Introduction

Liver disease in childhood is rare and is frequently the cause of dismay as the medical care provider attempts to recall the myriad of diagnoses that they read about during their training but may never have encountered. In the minds of most, jaundice or elevated liver function tests equals liver disease, but many questions tend to surface: What is the etiology? Can referral wait until more diagnostic information is available? What are the appropriate tests to do and how urgently? What is the likely progression and are there potentially life-threatening consequences of delayed diagnosis and treatment? None of these questions can be answered without formulating a reliable differential diagnosis.

The aim of this chapter is to describe hepatic disease phenotypes based simply on age and primary manifestation of liver disease such as cholestasis, hepatomegaly, or acute liver failure (see Table 6.1) and to provide a reasonably comprehensive list of hepatic diseases that may present with these clinical phenotypes. The hope is to help primary medical providers determine the differential diagnosis and thus guide early studies and appropriate referral and pediatric gastroenterologists and trainees to determine a comprehensive differential diagnosis for their patients on which to base a rational work-up and management plan. This chapter is not intended to be a plan for the detailed investigation of a child with liver disease or a commentary on the probability of any given diagnosis when encountering a patient that fulfills a particular clinical phenotype, but to list the diagnoses that have been recognized, even if only very rarely. Any schema describing the investigations to work through a differential diagnosis is dependent on local conditions dictated by resource availability, priorities, and the probability of a specific diagnosis. For example, in the northwest of the USA, dengue fever would not be included in most differential diagnoses of a local patient, but in Southeast Asia, this would be a major priority.

Hepatology patients range from day-old premature infants to 18-year-old young adults and from seemingly healthy children in the outpatient clinic to profoundly sick infants in the intensive care unit (ICU) on life support. The best way to determine a diagnosis safely and efficiently is to develop a deep understanding of the pathophysiology of liver disease, but even for the most experienced, a checklist of diagnostic possibilities may be helpful to ensure no oversights.

Physicians have always suspected a patient of having disease of the liver from a relatively limited number of clinical signs or symptoms, namely, jaundice, a palpable liver mass or generalized hepatomegaly, splenomegaly, or ascites [1]. Within the last century, blood test abnormalities [2] or aberrant anatomical findings on imaging, commonly...
Table 6.1  List of clinical phenotypes in pediatric patients with liver involvement

| Phenotypes                                                                 |
|---------------------------------------------------------------------------|
| The sick infant in NICU with other known disease (frequently a premature infant with respiratory distress syndrome or chronic lung disease of prematurity and often on parenteral feeding support) |
| (a) Congenital ascites with hepatomegaly or hepatosplenomegaly              |
| (b) Hemorrhage (e.g., gastrointestinal or intracranial) with coagulopathy or low platelets |
| (c) Necrotizing enterocolitis or surgical resection for congenital bowel malformation |
| (d) Hepatomegaly or liver dysfunction associated with congenital heart disease or heart failure |
| (e) An abdominal mass                                                      |
| (f) Cholestatic jaundice or abnormal transaminases                         |
| The sick infant in the emergency room or transferred from another hospital |
| (a) Hepatitis – acute hepatitis or fulminant hepatic failure               |
| (b) Metabolic decompensation – acidosis, hyperammonemia, or hypoglycemia  |
| (c) Abdominal mass with heart failure or Kasabach-Merritt syndrome        |
| (d) Hepatomegaly and abnormal liver function with systemic infection       |
| The stable infant referred to clinic with liver disease                    |
| (a) Cholestasis                                                            |
| (b) Elevated liver function tests                                          |
| (c) Hepatomegaly                                                          |
| (d) Abnormalities found on ultrasound                                      |
| (e) Asymptomatic infant of mother with chronic viral hepatitis            |
| (f) Asymptomatic sibling of child with known liver disease                 |
| Younger child with liver involvement (cholestasis, transaminitis, and/or hepatomegaly) |
| (a) Acute hepatitis                                                       |
| (b) Presentation of a chronic liver disease                               |
| (i) Jaundice                                                              |
| (ii) Ascites                                                              |
| (iii) Gastrointestinal bleeding                                           |
| (c) Hepatomegaly or hepatosplenomegaly on routine exam                    |
| (d) Abdominal mass                                                        |
| (e) Elevated liver function tests on routine screening or tests drawn for other reasons |
| (f) Abnormal liver or spleen finding on abdominal ultrasound done for other reasons |
| Older child/adolescent with liver involvement (cholestasis, transaminitis, and/or hepatomegaly) |
| (a) Acute hepatitis                                                       |
| (b) Presentation of a chronic liver disease                               |
| (i) Jaundice                                                              |
| (ii) Ascites                                                              |
| (iii) Gastrointestinal bleeding                                           |
| (c) Hepatomegaly or hepatosplenomegaly on routine exam                    |
| (d) Abdominal mass                                                        |
| (e) Elevated liver function tests on routine screening or tests drawn for other reasons |
| (f) Abnormal liver or spleen finding on abdominal ultrasound done for other reasons |
| Acute liver failure                                                       |
| (a) Acute hepatitis with coagulopathy and encephalopathy                  |
| Consult from other specialties with liver dysfunction in association with known disease |
| (a) Gastroenterology                                                      |
| (i) Abnormal liver function or hepatomegaly associated with known gastrointestinal disease, e.g., inflammatory bowel disease or celiac disease |
| (ii) Transaminitis or cholestasis in children on long-term parenteral nutrition for intestinal failure |
| (b) Cardiology                                                            |
| (i) Ascites (often chylous) with Fontan circulation                        |
| (ii) Hepatosplenomegaly, abnormal LFTs, or ascites-associated heart failure |
| (iii) Ischemic hepatitis (shock liver) and acute liver failure post-cardiac surgery |
| (iv) Alagille syndrome                                                     |
sonography, have suggested liver problems prior to the appearance of clinical signs. Patients commonly have other features of disease such as hypoglycemia, metabolic bone disease, or anemia, and these additional features do indeed constitute the patient’s disease phenotype and aid with the refining of a differential diagnosis. However, one should be wary of attempting to define precise and detailed liver disease phenotypes because they may fail to take into account the great variability in how individual disease states may be manifest and consequently lead to a diagnosis being overlooked if not “classical” in its presentation.

### Disclaimer

The goal of this chapter is to form the basis of an organized list of diseases of the pediatric liver. It is likely that the most significant gaps will relate to extremely rare hepatological diagnoses and multisystem genetic syndromes with occasional incidental hepatic associations.

Many diagnoses are the subject of detailed discussion in other chapters (and cross-reference will be included where appropriate); however, the more esoteric and unusual may require other resources for in-depth review.

### Clinical Assessment: The Importance of a Careful History and an Expert Physical Examination

The value of careful history taking cannot be overemphasized. It is important to understand the timing and the evolution of the features of liver disease, as well as any symptoms originating outside of the liver and gastrointestinal tract. A full inquiry about birth and pregnancy history, previous medical history, family history, and social history is crucial and should include any exposure to drugs and dietary supplements; household, garden, or garage products; and complementary medicinal products. Similarly, a careful history of contact with infectious disease, foreign travel,
and occupational exposure should be obtained. It is important to examine the urine and stool color if possible or, at a very minimum, have the parents describe these colors; stool color charts have been designed for this purpose (see chapter 13). It is not adequate to ask them whether the urine and stools are normal.

Similarly a skilled physical examination will not only assist with making a prompt diagnosis but can save considerable cost to the care of the patient. Eliciting clinical signs on physical examination of a patient may not be easy, particularly with a squirming infant, a frightened toddler, a giggling child, or an overtly belligerent adolescent, but the skills must be well learned and then practiced patiently and conscientiously throughout one’s career. It is not enough to expect the correct diagnosis to eventually reveal itself if a multitude of laboratory tests and imaging studies are ordered. In the absence of an expert physical examination, a child with ascites of cardiac origin may undergo multiple studies of the liver over many weeks before the correct etiology is recognized. Similarly the patient with pancytopenia, but in whom the modest splenomegaly is not recognized, may be investigated extensively (and expensively) in the hematology department before portal hypertension with hypersplenism is diagnosed.

