Hepatomegaly in Neonates and Children

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OBJECTIVES

After completing this article, readers should be able to:

1. **Identify the possible causes of simultaneous hepatomegaly and splenomegaly.**
2. **List the important diagnostic considerations in patients who have hepatomegaly.**
3. **Delineate the most helpful initial radiographic test.**
4. **Describe what clinical findings occurring concomitantly in a patient who has hepatomegaly suggest metabolic or storage disease.**
5. **List the risk factors for infectious hepatitis.**

Introduction

Hepatomegaly can represent intrinsic liver disease or may be the presenting physical finding of a generalized disorder. Early diagnosis and treatment of children who have liver disease is important because specific treatments are available for some diseases that can prevent disease progression or hepatic failure.

The presence of a palpable liver does not always indicate hepatomegaly. Normal liver size is based on normative values of liver span by percussion, degree of extension below the right costal margin, or length of the vertical axis estimated from imaging techniques. In general, a liver edge greater than 3.5 cm in newborns and greater than 2 cm in children below the right costal margin suggests enlargement. Liver span is determined by measuring the distance between the upper edge, determined by percussion, and the lower edge, determined by palpation, in the midclavicular line. The lower border also may be determined by auscultation. With the stethoscope placed below the xiphoid, the examiner should gently scratch superiorly, starting in from the right lower quadrant, and listen for sound enhancement as the finger passes over the liver edge. Liver span increases linearly with body weight and age in both genders and correlates more with weight than with height. The normal range for liver span by percussion at 1 week of age is 4.5 to 5 cm. At 12 years, the normal value for boys is 7 to 8 cm and for girls is 6 to 6.5 cm.

The liver can be displaced inferiorly by the diaphragm or thoracic organs, giving the impression of hepatomegaly. Accumulation of fluid or air in the thorax (eg, pneumothorax) also may displace the liver inferiorly. A retroperitoneal mass, choledochal cyst, or perihepatic abscess also may be mistaken for hepatomegaly. Children who have orthopedic abnormalities such as narrow chest walls or pectus excavatum can erroneously appear to have hepatomegaly. A normal variant of the right lobe of the liver, called a Riedel lobe, may extend far below the right costal margin and be confused as pathologic hepatic enlargement. However, patients who have a Riedel lobe will have no signs, symptoms, or laboratory evidence of liver disease.

Pathogenesis

Hepatomegaly generally occurs via five mechanisms: inflammation, excessive storage, infiltration, congestion, and obstruction (Table 1). Infections from viruses, bacteria, fungi, and parasites promote inflammation-induced hepatomegaly. Toxins, radiation, autoimmune disease, and Kupffer cell hyperplasia also may cause hepatomegaly by this mechanism.

Storage products that accumulate in the enlarged liver include glycogen, fats, metals, and abnormal proteins. Glycogen storage occurs in glycogen storage disease and diabetes mellitus and in some patients receiving parenteral nutrition. Steatosis, the accumulation of fat in the liver, occurs most commonly in overweight children and less commonly in the presence of certain metabolic diseases and diabetes. Metals and abnormal proteins can be stored inappropriately in the liver. For example, hepatomegaly is caused by the accumulation of copper in Wilson disease and the accumulation of abnormal protein in alpha-1-antitrypsin deficiency.

Cellular infiltration can occur from primary tumors of the liver or metastatic disease. Primary tumors can be malignant or benign. Malignant tumors include hepatoblastoma or hepatocellular carcinoma. Benign tumors include hemangiomas, teratomas, and focal nodular hyperplasia. Metastatic infiltration occurs in leukemia, lymphoma, neuroblastoma, and histiocytosis. Parasitic cysts, although uncommon in North America, are a common cause of liver enlargement worldwide. Extramedullary hematopoiesis and hemophagocytic syndrome cause hepatomegaly due to infiltration by blood cells.

Congestive blood flow in the liver causes hepatomegaly. Suprahepatic obstruction from congestive heart failure, restrictive pericardial disease, hepatic vein thrombosis (Budd-Chiari), or suprahepatic vascular webs are examples. Veno-occlusive disease causes hepatomegaly by obstructing intrahepatic blood flow. This problem occurs mainly in bone marrow transplant patients. Lastly, obstruction of biliary flow causes hepatic enlargement. This may be due to tumors outside the liver or congenital and acquired problems of the biliary system. Biliary atresia, choledochal cysts, and cholelithiasis are examples of diseases in which bile flow is obstructed.

