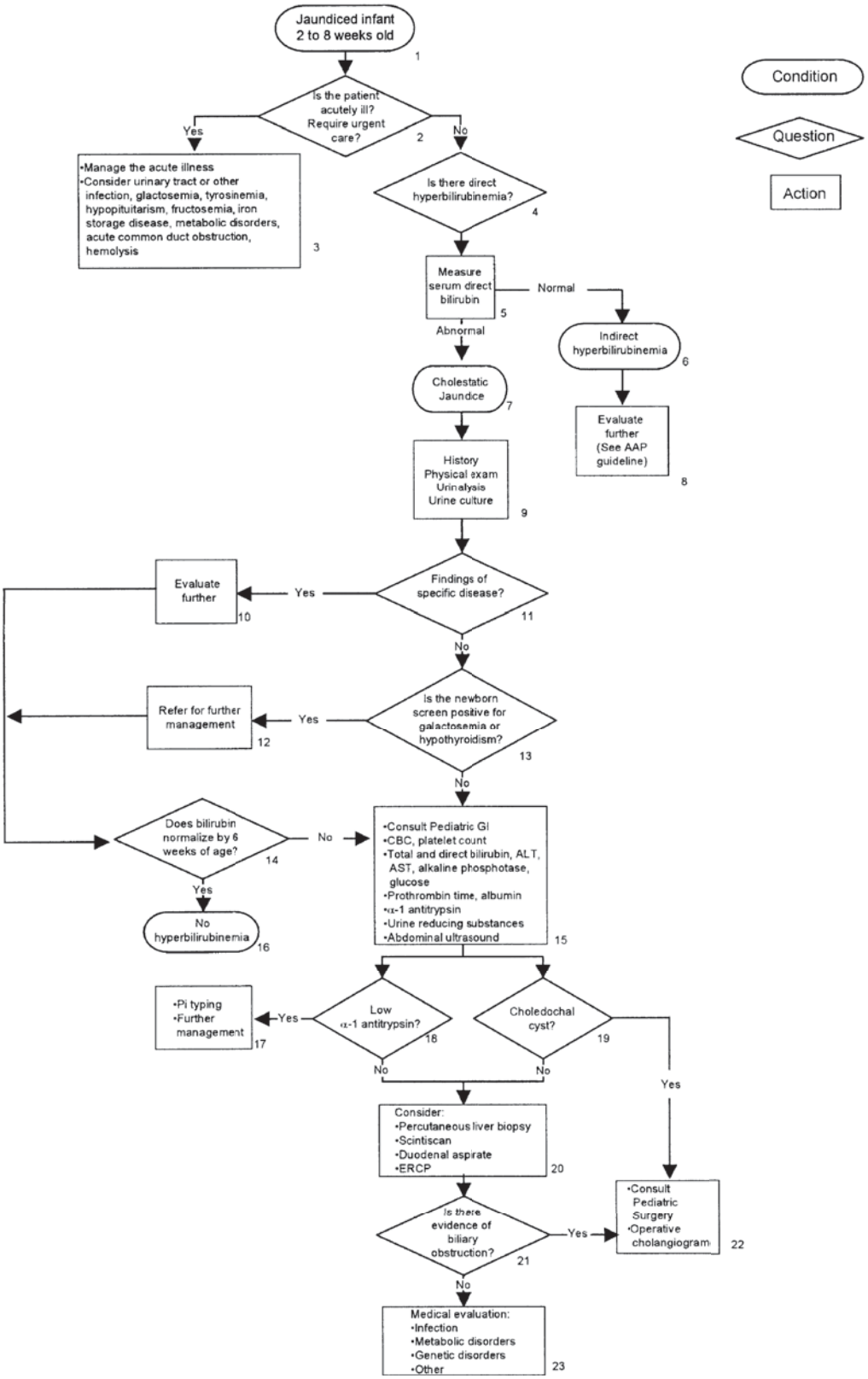

FIG. 1. Cholestasis clinical practice guideline. Algorithm for a 2- to 8-week-old infant. (North American Society for Pediatric Gastroenterology, Hepatology & Nutrition Cholestasis Guideline Committee.)