In the clinical assessment of a patient with suspected liver disease, there are a number of general considerations to be taken into account when trying to formulate a differential diagnosis. The first of these is age at presentation, primarily because many diseases have a typical age (range) of onset. This may allow us to eliminate some diseases completely, for example, primary biliary cirrhosis has never been described in a young child, and to relegate the possibility of yet others, for example, hepatomegaly first encountered in an adolescent is unlikely to be due to glycogen storage disease. Evidence of liver disease present at birth may imply an intrauterine process such as defects of embryonic developmental genes, congenital infections, or isoimmune phenomena, whereas early postnatal disease may indicate an inborn error of metabolism or infection acquired perinatally.

The next general consideration is whether there is a predisposition to developing certain forms of liver disease, i.e., other medical conditions that may predispose to specific liver diseases such as primary sclerosing cholangitis in patients with preexisting ulcerative colitis or hepatoblastoma in a child with Beckwith-Wiedemann syndrome. Similarly the onset of liver disease during pregnancy such as HELLP (hypertension, elevated liver tests, and low platelets) syndrome or acute fatty liver of pregnancy may indicate metabolic disease in the fetus and usually carrier status in the woman. A detailed family history will help reveal potential familial predisposition such as parental consanguinity or a previous sibling with a single-gene defect. Occasionally there is manifestation of a heterozygous status in relatives such as choledolithiasis in the family of the child with MDR3 deficiency. In a patient suspected of having autoimmune hepatitis, a history in the extended family of other autoimmune conditions such as lupus or hypothyroidism is likely to be relevant.

Environmental exposure to infectious or toxic agents is another general consideration that may alter probabilities within a list of differential diagnoses. Infectious etiologies may gain priority due to an endemic risk at place of abode or recent travel to an at-risk area. A history of drinking or bathing in water from a local supply while traveling raises the possibility of a whole range of infectious agents capable of inducing liver injury. International travel is not, however, a prerequisite for unusual infections that may manifest as liver disease; for example, Histoplasma capsulatum, a cause of granulomatous hepatitis especially in the immunocompromised, is endemic in some central and southern US states [3], and baylisascariasis, a rare cause of hepatomegaly and meningoencephalitis, has been described in young children who have ingested soil contaminated with raccoon feces [4]. Knowledge that a mother has a chronic transmissible infection, particularly hepatitis B but also including hepatitis C, HIV, malaria, and Chagas disease [5], may simplify the diagnosis of an infant with liver disease. Exposure to industrial toxins, particularly from pollutant
spills, is usually reported, but particularly in the developing world, there may not be a full disclosure; therefore, direct questioning is essential. Also all drug exposures should be assessed including herbal and homeopathic remedies and dietary supplements. Ingestion of wild mushrooms is a particular risk. Amanita species are found in many parts of the world, while other foods collected straight from nature may be either directly toxic or chemically contaminated. Not all effects of environmental exposure occur immediately upon exposure; minocycline-induced autoimmune hepatitis takes a period of 12–20 months from initiation of treatment for teenage acne, for instance, before liver dysfunction appears [6].

Triggering factors are specific environmental exposures that do not cause disease but reveal its presence. Glycogen storage disease type 1 may become manifest only at weaning from breastfeeding or during an episode of poor intake due to intercurrent illness. Hereditary fructose intolerance may be revealed by the inadvertent administration of intravenous fructose or medicine containing sucrose or sorbitol [7] and the administration of valproate to an infant with seizures due to an unrecognized mitochondrial cytopathy may trigger acute liver failure [8].

**Why Diagnosing Liver Disease May Be Difficult**

Pediatric liver disease is not common in the general practitioners’ experience, and therefore, the diagnoses and its diagnostic work-up may be relatively unfamiliar. Additionally, although established liver disease is rare, it is not uncommon to see mild abnormalities of liver function tests. In infants jaundice is frequently seen in the form of physiologic neonatal jaundice and breast milk jaundice. Although these causes manifest as unconjugated hyperbilirubinemia, it does mean that the mere presence of jaundice in a newborn infant does not necessarily raise the suspicion of liver disease. The difficulties of diagnosis are doubly increased when dealing with acute liver failure; not only are there severe constraints on the time available for a full diagnostic work-up but hepatic metabolic function is severely deranged, sometimes making the differentiation between primary and secondary metabolic abnormalities virtually impossible by biochemical means. Fortunately there are now much greater nucleic acid-based options for primary diagnosis of specific inborn errors of metabolism, but results can take time to become available. Another concern in the early detection of pediatric liver disease relates to the difficulty of maintaining basic clinical examination skills in an age of advanced imaging techniques. The ability of the physician to use hands and eyes to detect clinical signs such as hepatomegaly, ascites, and cutaneous features of liver disease needs to be carefully nurtured among medical students and junior medical staff. Finally, there are a number of terms that are commonly used in regard to liver disease that mean the diagnosis has not been identified such as “idiopathic” fulminant hepatic failure, “cryptogenic” cirrhosis, and “neonatal hepatitis.” It is important to remember that these are not diagnoses but an admission that the diagnostic work-up has failed to identify the primary cause of liver disease. The acceptance of these terms as seemingly discreet diseases may be in some way responsible for incomplete diagnostic work-up. Narkewicz et al. describe how frequently a suboptimal diagnostic work-up is seen in children presenting with acute liver failure when given a diagnosis of idiopathic liver failure even in the context of a multicenter study [9].

**Phenotypes**

**The Sick Newborn**

Most consultations done for suspected liver disease in the newborn nursery or neonatal intensive care are on infants with other reasons to be there and have not yet been home. Less frequently their primary reason is because of liver dysfunction at or within days of birth. Liver dysfunction may be inherent from congenital infection or inborn error of metabolism or secondary to other peri- or postnatal events such as isch-
emia, necrotizing enterocolitis, congenital heart disease, abdominal surgery, or the need for parenteral feeding.

Clinical features which may indicate liver disease include ascites, hyperammonemia, hypoglycemia and coagulopathy, hepatomegaly with or without splenomegaly, cholestasis, and abnormal liver function tests. Congenital liver disease may result in early fetal loss, but the classical presentation is the hydropic infant with hepatomegaly, congenital ascites, hypoalbuminemia, coagulopathy, and very-early-onset cholestasis. These findings are not specific for primary congenital liver disease as congenital ascites is commonly due to severe fetal anemia, both isoimmune and nonimmune causes such as alpha thalassemia, or fetal heart failure, and is mostly seen in the setting of generalized hydrops fetalis (see Table 6.2 for a more complete list of causes). When primary liver disease is suspected, an important diagnosis to consider is “neonatal hemochromatosis.” Studies by Whitington and colleagues have demonstrated that the majority of these cases are due to a maternal factor (presumably an IgG alloantibody) crossing the placenta and inducing complement-mediated hepatocellular injury, one result of which is excessive iron deposition [10]. This immune-mediated “neonatal hemochromatosis” condition has been renamed gestational alloimmune liver disease (GALD) (see chapter 10).