History

A thorough evaluation of hepatomegaly should begin with a com-

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TABLE 1. Mechanisms of Hepatomegaly and Representative Diseases

MECHANISM	REPRESENTATIVE DISEASES
Inflammation	• Infections • Toxins • Drugs • Neonatal hepatitis • Autoimmune disease • Kupffer cell heperplasia
Inappropriate Storage	• Glycogen Glycogen storage disease, diabetes mellitus, parenteral nutrition • Lipids Wolman disease, Neimann-Pick disease, Gaucher disease • Fat Fatty acid oxidation defect, obesity, diabetes mellitus, parenteral nutrition, mucopolysaccharidoses types I through IV • Metals Copper: Wilson disease Iron: hemochromatosis • Abnormal proteins Alpha-1-antitrypsin Carbohydrate-glycoprotein deficiency
Infiltration	• Primary neoplastic tumors Hepatoblastoma/Hepatocellular carcinoma • Primary non-neoplastic tumors Hemangioma, hemangioendothelioma, teratoma, focal nodular hyperplasia • Metastatic or disseminated tumors Leukemia, lymphoma, neuroblastoma, histiocytosis • Cysts Parasitic cyst, choledochal cyst, polycystic liver disease • Hemophagocytic syndromes • Extramedullary hematopoiesis
Vascular Congestion	• Suprahepatic Congestive heart failure Restrictive pericardial disease Suprahepatic web Hepatic vein thrombosis (Budd-Chiari syndrome) • Intrahepatic Veno-occlusive disease
Biliary Obstruction	• Cholelithiasis • Choledochal cyst • Biliary atresia • Tumors Hepatic Biliary Pancreatic Duodenal

plete history. In the neonate, a history of hyperbilirubinemia after 2 weeks of age requires rapid assessment of the underlying disorder to rule out extrahepatic biliary atresia. A family history of early infant death or hepatic, neurodegenerative, or psychiatric disease suggests a metabolic etiology. Eliciting a careful birth history may uncover risk factors for perinatally acquired infections, such as maternal intravenous drug use, maternal infections, or previous blood transfusions. Prenatal history of Rh or ABO incompatibility suggests isoimmunization and hemolysis as the cause of hepatomegaly. Maternal infections that can be transmitted to the fetus or neonate include hepatitis B, toxoplasmosis, syphilis, cytomegalovirus, rubella, herpes simplex, enterovirus, rubella, and human immunodeficiency virus. A history of an umbilical catheter increases the risk for hepatic abscess. A history of prolonged hyperbilirubinemia in infancy

may point to cystic fibrosis or alpha-1-antitrypsin deficiency. Delayed passage of meconium also suggests cystic fibrosis.

In the child and adolescent, careful questioning about foreign travel, ingestion of shellfish or drugs, and environmental toxins may reveal risk factors for acute hepatitis or parasitic disease. A history of poor weight gain, vomiting, diarrhea, distinctive odors, loss of developmental milestones, complex seizure disorder, or hypotonia suggests a metabolic disease. A history of hyperbilirubinemia with or without acholic stools and dark urine indicates hepatic dysfunction. Acholic stool usually suggests obstruction of the biliary tract, but it also can be seen in severe hepatocellular injury. Acute onset of hepatomegaly associated with hyperbilirubinemia in an older child raises the suspicion of infection with hepatitis A. Exposure to blood products, having a tattoo, and illicit intravenous drug use are risk factors for hepatitis C and B infection. Commonly used medications that may cause hepatic enlargement include nonsteroidal anti-inflammatory agents, isoniazid, propylthiouracil, and sulfonamides. Systemic symptoms related to chronic inflammatory diseases should be sought in the older child who has hepatomegaly. A history of inflammatory bowel disease or immunodeficiency increases the likelihood for primary sclerosing cholangitis.