TABLE 2. Parameters of clinical interest in the history of the cholestatic infant

Family history	
Consanguinity	Increased risk of autosomal recessive disorders
Neonatal cholestasis in the parents or siblings	Cystic fibrosis, α-1-antitrypsin deficiency, progressive familial intrahepatic cholestasis, Alagille syndrome are all genetic conditions causing neonatal cholestasis
History of repeated fetal loss or early demise	Gestational alloimmune liver disease
Spherocytosis and other hemolytic diseases	Known to aggravate conjugated hyperbilirubinemia
Prenatal history	
Prenatal ultrasonography findings	Presence of choledochal cyst, cholelithiasis, bowel anomalies or concern for syndrome
Cholestasis of pregnancy	May be seen in heterozygotes for *PFIC* gene mutations; mitochondrial disorder
Acute fatty liver of pregnancy	Neonatal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency
Maternal infections	TORCH infections
Infant history	
Gestational age	Prematurity as a risk factor for neonatal hepatitis
SGA	Increased risk of neonatal cholestasis, congenital infections
Alloimmune hemolysis; glucose-6-P-dehydrogenase deficiency; hydrops fetalis	Increased risk of neonatal cholestasis
Neonatal infection	Urinary tract infection, sepsis related cholestasis, CMV, HIV, syphilis, etc
Newborn screen	Panhypopituitarism galactosemia, fatty acid oxidation defects, cystic fibrosis
Source of nutrition: breast milk, formula, PN	Galactosemia, hereditary fructose intolerance, PN-associated liver disease
Growth	Genetic and metabolic disease
Vision	Septo-optic dysplasia
Hearing	PFIC1, TJP2
Vomiting	Metabolic disease, bowel obstruction, and pyloric stenosis
Stooling	Delayed stooling: CF, panhypopituitarism; diarrhea: infection, metabolic disease
Stool color	Acholic stools: cholestasis, biliary obstruction
Urine characteristics: smell and color	Dark urine (conjugated hyperbilirubinemia), metabolic disease
Excessive bleeding	May indicate coagulopathy, vitamin K deficiency
Disposition: irritability, lethargy	Metabolic disease or sepsis, panhypopituitarism
Abdominal surgery	Necrotizing enterocolitis, intestinal atresia

CF = cystic fibrosis; CMV = cytomegalovirus; HIV = human immunodeficiency virus; PFIC = progressive familial intrahepatic cholestasis; PN = parenteral nutrition; TJP = tight-junction protein; TORCH = Toxoplasma gondii, other viruses, rubella, cytomegalovirus, and herpes simplex virus.

Please refer to the American Academy of Pediatrics guidelines for the management of unconjugated hyperbilirubinemia in the newborn infant 35 or more weeks of gestation (77).

Recommendations:

1. *Any formula-fed infant noted to be jaundiced after 2 weeks of age should be evaluated for cholestasis with measurement of total and conjugated (direct) serum bilirubin (1A). Depending upon local practice, breast-fed babies that appear otherwise well may be followed clinically until 3 weeks of age, at which time if they appear icteric should then undergo serum evaluation of total and conjugated (direct) serum bilirubin.*
2. *Measurements of serum bilirubin should always be fractionated into unconjugated (indirect) or conjugated (direct) hyperbilirubinemia (1A).*
3. *Conjugated (direct) hyperbilirubinemia (>1.0 mg/dL, 17 μmol/L) is considered pathological and warrants diagnostic evaluation (1A).*