There are also infants who were seemingly healthy at birth but within a few hours to a few days develop features of acute liver failure (see Table 6.3) with coagulopathy and hyperammonemia. There is considerable overlap with

| Immune | Isoimmune hemolytic disease of newborn |
|--------|----------------------------------------|
|        | Gestational alloimmune liver disease (neonatal hemochromatosis) |
|        | Congenital lupus erythematosus |
| Nonimmune anemias | Other hemolytic disorders affecting fetus |
|                  | Disorders of red cell production, e.g., α-thalassemia |
|                  | Congenital leukemia |
|                  | Fetal hemorrhage |
|                  | Twin-to-twin transfusion |

| Infectious | Parvovirus B19 |
|------------|---------------|
|            | Cytomegalovirus (CMV) |
|            | Syphilis |
|            | Herpes simplex |
|            | Toxoplasmosis |
|            | Hepatitis B |
|            | Adenovirus |
|            | Ureaplasma urealyticum |
|            | Listeria monocytogenes |
|            | Enterovirus |
|            | Lymphocytic choriomeningitis virus (LCMV) |
| Chromosomal | Cri-du-chat syndrome (chromosomes 4 and 5) |
|            | Trisomy 13 |
|            | Trisomy 18 |
|            | Trisomy 21 (Down syndrome) |
|            | Turner syndrome |
| Genetic syndromes | Smith-Lemli-Opitz syndrome |
|                  | Beckwith-Wiedemann syndrome |
|                  | Kippe-Trenaunay-Weber syndrome |
|                  | Yellow nail syndrome |
| Metabolic | Glycogen storage disease, type IV |
|           | Gaucher disease, type II |
|           | Morquio disease (MPS IV) |
|           | Hurler syndrome (MPS I) |
|           | Sly syndrome (MPS VII) |
|           | Faber disease |
|           | GM1 gangliosidosis |
|           | Sialidosis II |
|           | I-cell disease |
|           | Niemann-Pick type C |
|           | Wolman |
|           | Infantile sialic acid storage disorder |
|           | Primary carnitine deficiency |
|           | Congenital defects of glycosylation |

| Cardiovascular | Congenital heart disease |
|               | Congenital arrhythmias |
|               | Congenital myocarditis |
| Liver tumors | Hepatoblastoma |
|              | Mesenchymal hamartoma |
|              | Hemangiendothelioma |
| Miscellaneous | Intussusception |
|              | Meconium peritonitis |
|              | Lymphangiectasia |
|              | Urinary tract malformations |
|              | Placental abnormalities |
|              | Teratoma |
|              | Extra-abdominal tumors |
|              | Hypothyroidism and hyperthyroidism |
the causes of congenital ascites although viral infection acquired at or around the time of birth is more likely, disseminated neonatal herpes simplex being a frequently encountered cause. Generalize septicemia and, in at-risk populations, congenital malaria may also present in this manner. Inborn errors of metabolism with infantile acute presentation may include lysosomal storage defects but are more likely to be defects of intermediate metabolism such as galactosemia, organic acidemias, and glycogen storage disease type I (see chapter 8). GALD may also present similarly although there is usually evidence of chronic liver disease. An important diagnosis to exclude, because liver transplantation is contraindicated, is hemophagocytic lymphohistiocytosis (HLH), but HLH characteristically has a more delayed onset with patients tending to present later in infancy (see chapters 12 and 29). Severe liver dysfunction may be seen with vascular compromise as well, such as thrombosis of the inferior vena cava or hepatic veins, and with congenital portal vein anomalies. Heart failure secondary to congenital heart disease may result in an ischemic hepatitis, and rarely congenital leukemia or myelodysplasia can present with acute liver failure.

Commonly, despite intensive work-up, no specific cause is found; however, as has been cautioned in the introduction, the diagnosis of “idiopathic” neonatal hepatitis should not be assumed until all recognized causes have been excluded (see chapter 12). Certainly the proportion of patients with this label of idiopathic neonatal hepatitis has fallen over the years with the discovery of novel conditions and disease mechanisms, and it is to be hoped that eventually the term will become unnecessary. Until then idiopathic neonatal hepatitis should be seen as a challenge to further diagnostic adventure rather than an end in itself.

Although not all infants in the neonatal unit with evidence of liver disease are as sick as patients with hydrops or acute liver failure, the differential diagnosis for hepatitis with or without cholestasis remains large (see Table 6.4). Certainly the diagnoses that were entertained for the sicker group of infants may be found manifest with less severe disease; thus, congenital infection, storage disorders, and GALD still appear in the differential diagnosis for infants with simple cholestasis and elevated transaminases, but a larger spectrum of etiologies also needs to be considered including genetic and chromosomal

| Table 6.3 Causes of acute liver failure in infancy |
|-----------------------------------------------|
| **Infectious**                               |
| **Viral**                                    |
| Herpes simplex                               |
| Varicella zoster                              |
| Cytomegalovirus                               |
| Human herpes virus 6                         |
| Adenovirus                                   |
| Enterovirus                                  |
| Hepatitis B                                  |
| Parvovirus B19                                |
| Influenza                                    |
| **Protozoal**                                |
| Septicemia                                   |
| Malaria                                      |
| **Bacterial**                                |
| **Genetic**                                  |
| Tyrosinemia type 1                           |
| Galactosemia                                  |
| Hereditary fructose intolerance              |
| Fructose 1,6-bisphosphatase deficiency        |
| Organic acidemias                            |
| Urea cycle disorders                         |
| Fatty acid oxidation defects                 |
| Mitochondrial/respiratory chain defects       |
| Carnitine defects                            |
| Niemann-Pick type C                          |
| Glycogen storage disease type 1              |
| **Immune**                                   |
| Neonatal hemochromatosis                     |
| Hemophagocytic lymphohistiocytosis           |
| Autoimmune hemolytic anemia with giant cell hepatitis |
| **Vascular**                                 |
| Heart failure                                |
| Cardiac surgery                              |
| Ischemic hepatitis                           |
| Budd-Chiari                                  |
| Congenital portal vein anomalies             |
| **Neoplastic**                               |
| Infantile leukemia                           |
| Hemangiendothelioma                          |
| **Nutritional/toxic**                        |
| Drugs/toxins                                 |
| **Other**                                    |
| Reye syndrome                                |
| Table 6.4 Causes of hepatitis and/or cholestasis in infancy |
|----------------------------------------------------------|
| **Infectious**                                            |
| **Viral**                                                 |
| Herpes simplex                                           |
| Varicella zoster                                          |
| Cytomegalovirus                                          |
| Human herpes virus 6                                     |
| Adenovirus                                               |
| Enterovirus                                              |
| Hepatitis B                                              |
| Rubella                                                  |
| Parvovirus B19                                           |
| Human immunodeficiency virus (HIV)                       |
| **Bacterial**                                             |
| Syphilis                                                 |
| Listeria                                                 |
| Septicemia                                               |
| Urinary tract infection                                  |
| Acute cholecystitis                                      |
| Acute cholangitis                                        |
| Pyogenic liver abscess                                   |
| **Fungal**                                                |
| Hepatosplenic candidiasis                                |
| Other systemic fungemias                                 |
| **Protozoal**                                             |
| Malaria                                                  |
| Toxoplasmosis                                            |
| Congenital Chagas disease                                |
| **Immune**                                                |
| Neonatal hemochromatosis                                 |
| Hemophagocytic lymphohistiocytosis                        |
| Neonatal lupus                                           |
| Autoimmune hemolytic anemia with giant cell hepatitis     |
| Erythroblastosis fetalis                                 |
| Graft versus host syndrome                               |
| Autoimmune hepatitis                                     |
| Kawasaki disease                                         |
| Myeloproliferative disorder                              |
| **Nutritional/toxic**                                    |
| TPN/intestinal failure                                   |
| Drugs/toxins/herbals                                     |
| Breast milk jaundice                                     |
| Indian childhood cirrhosis                               |
| Other copper toxicoses                                    |
| **Metabolic**                                             |
| Crigler-Najjar                                          |
| Dubin-Johnson syndrome                                   |
| Rotor syndrome                                           |
| Tyrosinemia type 1                                       |
| Galactosemia                                             |
| Glycogen storage diseases                                |
| Organic acidemias                                        |
| Urea cycle disorders                                     |
| Citrin deficiency                                        |
| Fatty acid oxidation defects                             |
| Cholesterol synthesis defects                            |
| Mitochondrial/respiratory chain defects                  |
| **Endocrine**                                             |
| Panhypopituitarism                                       |
| Hypothyroidism                                           |
| Hypoadrenalism                                           |
| Hyperinsulinism                                          |
| **Cardiovascular**                                       |
| Portal vein thrombosis                                   |
| Congenital anomalies of portal vein                      |
| Ischemic hepatitis                                        |
| Heart failure                                            |
| Hepatic artery-portal vein fistula                       |
| Sinusoidal obstruction syndrome                           |
| Budd-Chiari                                              |
| **Neoplastic**                                           |
| Langerhans cell histiocytosis                            |
| Hepatoblastoma                                           |
| Leukemia                                                 |
| Other primary or metastatic liver tumors                  |