Physical Examination

A careful physical examination often can narrow the diagnostic considerations (Table 2). In addition to size, liver nodularity and firmness should be assessed. Auscultation over the liver may detect bruits or increased flow to the liver. The stigmata of generalized disease processes should be sought. Jaundice (yellowing of the skin and sclera) usually becomes apparent when the serum bilirubin concentration reaches 34.2 to 51.3 mcmol/L (2 to 3 mg/dL). Other nonspecific signs and symptoms of hepatic disease include fatigue, anorexia, weight loss, blood in the stool, and abdominal distention. Signs of chronic liver disease, such as spider angiomas, xanthomas, and palmar erythema, are more common among adults. Fever suggests a systemic illness or infection. A neonatal history of intrauterine growth retardation, microcephaly, chorioretinitis, and purpura accompanied by hepatomegaly strongly suggests congenital infection, which will allow the clinician to tailor the diagnostic evaluation accordingly.

TABLE 2. Useful Signs and Symptoms in the Diagnosis of Hepatomegaly

SIGN/SYMPTOM	POSSIBLE DIAGNOSIS
Fever	Systemic illness Acute and chronic hepatitis Viral infections Hepatic abscess Hemophagocytic lymphohistiocytosis
Abdominal Findings Splenomegaly Palpable cyst Hepatic bruit	Portal hypertension Storage disease Infiltration Reticuloendothelial hyperplasia Hemangiomatosis
Vomiting/Diarrhea	Reye and Reye-like syndromes Fatty acid oxidation disorders Congenital lactic acidemias Organic acidemias Urea cycle defects Glycogen storage disease types 1 and 3 Hereditary fructose intolerance Fulminant hepatic failure Wolman disease
Failure to Thrive/ Developmental Delay	Glycogen storage disease Hereditary fructose intolerance Organic acidemias Wolman disease Cystic fibrosis
Distinctive Odors	Organic acidemias Hepatic failure
Neurologic Deterioration	Peroxisomal disorders Zellweger syndrome Lysosomal storage disease Neimann-Pick disease Gaucher disease G_{M_1} gangliosidosis Mucopolysaccharidosis Wilson disease
Skin Findings Cutaneous hemangioma Papular acrodermatitis Purpura	Hemangiomatosis Viral hepatitis TORCH infections
Eye Findings Cataracts Kayser-Fleischer rings Chorioretinitis Posterior embryotoxon	Wilson disease TORCH infections Alagille syndrome
Dysmorphic Features	Metabolic and storage diseases Alagille syndrome

Portal hypertension, hepatic infiltration by malignant cells, or storage disease cause splenomegaly as well as hepatomegaly. Other signs of portal hypertension include ascites or a prominent abdominal venous pattern. Massive splenomegaly is more common with storage diseases and malignancies than with portal hypertension. An altered sensorium may be due to a metabolic disease. Failure to thrive and hepatomegaly in infancy result from a metabolic disease such as glycogen storage, hereditary fructose intolerance, galactosemia, or cystic fibrosis. If the patient has a distinctive breath or urine odor, consider organic acidemias. Cutaneous hemangiomas or a hepatic bruit suggests hemangiomatosis. Patients who exhibit progressive neurologic deterioration may have glycogen or lipid storage disease or Wilson disease. The constellation of mongoloid facies, hypotonia, and neurologic deterioration suggests Zellweger syndrome, a disorder of peroxisomal function. Coarse facial features are seen with the mucopolysaccharidoses. Ocular findings of Kayser-Fleischer rings or cataracts occur in Wilson disease. Papular acrodermatitis (or Gianotti-Crosti syndrome) is a self-limiting dermatosis that may be seen in patients who have viral hepatitis.