TABLE 3. Physical findings in children with neonatal cholestasis

Assessment of general health	Ill appearance may indicate infection or metabolic disease, infants with biliary atresia typically appear well
General appearance	Dysmorphic features: Alagille syndrome in the neonate rarely exhibits characteristic facial appearance with a broad nasal bridge, triangular facies, and deep-set eyes. Typical facial features may appear at around 6 months of age, but are often nonspecific (69)
Vision/slit lamp examination	
Hearing	Congenital infection, storage disease, septo-optic dysplasia, posterior embryotoxon, cataracts
Congenital infections, PFIC1, TJP2, mitochondrial	
Cardiac examination: murmur, signs of heart failure	Congenital heart disease: Alagille syndrome, biliary atresia splenic malformation syndrome
Abdominal examination	Presence of ascites; abdominal wall veins, liver size and consistency, spleen size and consistency (or absence thereof), abdominal masses, umbilical hernia
Stool examination (crucial—the primary physician should make every effort to view stool pigment)	Acholic or hypopigmented stools suggest cholestasis or biliary obstruction
Neurologic	Note overall vigor and tone

PFIC = progressive familial intrahepatic cholestasis; TJP = tight-junction protein.

TABLE 4. Targeted investigations of the persistently cholestatic infant

- Tier 1: Aim to evaluate after cholestasis has been established in order to both identify treatable disorder as well as to define the severity of the liver involvement
  - Blood—CBC + differential, INR, AST, ALT, AP, GGTP, TB, DB (or conjugated bilirubin), albumin and glucose. Check α-1-antitryspin phenotype (Pi typing) and level, TSH, T4 if newborn screen results not readily available
  - Urine—urinalysis, culture, reducing substances (rule out galactosemia)
  - Consider bacterial cultures of blood, urine and other fluids especially if infant is clinically ill.
  - Verify results of treatable disorders (such as galactosemia and hypothyroidism) from newborn screen
  - Obtain fasting ultrasound
- Tier 2: Aim to complete a targeted evaluation in concert with pediatric gastroenterologist/hepatologist
  - General—TSH and T4 values, serum bile acids, cortisol
  - Consideration of specific etiologies
    - Metabolic—serum ammonia, lactate level, cholesterol, red blood cell galactose-1-phosphate uridyltransferase, urine for succinylacetone and organic acids. Consider urine for bile salt species profiling
    - ID—direct nucleic acid testing via PCR for CMV, HSV, listeria
    - Genetics—in discussion with pediatric gastroenterologist/hepatologist, with a low threshold for gene panels or exome sequencing
  - Sweat chloride analysis (serum immunoreactive trypsinogen level or CFTR genetic testing) as appropriate
  - Imaging
    - CXR—lung and heart disease
    - Spine—spinal abnormalities (such as butterfly vertebrae)
    - Echocardiogram—evaluating for cardiac anomalies seen in Alagille syndrome
    - Cholangiogram
  - Liver biopsy (timing and approach will vary according to institution and expertise)
  - Consideration for consultations
    - Ophthalmology
    - Metabolic/Genetic (consider when to involve, especially when there is consideration for gene panels or whole exome sequencing)
    - Cardiology/ECHO (if murmur present or has hypoxia, poor cardiac function)
    - General pediatric surgery
    - Nutrition/dietician

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CBC = complete blood count; CFTR = cystic fibrosis trans-membrane receptor; DB = conjugated (direct) bilirubin; ECHO = echocardiogram; GGTP = gamma-glutamyl transferase; HSV = herpes simplex virus; ID = infectious diseases; INR = international normalized ratio; PCR = polymerase chain reaction; TB = total bilirubin; TSH = thyroid-stimulating hormone.

investigations (Table 4, Tier 1) are recommended. A disciplined and stepwise approach to the infant with confirmed cholestasis in concert with a pediatric gastroenterologist/hepatologist can then follow in the ordering of laboratory tests appropriate in each situation, and enabling a targeted workup (Table 4, Tier 2). Some local variation is unavoidable because of available expertise (Table 4). ''Red flags,'' which mandate evaluation for BA include acholic stools, high GGT cholestasis without alternative etiology, and abnormal or absence of gallbladder on ultrasound. Conditions that mimic BA such as α-1-antitrypsin deficiency, CF, ALGS, and others should be excluded early on in the evaluation process.