**Table 6.4 (continued)**

| Congenital defects of glycosylation                        |
| Bile acid synthesis defects                                |
| Peroxisomal defects                                       |
| Niemann-Pick type C                                       |
| Lysosomal storage diseases                                |
| Mucopolysaccharidoses                                     |
| Alpha 1-antitrypsin deficiency                            |
| Cystic fibrosis                                           |
| Defects of biliary transport (PFIC)                       |
| Familial cholanemias                                      |
| Erythropoietic protoporphyria                             |
| **Syndromic**                                             |
| Trisomy 21                                                |
| Trisomy 18                                                |
| Trisomy 13                                                |
| Cat-eye syndrome                                          |
| Alagille syndrome                                         |
| ARC syndrome                                              |
| Aagenaes syndrome                                         |
| Donohue syndrome                                          |
| MODY 5                                                    |
| Jeune syndrome                                            |
| COACH syndrome                                            |
| Joubert syndrome                                          |
| Bardet-Biedl syndrome                                     |
| Ivemark syndrome                                          |
| Beckwith-Wiedemann syndrome                               |
| NISCH syndrome                                            |
| North American Indian childhood cirrhosis                 |
| Cri-du-chat syndrome                                      |
| GRACILE syndrome                                          |
| McCune-Albright syndrome                                  |
| Septo-optic dysplasia                                     |
| Smith-Lemli-Opitz syndrome                                |
| **Cardiovascular**                                        |
| **Neoplastic**                                            |
| Portal vein thrombosis                                    |
| Congenital anomalies of portal vein                      |
| Ischemic hepatitis                                        |
| Heart failure                                            |
| Hepatic artery-portal vein fistula                       |
| Sinusoidal obstruction syndrome                           |
| Budd-Chiari                                              |
| Langerhans cell histiocytosis                            |
| Hepatoblastoma                                           |
| Leukemia                                                 |
| Other primary or metastatic liver tumors                  |
syndromes that may be apparent from abnormal physical features, as well as vascular, endocrine, and neoplastic causes. Additionally, in those infants who have intestinal failure (usually related to surgical resection for necrotizing enterocolitis or congenital intestinal anomalies), cholestasis is related to enteral starvation and the need for intravenous feeding (see chapter 17). Less commonly iatrogenic causes of neonatal liver disease may be seen, such as portal vein thrombosis or extravasation of parenteral fluids into the liver substance (see Fig. 6.1) complicating umbilical venous catheterization [11].

Although hepatomegaly, abnormal transaminase, and even cholestasis may be present in multisystem diseases, these may not be the key features on which the diagnosis is based. For example, in many lysosomal storage conditions, abnormal facies, neurological findings, skeletal malformations, or other tissue involvement may point to the diagnosis (a list of metabolic defects that have been associated with liver disease is shown in Table 6.5). Certain syndromes such as ARC (arthrogryposis, renal anomalies, and cholestasis), Aagenaes, Donahue, or Beckwith-Wiedemann syndrome also have characteristic physical manifestations, and the presence of hepatomegaly or liver function abnormalities simply supports the diagnosis. Liver involvement in multisystem diseases may manifest in some infants with hepatomegaly alone and will be reliant upon a careful physical examination to identify the relevant finding. The request for a hepatological opinion in such circumstances is to determine if the findings are consistent with the primary diagnosis, if there is a second diagnosis responsible for the liver abnormalities observed, to estimate prognosis, and to advise on appropriate management of the liver dysfunction.

The Sick Infant

Infants discharged from the nursery presenting within days of birth with acute liver failure (see Table 6.3) (see chapter 23) have a large diagnostic overlap with those who have been seen as a consultation presenting in the newborn period. Inborn errors of metabolism, perinatally acquired infection, GALD, and other conditions may have an apparent period of health prior to postnatal decompensation.

The history collected from family must include preceding signs and symptoms, details of the pregnancy and delivery, a dietary history with
| Enzyme defects | Specific disease | Manifestations |
|----------------|-----------------|----------------|
| Defects of bilirubin conjugation | Gilbert | UH |
| | Crigler-Najjar | UH |
| Defects of carbohydrate metabolism | Galactosemia | NC, ALF, CLD |
| | Hereditary fructose intolerance | NC, ALF, CLD |
| | Fructose 1,6-bisphosphatase def. | NC, ALF |
| | PEPCKD | S, R |
| | GSD 1a | HM, T, adenoma |
| | GSD3 | HM, T, CLD |
| | GSD4 | NC, T, CLD |
| | GSD6 | HM, T |
| | GSD9 | HM, T |
| | Glycerol-3-phosphate dehydrogenase deficiency 1 | HM, T |
| Defects of amino acid metabolism | Tyrosinemia type 1 | NC, ALF, CLD, HCC |
| | s-Adenosylhomocysteine hydrolase | NC, CLD |
| | Maple syrup urine disease | NC |
| | Methylmalonic acidemia | R, HM |
| | Propionic acidemia | R |
| | Isovaleric acidemia | R |
| | 3-Methylcrotonylglycinuria | R |
| | 3-OH-3-methylglutaryl-CoA lyase def. | R |
| | Holocarboxylase synthase deficiency | R |
| (Urea cycle disorders) | N-Acetylglutamate synthase def. | R |
| | Carbamoylphosphate synthase def. | R |
| | Ornithine transcarbamylase def. | R |
| | Citrullinemia | R |
| | Argininosuccinic aciduria | R, T |
| Defects of fatty acid oxidation | VLCAD def. | HM, R |
| | LCHAD def. | T, R, ALF |
| | MCAD def. | R |
| | 3-Hydroxyacyl-CoA dehydrogenase def. | R, ALF |
| Defects of ketogenesis | 3-HMG-CoA lyase | HM |
| Defects of carnitine metabolism | Primary carnitine deficiency | HM, R |
| Defects of mitochondrial metabolism | Mitochondrial DNA mutations | NC, T, ALF, R, CLD |
| | Mitochondrial DNA deletions | NC, T, ALF, R, CLD |
| | Mitochondrial DNA depletion | NC, T, ALF, R, CLD |
| | Respiratory chain defects | T, R, ALF, CLD |
| | Multiple Acyl-CoA dehydrogenase def. | HM, R |
| Peroxisomal defects | Zellweger syndrome | NC, T, HM, CLD |
| | Neonatal adrenoleukodystrophy | NC, T, HM, CLD |
| | Infantile Refsum | NC, T, HM, CLD |
| | Pipecolic acidemia | NC, T, HM, CLD |
| | Bifunctional protein def. | NC, T, HM, CLD |
| Defects of lipoprotein metabolism | Tangier disease | HM, SM |
| | Abetalipoproteinemia | HM, S |
| Defect of cholesterol synthesis | Cerebrotendinous xanthomatosis | NC |
| | Smith-Lemli-Opitz syndrome | NC |
| | Mevalonate kinase def. | NC |
| Enzyme defects                          | Specific disease                          | Manifestations          |
|----------------------------------------|-------------------------------------------|-------------------------|
| Lysosomal storage diseases             | GM1 gangliosidosis                        | HM, SM                  |
|                                       | GM2 (Sandhoff) gangliosidosis             | HM, SM                  |
|                                       | Niemann-Pick A and B                      | HM, SM                  |
|                                       | Niemann-Pick C                            | NC, SM, CLD, HCC        |
|                                       | Gaucher                                   | HM, SM                  |
|                                       | Farber                                    | HM, SM                  |
|                                       | Lysosomal acid lipase def. (Wolman and CESD) | NC, T, S, HM, SM, CLD  |
|                                       | Mucopolysaccharidoses (I, II, III, IV, VII) | HM, SM                  |
|                                       | Multiple sulfatase def.                   | HM, SM                  |
|                                       | I-cell disease                            | HM, SM                  |
|                                       | Pseudo-Hurler polydystrophy               | HM, SM                  |
|                                       | Aspartylglucosaminuria                    | HM, SM                  |
|                                       | Fucosidosis                               | HM, SM                  |
|                                       | α-Mannosidosis                            | HM, SM                  |
|                                       | Sialidosis                                | HM, SM                  |
|                                       | Galactosialidosis                         | HM, SM                  |
|                                       | Infantile sialic acid storage disease     | HM, SM                  |
| Congenital defects of glycosylation    | Type I subtypes a, b, h                   | NC, T, HM, SM, CLD      |
|                                       | Type II subtypes b, e, h                  | NC, T, HM, SM, HSM      |
| Porphyrrias                            | Erythropoietic protoporphyria              | T, CLD                  |
| Defects of bile acid metabolism        | Cerebrotendinous xanthomatosis            | NC                      |
|                                       | 3β-Hydroxy-Δ5-C27-steroid oxidoreductase def. | NC, T, CLD            |
|                                       | Oxysterol 7α-hydroxylase def.             | NC, T, CLD              |
|                                       | 2-Methyacyl-CoA racemase def.             | NC, T, FSVM             |
|                                       | BAAT def. (bile acid CoA:amino acid N-acyltransferase) | NC, T, FSVM, P |
|                                       | TJIP2 def. (tight junction protein)       | FSVM, P                 |
|                                       | Epoxide hydrolase def.                    | FSVM, P                 |
| Endoplasmic reticulum storage diseases | α1-Antitrypsin def.                       | NC, T, CLD              |
|                                       | Fibrinogen storage disease                | T, CLD                  |
|                                       | Hereditary amyloidosis                    | T, HM, CLD              |
| Defects of metal metabolism           | Wilson disease                            | T, HM, ALF, CLD         |
|                                       | Hemochromatosis                           | T, CLD, HCC             |
| Transporter defects                    | Defects of bilirubin transport            | NC                      |
|                                       | Dubin-Johnson syndrome                    | NC                      |
|                                       | Rotor syndrome                            | NC                      |
| Defects of biliary transport           | FIC1 def. (PFIC 1)                        | NC, T, CLD              |
|                                       | BSEP def. (PFIC 2)                        | NC, T, CLD, HCC         |
|                                       | MDR3 def. (PFIC 3)                        | NC, T, CLD              |
| Defects of carbohydrate transport     | GSD1b                                     | HM, T, adenoma          |
|                                       | Fanconi-Bickel                            | HM,                     |
| Defects of amino acid transport       | HHHH syndrome                             | R                       |
|                                       | Citrin def.                               | NC, T, S, R             |
|                                       | Lysinuric protein intolerance             | R                       |
| Defects of ion transport              | Cystic fibrosis                           | NC, T, CLD              |