Laboratory Studies

Useful laboratory tests for patients who have hepatomegaly are listed in Table 3. Routine evaluations include a complete blood count with differential count and smear, serum chemistry with hepatic profile, and urinalysis and urine culture. Results of the history and physical examination should tailor the laboratory evaluation and suggest the need for further diagnostic testing. Laboratory studies must be interpreted in the context of age-related changes because many hepatic enzyme levels fluctuate substantially with age. Two true "liver function tests" are measurement of serum albumin and prothrombin time, which assess the synthetic function of the liver directly and may be helpful in monitoring responses to therapy and suggesting a prognosis. The presence of hyperbilirubinemia in a patient who has hepatomegaly suggests cholestasis or hemolytic disease. Cholestatic disease causes predominantly elevations in congugated bilirubin, alkaline phosphatase, and gamma glutamyl transpeptidase. Bilirubin can be fractionated to distinguish between hepatic dysfunction (conjugated/direct bilirubin) and hemolytic

TABLE 3. Diagnostic Tests Useful in the Evaluation of the Patient Who Has Hepatomegaly

TYPE OF STUDIES	USEFUL STUDIES	STUDIES TO CONSIDER
Laboratory	Urinalysis Complete blood count Reticulocyte count Electrolytes Glucose Total protein Serum albumin Serum aminotransferases Fractionated bilirubin Alkaline phosphatase Prothrombin time	Erythrocyte sedimentation rate Ammonia Lactic acid, pyruvic acid Triglycerides Carnitine, acylcarnitine Plasma amino acids Urine organic acids Fibrinogen D-dimers TORCH titers Hepatitis serologies Alpha-fetoprotein Purified protein derivative of tuberculin Sweat chloride Ceruloplasmin Twenty-four-hour urinary copper excretion Blood culture Stool for ova and parasites Ferritin TIBC Serum alpha-1-antitrypsin Antinuclear antibodies Anti-smooth muscle antibodies Anti-liver/kidney microsomal antibodies
Imaging	Abdominal ultrasonography with Doppler flow	Abdominal computed tomography or magnetic resonance imaging Radionuclide biliary scan Cholangiography Cardiac ultrasonography
Pathology	Liver biopsy	Bone marrow biopsy

disease or congenital disorders of bilirubin metabolism (unconjugated/indirect bilirubin).

Hepatocellular injury results in a predominant rise in hepatic aminotransferases, which suggests a viral or toxic insult. Alanine aminotransferase is more liver-specific than aspartate aminotransferase, which also is found in other tissues such as muscle. Because cholestasis results in some hepatocyte injury, the pattern of laboratory abnormalities may not be distinct. However, the rise in aminotransferases will be higher than the rises in alkaline phosphatase and gamma-glutamyl transferase levels. The degree of aminotransferase elevation does not correlate well with clinical prognosis; declining aminotransferase levels may indicate a decrease in functioning hepatocytes from ongoing necrosis.

Hepatic synthetic function is assessed by serum albumin and prothrombin time. Prothrombin time rapidly reflects changes in hepatic synthetic function because of the short half-life of some clotting factors. Prolonged prothrombin time may be the result of malabsorption of vitamin K. A decrease in albumin indicates a more chronic problem, but it also may indicate another process, such as protein-losing enteropathy and chronic infection.

Measurement of serum glucose, ketones, lactic acid, pyruvic acid, amino acids, and uric acid along with urine organic acids is helpful when a metabolic defect is suspected.

Imaging Studies

Imaging studies can help define the problem and direct further diagnostic evaluations. Plain films generally are not useful diagnostically, except in certain cases. The liver may appear denser with iron storage or less dense with fatty infiltration. Calcifications in the liver, the vasculature, or the biliary tree may suggest malignancy or parasites, portal vein thrombosis, or gallstones, respectively.

Ultrasonography with Doppler flow imaging of hepatic vessels usually is the most helpful initial study. It can determine the size and consistency of the liver and visualize mass lesions as small as 1 cm. Ultrasonography is the imaging modality of choice for the biliary tree. It can identify stones, biliary sludge, and biliary anatomy. Hepatic and portal vein blood flow and collateral circulation also are assessed by Doppler ultrasonography.

Computed tomography (CT) or magnetic resonance imaging (MRI) may be superior to ultrasonography in detecting small focal lesions, such as tumors, cysts, or abscesses. When a tumor is suspected, CT is useful to define its extent. CT may be superior for detecting subtle differences in liver density. CT or MRI may differentiate obstructive from nonobstructive causes of cholestasis.