DIAGNOSTIC IMAGING

A fasting abdominal ultrasound is an easy and noninvasive first diagnostic imaging investigation to assess for visible obstructing lesions of the biliary tree or identification of choledochal cyst, and to assess for signs of advanced liver disease or vascular and/or splenic abnormalities (89). Several hepatic sonographic parameters such as the triangular cord sign, abnormal gall bladder morphology, lack of gall bladder contraction after oral feeding, nonvisualization of the common bile duct, hepatic artery diameter, and hepatic artery diameter to portal vein diameter ratio, subcapsular blood flow have been suggested to aid in the diagnosis of BA (90–94), although none can singularly confirm a diagnosis of BA. It is useful, however, to know that many, but not all, infants with BA have a small or undetectable gall bladder (95). In addition, findings such as abdominal heterotaxy, midline liver, polysplenia, asplenia, and preduodenal portal vein increase the concern for BA with malformations. It is imperative to remember that a normal ultrasonography (US), however, does not rule out nonsyndromic BA.

Hepatobiliary scintigraphy (HBS) has been used to confirm biliary tract patency, but can be limited by its low specificity (range 68.5%–72.2%), and a nondiagnostic result when bile flow is limited as a result of a wide variety of etiologies (96). Patients with interlobular bile duct paucity, idiopathic neonatal hepatitis, low birth weight, and those on PN may have nonexcreting scans (97). This limited accuracy of HBS in differentiating idiopathic neonatal hepatitis from BA was demonstrated in a study by Yang et al (98) in which magnetic resonance cholangiopancreatography (MRCP), US, technetium 99m-iminodiacetic acid HBS, HBS single photon emission computed tomography (HBS SPECT), and liver biopsy were compared. The goal of this study of 69 infants with cholestatic jaundice and a final diagnosis of idiopathic neonatal hepatitis, and BA was to determine which modality may help distinguish between these 2 diagnoses. All of the 69 infants underwent MRCP, US, HBS, SPECT, and liver biopsy. HBS had sensitivity and a specificity of 88.2% and 45.7% for detecting BA, respectively, with an accuracy of 66.7%. Scintigraphy adds little to the routine evaluation of the cholestatic infant, but may be of value in determining patency of the biliary tract, thereby excluding BA. In this study, liver biopsy had the highest sensitivity in detecting BA at 100%, a specificity of 94.3% and an accuracy rate of 96.9%.

A recent meta-analysis addressing the utility of HBS yielded a pooled sensitivity of 98.7% (98.1–99.2%) and a specificity of 70.4% (range 68.5%–72.2%) of a nondraining HBS for excluding BA. This shows that false negative results (excretion of the tracer into the bowel despite BA) are extremely rare (96). Limited reports describe infants with apparently initially excreting HBS and a subsequent diagnosis of BA, although the technical limitations of the study may have been a factor in its utility (100,101).

Many clinicians and radiologists administer phenobarbital for 5 days before the study, in an attempt to enhance biliary excretion of the isotope and increase its discriminatory value (99), which often unnecessarily delays the diagnosis of BA and the necessary HPE (57,89). Further work is necessary to assess the utility of premedication for HBS (100,101).

Despite the use of the diagnostic tests described above, it is still not easy to discriminate between BA and other causes of neonatal cholestasis. As detection of patency of the extrahepatic biliary tree is the primary goal of diagnostic evaluations in infants with cholestasis, the role of endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of BA has been studied by various groups (102,103). Although ERCP has proved effective with high positive and negative predictive values for BA (sensitivity 86%–100%, specificity 87%–94%, positive predictive value 88%–96%, negative predictive value 100%) (102,104), ERCP requires an