(continued)
Infants have limited responses to severe illness, and the complaints from family may be nonspecific and include poor feeding, vomiting, lethargy, and seizures. There is little in the physical examination that will differentiate cause in such cases, but it is important to remember that many of the diagnoses may result in multisystem involvement and not just liver failure. Therefore, investigation should also be directed at detecting encephalitis, myocarditis, renal failure, adrenal and thyroid insufficiency, and almost any other tissue involvement. Significant encephalopathy in infants is more likely to be due to primary metabolic encephalopathy or infectious encephalitis, as hepatic encephalopathy tends to occur in infants only very late in the course of their liver disease, if at all.

While investigating the specific diagnosis is important, the most urgent need is to respond to the immediate threats to life. Empiric antibacterial and antiviral medications should be considered once appropriate cultures (blood, urine) and viral studies (herpes simplex) have been collected. Manage hypoglycemia, fluid and electrolyte imbalance, and acidosis if present. Intravenous fluids must supply adequate glucose to prevent catabolism, while defects of protein or lipid metabolism (or both as in glutaric aciduria type II) are being investigated – hepatic glucose release for healthy infants may be in the range of 12–14 mg/kg/min, and therefore, this should be the delivery rate to prevent hypoglycemia and endogenous protein catabolism. Coagulopathy may be very severe without outward signs, so it is imperative to check coagulation profile with initial suspicion of liver dysfunction. Occasionally biliary atresia or other cholestatic infantile conditions present acutely with hemorrhage or ecchymoses secondary to vitamin K deficiency.

For details on diagnostic workup and management, see chapter 23.

The Stable Infant with Liver Disease

The infant referred to clinic with jaundice in the first few weeks of life is another common scenario for the general pediatrician and pediatric gastroenterologist. The general pediatrician sees more children with unconjugated hyperbilirubinemia secondary to prolonged physiologic jaundice or breast milk jaundice than they do children with cholestatic jaundice. Infants with unconjugated hyperbilirubinemia have colorless urine and pigmented stools (yellow-green or brown) [12]. It is important to recognize that infants without conjugated hyperbilirubinemia do not pass yellow or amber urine because they drink at least 100 mL/kg/day and therefore pass dilute urine, unlike adults who frequently pass more concentrated yellow urine. Unconjugated jaundice still needs to be investigated if it is either very early in onset, prolonged beyond 10–14 days, very high levels, or of late onset. If breast milk jaundice is suspected and there is no evidence of hemolysis or infection, thyroid function is normal, and bilirubin levels are not progressively increasing,
breast-feeding does not need to be discontinued. However, if the bilirubin level continues to rise, defects of bilirubin conjugation (Crigler-Najjar syndrome) should be considered. The high frequency of unconjugated jaundice in the infant population is one factor that has been suggested for late referrals of infants with biliary atresia; the rare case of conjugated hyperbilirubinemia is like a proverbial needle in the haystack of infants with unconjugated jaundice! It is important for the general pediatrician to remain alert to the possibility that an infant’s jaundice is cholestatic and request split bilirubin levels—total and direct or better still conjugated and unconjugated bilirubin levels (see chapter 3).

Referrals to the pediatric gastroenterologist or hepatologist are most commonly for conjugated hyperbilirubinemia, although the type of jaundice is not always characterized before referral. Due to the importance of a timely hepatoportoenterostomy to the prognosis of the affected infant, the diagnosis of biliary atresia needs to be ruled out promptly. There has been much discussion on the best combination of sonography, scintigraphy, liver biopsy, and cholangiography (see chapter 13), but efficiency of work-up demands a certain degree of experience in the team and institution caring for the infant. If it is not possible to make this diagnosis in a few days, the infant should be transferred to a center that has the required experience and where the appropriate surgical expertise exists to proceed to portoenterostomy. There is no justification for delaying transfer until the diagnosis is certain.

The investigations for other causes of infantile liver disease should be carried out concomitantly with the evaluation for biliary atresia. The priorities depend on the most likely causes relevant to the population served. Citrin deficiency, for example, is a relatively common cause of neonatal cholestasis in Japan and China but rare in Northern Europe, while for $\alpha_1$-antitrypsin deficiency and cystic fibrosis, the relative regional prevalence is reversed. It is wise to have an established protocol for first-line investigations according to your particular population, followed by a second line of investigations for less frequently encountered conditions and finally the very rare causes investigated sequentially to make best use of both patient’s and hospital’s resources.

Quite frequently a healthy, asymptomatic infant with proven or suspected perinatally acquired hepatitis B or hepatitis C will be referred to clinic for confirmation of diagnosis, management, and parental counselling. The child may be accompanied by natural parents, but often the patient may be brought to clinic by a foster family and the child’s social worker or by the adoptive parents in the case of an adoptee from a region of the world where HBV is endemic. See chapter 15 for an approach to these infants. Another group of asymptomatic infants seen in clinic with liver-related questions include those with siblings affected by an inheritable liver disease whose parents either wish this child to be tested or who is already known to carry the mutation(s) and are seeking advice (e.g., $\alpha_1$-antitrypsin deficiency).