Radionuclide scanning is most helpful in the young infant to distinguish biliary atresia from neonatal hepatitis. In biliary atresia, hepatic uptake of the radionuclide is normal, but excretion into the intestine is absent. In neonatal hepatitis, uptake by the diseased liver parenchyma is impaired, but there is excretion into the intestines. Biliary atresia is diagnosed definitively by cholangiography.

Cholangiography directly visualizes the intra- and extrahepatic biliary tree, which is useful to define cause, extent, and level of obstruction. Intraoperative cholangiography is the method of choice in neonates for ruling out atresia; endoscopic cholangiography is an alternate and less invasive method for older children. Magnetic resonance cholangiopancreatography is a newer noninvasive modality for visualizing the biliary tree.

Pathology

Percutaneous liver biopsy can be performed in infants as young as 1 week of age. This procedure provides adequate tissue for both histologic and biochemical analyses. Clinical history, laboratory studies, and liver histology provide the diagnosis in the majority of cases of hepatomegaly. The histology demonstrates diseases of the parenchyma, provides tissue for enzyme quantitation, and identifies stored material.

Diagnostic Evaluation of the Neonate

The most frequent causes of hepatomegaly in a neonate are listed in Table 4A. A diagnostic approach to the neonate who has hepatomegaly is outlined in Figure 1. This algorithm is designed to discriminate among the most common diagnostic possibilities. The evaluation of hepatomegaly without splenomegaly in the neonate who has conjugated hyperbilirubinemia should proceed rapidly to exclude biliary atresia because diagnosis and surgical correction are most likely to be successful in establishing bile flow if performed by 8 to 10 weeks of life. A small or absent gallbladder also suggests biliary atresia. A radionuclide excretion study that shows no excretion into the duodenum is suspicious for biliary atresia. These patients should undergo liver biopsy. If the pathology is consistent with the diagnosis of biliary atresia, intraoperative cholangiography should be used to confirm the diagnosis before undertaking a Kasai hepatoportoenterostomy. Further evaluation for a specific cause of liver dysfunction is pursued if liver biopsy is not consistent with biliary atresia. Ultrasonography can identify choledochal cysts or other obstructing mass lesions. Idiopathic neonatal hepatitis is diagnosed after known causes of neonatal hepatitis are excluded. Conjugated hyperbilirubinemia associated with splenomegaly, failure to thrive, or vomiting suggests congenital infection, sepsis, or metabolic disease.

Unconjugated or mixed hyperbilirubinemia associated with splenomegaly suggests congenital infections, increased portal pressures, or extramedullary hematopoiesis. Findings on the physical examination will guide further diagnostic studies to identify the disorders, such as abdominal ultrasonography with Doppler flow, cardiac ultrasonography, or a bone marrow biopsy.

Hepatosplenomegaly in an infant who has no hyperbilirubinemia suggests an obstructive or infiltrative cause. Abdominal ultrasonography is

TABLE 4. Causes of Hepatomegaly by Age

A. NEONATE		B. CHILD	
COMMON	**UNCOMMON**	**COMMON**	**UNCOMMON**
Biliary tract obstruction	Hepatoblastoma/hemangiomatosis	Anemias	Autoimmune hepatitis
Congestive heart failure	Hemophagocytic syndrome/ histiocytosis	Biliary obstruction	Alpha-1-antitrypsin deficiency
Drugs	Isoimmunization	Congestive heart failure	Budd-Chiari syndrome
Maternal diabetes	Neuroblastoma	Cystic fibrosis	Constrictive pericarditis
Malnutrition		Drugs	Diabetes mellitus
Metabolic disorders		Leukemia/lymphoma	Gaucher disease
Parenteral nutrition		Obesity	Hemangiomas
Pseudohepatomegaly		Parasitic infections	Hepatic abscess
Sepsis		Parenteral nutrition	Hepatoblastoma
Storage diseases		Sepsis	Hepatocellular carcinoma
Viral hepatitis/TORCH infections		Systemic infections	Immune deficiencies
		Viral hepatitis	Metastatic tumors
			Neiman-Pick disease
			Other metabolic diseases
			Primary sclerosing cholangitis
			Systemic juvenile rheumatoid arthritis
			Systemic lupus erythematosus
			Veno-occlusive disease
			Wilson disease