Rarely a family seeks medical attention because they have either identified a lump in the abdomen or notice abdominal distention. More commonly nonspecific features such as poor feeding or growth, vomiting, sweatiness, or tachycardia may first bring the infant to medical attention. Occasionally hepatomegaly with or without splenomegaly may be identified as one feature of multisystem genetic disorders such as a ciliary dysfunction syndrome (see chapter 14) or a lysosomal storage disorder. In yet others, a completely asymptomatic mass may be identified on routine examination during a well-baby check. It is not always easy, especially in infants, to determine if an enlarge liver is due to diffuse enlargement of the liver or due to a circumscribed lesion or lesions.

The investigation of these infants depends largely on whether there is homogenous hepatic enlargement or the finding of a mass or masses arising from the liver (see Table 6.6). Ultrasound findings are the best guide to further diagnostic approach. Bland hepatomegaly would point to the possibilities of hepatitis, metabolic storage, outflow obstruction as in heart failure, or syndromic...
organomegaly (e.g., Beckwith-Wiedemann syndrome). Discrete lesions on imaging imply tumor, cyst, or abscess. Undoubtedly, further imaging can help refine the diagnosis in these cases (see chapter 5), and some lesions may have highly characteristic findings on well-conducted studies. Delaying referral to an experience center is not usually beneficial and can result in multiple nonuseful investigations being carried out. Early referral to an experience center who can direct an appropriate diagnostic workup (chapter 22) is recommended. For those without diagnostic findings on imaging, the lesions may need histological evaluation, and therefore, biopsy is necessary.

### Young Child with Liver Disease (1–4 Years)

Most patients with newly recognized liver disease (see Table 6.7) in this age range will present with hepatitis (inflammation of the liver) recognized by the primary provider because of elevated liver function tests. The blood tests are usually provoked by some combination of new onset of jaundice, fever, anorexia, vomiting, or malaise, although in a significant number of cases may be found on testing for nonspecific complaints of headache or abdominal pain or even on routine well-patient screening.

Causes of hepatitis include infectious, commonly viral, autoimmune, and some metabolic diseases which had escaped detection in ear-

| Benign tumor                      | Infectious         | Traumatic               |
|-----------------------------------|--------------------|-------------------------|
| Hemangioma                        | Amebic abscess     | Hepatic hematoma        |
| Infantile hemangioendothelioma    | Pyogenic liver abscess | Fluid extravasation from UVC |
| Mesenchymal hamartoma             |                    |                         |
| Adenoma                           |                    |                         |

| Malignant tumor                   | Other              |
|-----------------------------------|--------------------|
| Hepatoblastoma                    | Choledochal cyst   |
| Rhabdoid tumor                    | Mucocele of gall bladder |
| Rhabdomyosarcoma                  | Simple hepatic cyst |
| Neuroblastoma                     | Riedel’s lobe      |
| Other hepatic malignancy          |                    |

### Table 6.7 Causes of cholestasis in the younger child (1–4 years)

| Infectious          | Viral          | Infectious          | Viral          |
|---------------------|---------------|--------------------|---------------|
| Hepatitis A         |               | Hepatitis B        |               |
| Hepatitis B         |               | Hepatitis C        |               |
| Cytomegalovirus     |               | Epstein-Barr       |               |
| Adenovirus          |               | Parvovirus B19     |               |
| Bacterial           |               | Bacterial          |               |
| Urinary tract infection |         | Septicemia         |               |
|                     |               | Acute cholangitis  |               |
|                     |               | Pyogenic abscess   |               |
|                     |               | Leptospirosis      |               |
| Parasitic           |               | Parasitic          |               |
| Malaria             |               | Malaria            |               |
| Trematodes (liver fluke) |       | Ascariasis         |               |
| Ascariasis          |               | Hydatid (Echinococcus) |       |
|                     |               | Amebic abscess     |               |
| Immune              |               | Immune             |               |
| Autoimmune hepatitis |         | Autoimmune hepatitis |           |
| Sclerosing cholangitis |       | Sclerosing cholangitis |           |
| Kawasaki disease    |               | Kawasaki disease   |               |
|                     |               | Graft versus host disease |     |
|                     |               | Immunodeficiences  |               |
| Metabolic           |               | Metabolic          |               |
| α1-Antitrypsin deficiency |     | α1-Antitrypsin deficiency |     |
| Tyrosinemia         |               | Tyrosinemia        |               |
| FIC1 def. (PFIC1)   |               | FIC1 def. (PFIC1)  |               |
| BSEP def. (PFIC2)   |               | BSEP def. (PFIC2)  |               |
| MDR3 def. (PFIC3)   |               | MDR3 def. (PFIC3)  |               |
| Peroxisomal defects |               | Peroxisomal defects |               |
| Mitochondrial defects |           | Mitochondrial defects |           |
| Cholesteryl ester storage disease | | Cholesteryl ester storage disease |           |
| Dubin-Johnson syndrome |           | Dubin-Johnson syndrome |           |
| Rotor syndrome      |               | Rotor syndrome     |               |
| Erythropoietic protoporphyria | | Erythropoietic protoporphyria | |
Chronic liver diseases with a gradual progression may be first revealed in the young child, as in some cases of \(\alpha\)-1-antitrypsin deficiency (see chapter 9) and Alagille syndrome (see chapter 11). Despite there being no history of neonatal cholestasis, these diseases may progress silently to fibrotic liver disease, detected either by the astute primary doctor finding splenomegaly on routine examination or with the first onset of complications of cirrhosis or portal hypertension.

In the developed world, the infectious causes of liver disease are relatively limited especially in the essentially healthy child, but in the tropics, there are many more pathogens that may induce deranged liver function (see Table 6.8). On the other hand, obesity is now endemic (and some have said epidemic) in the developed world driven by excessive nutritional intake and an increasingly sedentary lifestyle. Nonalcoholic fatty liver disease is now regularly being diagnosed as early as second year of life (see chapter 18). Lastly, drug-induced or toxic hepatitis may result from inadvertent ingestion by the adventurous toddler or due to an idiosyncratic reaction to prescribed medication (see chapter 19) (see Table 6.9).

Non-hepatic causes of laboratory abnormalities and clinical signs and symptoms typically attributed to liver disease must also be considered. Although abnormal “liver” function tests equate in most practitioners’ mind to liver disease, there are important exceptions. “Transaminitis” without jaundice is commonly seen in diseases of skeletal and cardiac muscle. The inclusion of \(\gamma\)-glutamyl transferase and creatine kinase (or other muscle-derived enzyme such as aldolase) can help differentiate the tissue source of elevated levels of AST and ALT. Duchenne muscular dystrophy is a particularly important diagnosis to consider. Another cause of elevated transaminase levels in the absence of liver disease is due to macroenzymes (especially macro-AST) [13]. Serum enzymes may complex with immunoglobulins resulting in a high molecular weight complex that has a prolonged half-life because of reduced plasma clearance. Although macroenzymes have been associated with acute, chronic,
and malignant liver disease, most cases appear benign and self-limiting although the triggers for formation are not fully understood. Benign (or transient) hyperphosphatasia is frequently seen in young children possibly provoked by a mild intercurrent illness [14]. The alkaline phosphatase level can peak in the thousands and remains elevated for a few weeks to a few months before settling to the normal range. If the isoenzymes of alkaline phosphatase are assayed, the largest increase is seen in bone-derived isoenzyme although liver isoenzyme can be increased as well. In the absence of bone disease (e.g., rickets or fracture) and otherwise normal liver laboratory values, no further investigation is required.

Jaundice may be secondary to acute hemolysis; for example, a child with the glucose-6-phosphate dehydrogenase “favism” variant may be first exposed to broad (fava) beans as a young child and present with new-onset jaundice. Even massive ascites may not be what it seems; Fig. 6.2 shows the CT appearance of a young child with a giant omental cyst.

Hepatomegaly or a liver mass may turn out to be the anatomical variant, Riedel’s lobe, an elongated right lobe. Incidental hepatomegaly is the likely presenting feature for the benign glycogen storage diseases due to phosphorylase and phosphorylase kinase deficiency (GSD VI and IX, respectively). Sizable liver masses, however, at

| Table 6.8 | Infectious agents associated with hepatic involvement |
|-----------|--------------------------------------------------|
| **Viral** | **Bacterial** | **Fungal** |
| Hepatitis A | Urinary tract infection | Histoplasmosis |
| Hepatitis B | Septiciemia | Hepatosplenic candidiasis |
| Hepatitis C | Acute cholangitis | Disseminated aspergillosis |
| Hepatitis D | Acute cholecystitis | Trichosporon cutaneum |
| Hepatitis E | Pyogenic abscess | Penicillium marneffei |
| Herpes simplex | Perihepatitis (gonorrhea, chlamydia) | Coccidioidomycosis |
| Varicella zoster | Toxic shock syndrome (staphylococcus) | Cryptococciosis |
| Cytoegalovirus | Scarlet fever |  |
| Epstein-Barr virus | Salmonella typhi/paratyphi | Protozoal |
| Human herpes virus 6 | Shigella | Toxoplasmosis |
| Human herpes virus 7 | Yersinia | Malaria |
| Human herpes virus 8 | Clostridium perfringens | Amebic abscess |
| Rubella | Brucellosis | Toxocariasis |
| Adenovirus | Listeriosis | Cryptosporidium |
| Enterovirus | Borrelia (Lyme borreliosis) | Chagas disease |
| Parvovirus B19 | Leptospirosis | Leishmaniasis |
| Paramyxovirus | Syphilis | Babesiosis |
| Reoviruses (Colorado tick fever) | Bartonella (cat scratch, Carrión disease) |  |
| Influenza/parainfluenza | Actinomycosis | Parasitic |
| Coronavirus (SARS) | Legionella | Clonorchiasis |
| Human immunodeficiency virus (HIV) | Tularemia | Fascioliasis |
| Yellow fever | Melioidosis | Opisthorchiasis |
| Dengue fever | Tuberculosis | Dicrocoelium dendriticum |
| Other flavivirus hemorrhagic fever | Leprosy | Paragonimiasis |
| Lassa fever | Rocky Mountain spotted fever | Schistosomiasis |
| Lymphocytic choriomeningitis virus | Scrub typhus | Echinococcus (hydatid disease) |
| Other arenavirus hemorrhagic fevers | Ehrlichiosis | Ascariasis |
| Filovirus fevers (Ebola, Marburg) | Q fever | Strongyloides |
| Hantavirus hemorrhagic fever | | Trichinella |
| Other bunyavirus hemorrhagic fevers | | Capillariasis |
| | | Baylisascariasis |
Table 6.9 Pharmaceuticals and toxins that have been reported to cause liver disease

| Antibiotics          | CNS-acting drugs | Chemotherapeutics | Miscellaneous drugs | Dietary supplements and recreational drugs | Non-medicinal chemicals |
|----------------------|------------------|-------------------|---------------------|---------------------------------------------|------------------------|
| Amoxicillin/clavulanate | Decadron         | Methotrexate      | Acanthopanax       | Vitamin A                                   | Carbon tetrachloride   |
| Flucloxacillin       | Lamotrigine      | Carbamazepine     | Alcohol             | Hydroxy Cut                                 | Cholesterol            |
| Sulfonamides         | Phenobarbital    | 6-Mercaptopurine   | Allopurinol         | Ecstasy                                     | Vinyl chloride         |
| Erythromycin         | Phenytoin        | Cyclophosphamide  | Amiodarone          | Cocaine                                     | Other organic solvents |
| Azithromycin         | Valproate        | Pyrrolizidine alkaloids | Senna glycosides | Cocaine                                     | Pyrrolizidine alkaloids |
| Cephalosporins       | Felbamate        | Nitrosoureas      | Enalapril           | Aspirin                                     | Yellow phosphorus       |
| Minocycline          | Nimesulide       | Anabolic steroids | Chloretate          | Anabolan                                     | 2-Nitropropane          |
| Niflumaron          | Methylprednisolone | Anabolic steroids | Ketoprofen           | Chlorpheniramine                             | Copper                  |
| Isoniazid           | Methyldopa       | Rarely used singly | Ibuprofen           | Ephedra (ma huang)                          | Iron                    |
| Rifampin            | Fluoxetine       | Rarely used singly | Naproxen            | Caffeine                                    |                        |
| Quinine/quinolones  | Azoled anti-fungals | Rarely used singly | Naproxen            | Caffeine                                    |                        |
| Azole anti-fungals  | Antiretrovirals  | Rarely used singly | Naproxen            | Caffeine                                    |                        |

6 Phenotypes of Liver Diseases in Infants, Children, and Adolescents
this age are likely to be primary hepatoblastoma, neuroblastoma, or other abdominal malignancy (see chapter 22). Hepatocellular carcinoma (HCC) occurs in association with advanced chronic liver disease and in conditions with a specific predisposition such as tyrosinemia and PFIC type 2 but is vanishingly rare as a de novo tumor in an otherwise healthy young child. Benign lesions are most commonly detected on abdominal imaging that was done for other indications and, as discussed for infants, early referral to an experienced center will expedite appropriate management.

Older Child/Adolescent with Liver Disease (>5 Years)

Just like in the younger children, suspicion of liver disease arises from the appearance of specific symptoms such as jaundice, chance pickup on routine physical examination, or investigation of nonspecific and possibly unrelated medical concerns (see Table 6.10). Acute hepatitis due to hepatitis A and Epstein-Barr virus (EBV) is relatively common and new infection with hepatitis B and hepatitis C becomes more common in adolescent populations. Hepatitis E in endemic areas rarely causes significant clinical disease in young children but is more likely to cause acute hepatitis as subjects’ age and is particularly dangerous for the pregnant teenage girl (see chapter 15). Autoimmune hepatitis often presents with acute hepatitis and although more frequent in adolescent girls can occur in both sexes and at any age (see chapter 16). Most cases of Wilson disease diagnosed in childhood and adolescence manifest as acute, often fulminant, hepatitis, and although rare, an expedient diagnosis may prevent death or liver transplantation (see chapter 9).
Everyone involved in the care of children recognizes the obesity crisis that is so highly prevalent in the USA and is also sweeping the rest of the developed world. This single factor accounts for the majority of new referrals of children with elevated transaminases in the USA as a result of nonalcoholic fatty liver disease (NAFLD) (see chapter 18). This was an uncommon diagnosis 25 years ago, and despite multicenter collaborative efforts to design treatments for this condition, it is likely that the solution, if one is to be forthcoming, will be in the realm of public policy development to curtail obesity rather than single-patient medical management.

Gall stones and gall bladder disease can cause jaundice and elevated transaminases and increase as adulthood approaches (see chapter 20). Gilbert syndrome is an essentially benign condition manifest as an unconjugated jaundice with normal transaminases. The jaundice is frequently first noted around the time of puberty and these patients are often referred to liver clinics. As for younger children, elevated transaminases with no jaundice may be seen in many liver diseases, but muscle injury, myositis, muscular dystrophy, or cardiomyopathy should not be dismissed without a careful history, physical examination, and a creatine kinase level.