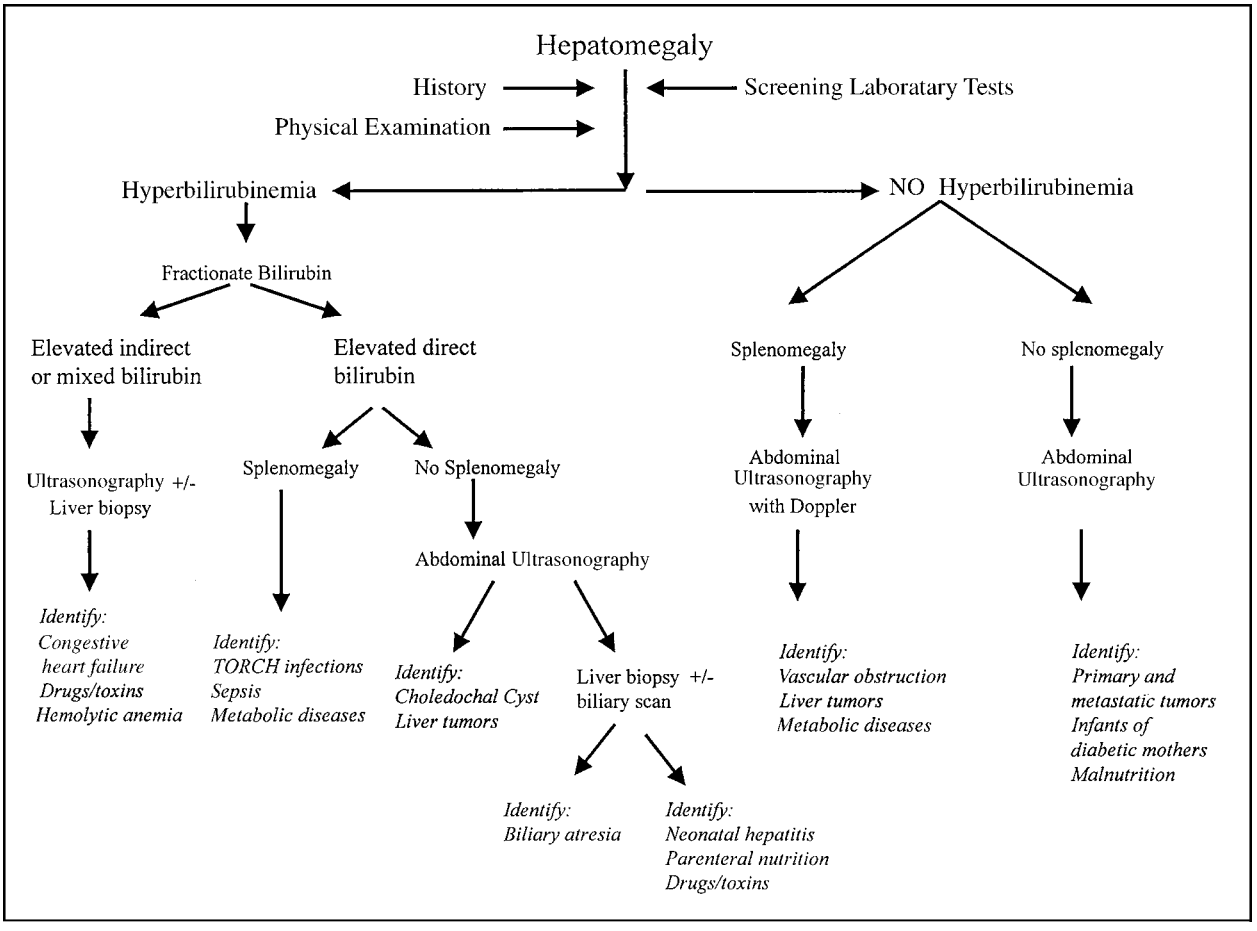

FIGURE 1. Diagnostic algorithm to arrive at the most common diagnoses for a neonate who has hepatomegaly.

indicated to evaluate liver consistency, patency of venous flow, and mass lesions. Liver biopsy is diagnostic for infiltrative diseases.

Hepatomegaly without hyperbilirubinemia or splenomegaly and ultrasonographic findings that are nondiagnostic usually lead to liver biopsy. Primary and metastatic tumors and storage diseases are diagnosed definitively by analysis of liver tissue.

Diagnostic Evaluation of the Older Child and Adolescent

The most common causes of hepatomegaly in children older than 1 year of age are listed in Table 4B.
A diagnostic approach for the older child is outlined in Figure 2. A complete history and physical examination often lead to the diagnosis, with only confirmatory testing necessary. For example, a history of known cystic fibrosis makes an extensive evaluation for hepatomegaly unnecessary. The presence of hyperbilirubinemia with associated elevated conjugated bilirubin and elevated aminotransferases prompts an evaluation for viral hepatitis. Other less common disorders that present similarly are drug or toxin exposures, autoimmune hepatitis, and Wilson disease. In the absence of positive serologies for viral hepatitis, testing for these diseases is warranted. Liver biopsy may be necessary to establish, direct, stage, or confirm the diagnosis.

Patients who have conjugated hyperbilirubinemia with a cholestatic pattern of liver test abnormalities usually have an obstructive process and benefit from ultrasonography and possibly cholangiography.

Patients who have an elevated unconjugated bilirubin level and an elevated reticulocyte count should be evaluated for hemolytic disease. Congestive heart failure, restrictive pericardial disease, and infections should be considered when there is no evidence of hemolysis.

In the absence of hyperbilirubinemia, a child who has hepatosplenomegaly should have a complete blood count with a smear and bone marrow biopsy to determine the presence of malignancy. Hepatosplenomegaly also can be caused by storage disorders, and a careful search for other organ involvement may provide clues to the diagnosis. If indicated by history or physical examination, ultrasonography to search for parasitic cysts is warranted. Finally, a child who does not have hyperbilirubinemia or splenomegaly should undergo ultrasonography and serology to rule out cystic or mass lesions and viral or autoimmune hepatitis.

Conclusion

The evaluation of the child who has hepatomegaly should proceed in a logical and stepwise fashion. A thor-

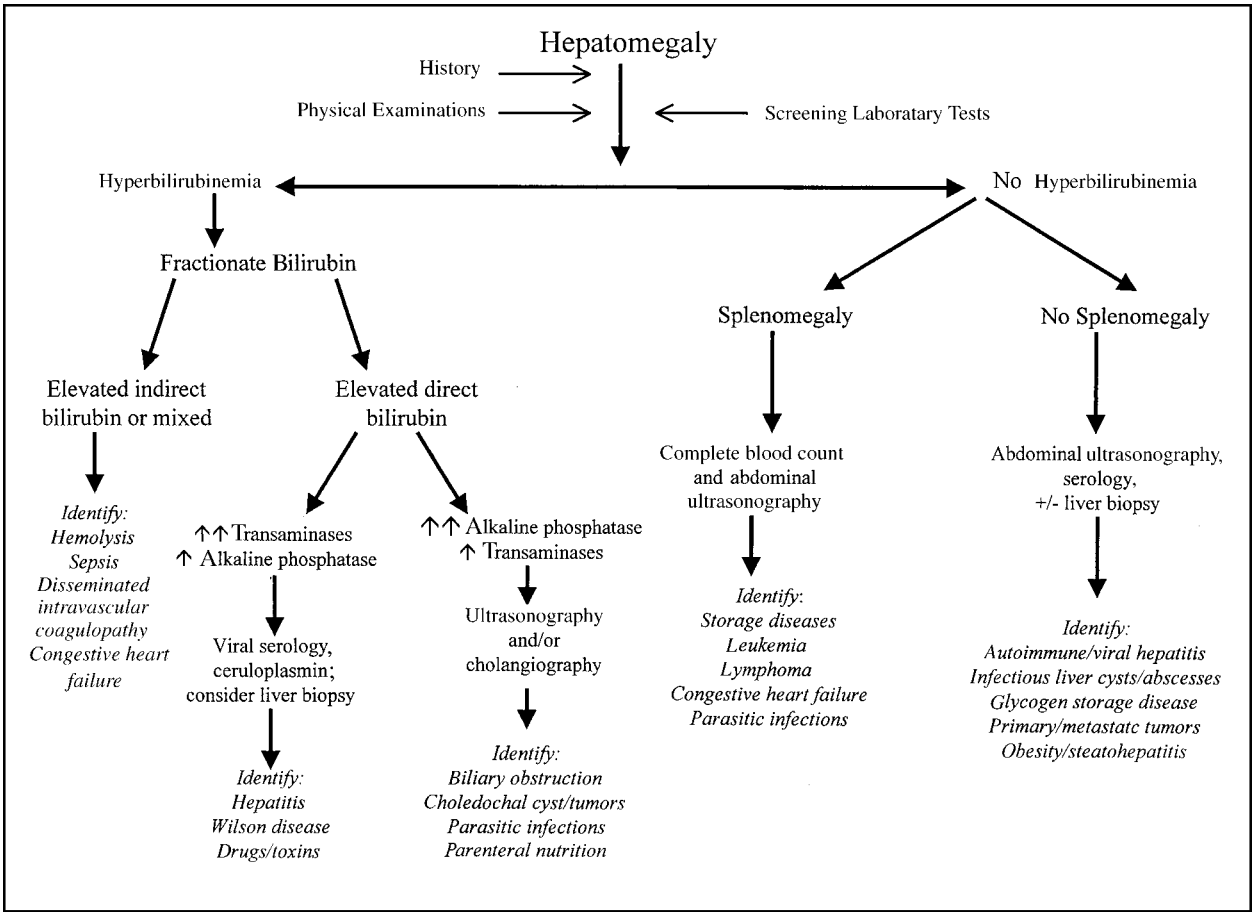

FIGURE 2. Diagnostic algorithm to arrive at the most common diagnoses for a child older than 1 year of age who has hepatomegaly.

ough history and physical examination often point to the most likely diagnoses. Further evaluation should be tailored to the more likely diagnoses.

SUGGESTED READING

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PIR QUIZ

Quiz also available online at www.pedsinreview.org.

10. A 3-month-old boy, whom you are seeing for the first time, has been feeding poorly for the past 3 weeks, according to his mother. He has been vomiting a few times each day. The pregnancy was unremarkable, and delivery occurred at term. His birthweight was 3,192 g, and he went home on the second day of life. The family medical history is unremarkable. Physical examination reveals normal vital signs, a current weight of 3,668 kg, hepatosplenomegaly, no jaundice, and reduced muscle bulk. You note the absence of a social smile. These findings are *best* explained by:
    A. Biliary atresia.
    B. Hepatic vein thrombosis.
    C. Hepatitis C infection.
    D. Hepatoblastoma.
    E. Wolman disease.

11. A 2-week-old boy presents with jaundice. Physical examination reveals hepatomegaly, but the spleen is not palpable. Direct bilirubin is 25.4 mcmol/L (8.3 mg/dL). Of the following, the *most* appropriate initial imaging modality is:
    A. Computed tomography.
    B. Doppler ultrasonography.
    C. Magnetic resonance angiography.
    D. Plain film radiography.
    E. Radionuclide scan.

12. During an assessment of a 1-month-old boy who is feeding poorly, you determine the liver span to be 7 cm. Which of the following additional findings *most* strongly suggests an underlying metabolic disorder as an explanation?
    A. Cutaneous hemangiomas.
    B. Microcephaly.
    C. Pectus excavatum.
    D. Splenomegaly.
    E. Unusual odor.

13. A previously healthy 7-year-old girl presents with a 1-week history of yellow eyes and decreased appetite. She has received all recommended immunizations and has been taking no medications. On physical examination, her skin appears icteric, and the liver span is 10 cm. Total bilirubin is 277 mcmol/L (16.2 mg/dL), direct bilirubin is 137 mcmol/L (8.0 mg/dL), alanine aminotransferase is 850 U/L, and alkaline phosphatase is 400 U/L. Of the following, the *most* likely source of the patient's illness is:
    A. Classmate who was diagnosed with hepatitis A 1 week ago.
    B. Father who is a hepatitis C carrier.
    C. Mother who contracted hepatitis B 4 years ago.
    D. Sashimi that the patient ate at a restaurant 1 month ago.
    E. Sister who had hepatitis A 1 year ago.

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