Chronic liver disease may present at any age (see chapters 25 and 26). As disease progresses jaundice may eventually appear. Abdominal distention from hepatomegaly or ascites may rarely lead to the request for medical attention. More commonly isolated splenomegaly is identified, and if portal hypertension is not considered, the child or teenager may go through detailed hematological investigations unnecessarily. Extrahepatic portal hypertension, due to portal vein thrombosis having occurred usually years

### Table 6.10 Causes of cholestasis in older children and adolescents

| Infectious | Viral | Hepatitis A |
|------------|-------|-------------|
|             |       | Hepatitis B |
|             |       | Hepatitis C |
|             |       | Hepatitis E |
|             |       | Cytomegalovirus |
|             |       | Epstein-Barr virus |
|             |       | Adenovirus |
| Bacterial   | Septicemia | |
|             | Acute cholangitis | |
|             | Pyogenic abscess | |
|             | Leptospirosis | |
|             | Rocky Mountain spotted fever | |
|             | Borrelia (Lyme’s) | |
|             | Salmonella typhi/paratyphi | |
|             | Tuberculosis | |
| Parasitic   | Malaria | |
|             | Trematodes (fluke) | |
|             | Ascariasis | |
|             | Leishmaniasis | |
|             | Echinococcus (hydatid) | |
|             | Amebic abscess | |
|             | Cryptosporidium | |
| Metabolic   | Wilson disease | |
|             | Cholesteryl ester storage disease | |
|             | Benign recurrent intrahepatic cholestasis | |
|             | Juvenile hemochromatosis | |
|             | HELLP syndrome (pregnant teenage women) | |
| Immune      | Autoimmune hepatitis | |
|             | Sclerosing cholangitis | |
|             | Primary biliary cirrhosis | |
|             | Kawasaki disease | |
|             | Graft versus host disease | |
|             | Immunodeficiencies | |
|             | Systemic lupus erythematosus | |
|             | Sarcoidosis | |
| Toxic       | Drugs/toxins/herbals | |
| Vascular    | Budd-Chiari | |
|             | Sinusoidal obstruction syndrome | |
|             | Congenital heart disease | |
|             | Constrictive pericarditis | |
|             | Heart failure | |
|             | Liver trauma | |
|             | Hereditary hemorrhagic telangiectasia | |

**Table 6.10 (continued)**

| Other | Choledochal cyst |
|-------|------------------|
|       | Caroli disease |
|       | Choledocholithiasis |
|       | Sickle-cell disease |
|       | Postnecrotic cirrhosis |
before frequently in infancy related to umbilical sepsis or catheterization, can present with splenomegaly. Alternatively, the detection of portal hypertension may be the first sign of chronic liver injury, for example, in autoimmune hepatitis or chronic viral hepatitis, resulting in cirrhosis, but with no history of previous ill health in the child (see Table 6.11). In these circumstances the liver is usually shrunken, and therefore not palpable, but on imaging is heterogenous and nodular and the biopsy specimen severely fibrotic.

With increasing age the incidence of embryonal tumors diminishes and the risk of HCC and metastatic liver tumors increases (see Table 6.12). Greatest risk for HCC is in association with chronic fibrotic liver disease, but the fibrolamellar variant can be encountered in the adolescent without preexisting liver disease. Benign lesions can get big enough to present as a mass or with abdominal discomfort and include nodular regenerative hyperplasia, focal nodular hyperplasia, and adenoma. Leukemias and lymphomas are the most common cancers in children and adolescents and may present with evidence of liver infiltration causing deranged liver function.

Although identification of asymptomatic chronic viral hepatitis via at-risk screening (immigration or infected family) is less common in this age group, they do occur. Adoptees and recent immigrants from HBV endemic regions may present with chronic HBV carriage for management advice. Additionally, family screening

| Table 6.11 Causes of portal hypertension |
|-----------------------------------------|
| Post-hepatic                           |
| Heart failure                          |
| Cardiomyopathy                         |
| Congenital heart disease               |
| Constrictive pericarditis              |
| Inferior vena cava thrombosis          |
| Congenital web in inferior vena cava   |
| Budd-Chiari syndrome                   |
| Tumor                                  |
| Intrahepatic                           |
| Post-sinusoidal                        |
| Veno-occlusive disease                 |
| Cirrhosis                              |
| Nodular regenerative hyperplasia       |
| Hypervitaminosis A                     |
| Sinusoidal                             |
| Schistosomiasis                        |
| Congenital hepatic fibrosis            |
| Sarcoidosis                            |
| Portosclerosis                         |
| Hepatic artery-portal vein fistula     |
| Pre-sinusoidal                         |
| Portal vein thrombosis                 |
| Portal vein stenosis                   |
| Cavernous transformation of portal vein|
| Congenital anomalies of portal vein    |
| Tumor                                  |
| Pre-hepatic                            |
| Splenic vein thrombosis                |
| Pancreatitis                           |
| Pancreatic pseudocyst                  |
| Tumor                                  |
| Retroperitoneal fibrosis               |
| Retroperitoneal abscess                |
| Sinistral (left sided)                 |
| Amebic abscess                         |
| Hydatid (Echinococcus)                 |
| Pyogenic liver abscess                 |
| Neoplastic                             |
| Malignant                              |
| Hepatoblastoma                         |
| Hepatocellular carcinoma               |
| Neuroblastoma                          |
| Neuroendocrine tumors                  |
| Rhabdoid tumor                         |
| Rhabdomyosarcoma                       |
| Embryonal sarcoma                      |
| Epithelioid hemangioendothelioma        |
| Cholangiocarcinoma                     |
| Hepatic teratoma                       |
| Other primary hepatic malignancy       |
| Metastatic malignancy in liver         |
| Benign                                 |
| Adenoma                                |
| Mesenchymal hamartoma                  |
| Fibronodular hyperplasia               |
| Hemangioma                             |
| Infectious                             |
| Nodular regenerative hyperplasia       |
| Simple cyst                            |
| Hematoma                               |
| Mucocele of gallbladder                |
| Choledochal cyst                       |
| Focal fatty infiltration               |
| Riedel’s lobe                          |
| Other                                  |
| Simple cyst                            |
| Hematoma                               |
| Mucocele of gallbladder                |
| Choledochal cyst                       |
| Focal fatty infiltration               |
| Riedel’s lobe                          |

| Table 6.12 Causes of hepatic masses beyond infancy - found either on physical examination or imaging |
|-----------------------------------------------|
| Neoplastic                                    |
| Malignant                                     |
| Hepatoblastoma                                |
| Hepatocellular carcinoma                      |
| Neuroblastoma                                 |
| Neuroendocrine tumors                         |
| Rhabdoid tumor                                |
| Rhabdomyosarcoma                              |
| Embryonal sarcoma                             |
| Epithelioid hemangioendothelioma               |
| Cholangiocarcinoma                            |
| Hepatic teratoma                              |
| Other primary hepatic malignancy              |
| Metastatic malignancy in liver                |
| Benign                                        |
| Adenoma                                       |
| Mesenchymal hamartoma                         |
| Fibronodular hyperplasia                      |
| Hemangioma                                    |
| Infectious                                    |
| Amebic abscess                                |
| Hydatid (Echinococcus)                        |
| Pyogenic liver abscess                        |
| Other                                         |
| Nodular regenerative hyperplasia              |
| Simple cyst                                    |
| Hematoma                                       |
| Mucocele of gallbladder                       |
| Choledochal cyst                              |
| Focal fatty infiltration                      |
| Riedel’s lobe                                 |
because of hereditary hemochromatosis may identify an older child with biochemical evidence of iron overload but normal or mildly altered transaminases (see chapter 9). Similarly, a diagnosis of Wilson disease mandates the screening of all first-degree relatives, including other children, before signs of liver injury exist.

### Acute Liver Disease and Failure

Acute liver disease is the recent onset of liver dysfunction in a patient with no history or investigational evidence of preexisting liver disease (see Table 6.13). This gets a little convoluted when one considers the acute onset of, say, Wilson disease, acute decompensation of chronic hepatitis B, or autoimmune liver disease, where the clinical picture is of a disease of no longer than a few weeks duration but in whom the liver biopsy shows established fibrosis. As is the convention for this chapter in general, we will limit the discussion to the clinical phenotype, i.e., those who have an apparent acute onset of disease with no history of preexisting liver disease.

Acute liver failure results from massive or submassive hepatocellular necrosis, but the syndrome is defined in terms of the duration of the illness (less than 8 weeks) and the presence of coagulopathy and hepatic encephalopathy (see chapter 23 for more details). One important consideration is to differentiate between the acute failure of liver functions manifest by coagulopathy, cholestasis, hyperammonemia, loss of glycemic control, encephalopathy, etc., and the criteria for entry into the PALF (Pediatric Acute Liver Failure) study. In an attempt to be inclusive and to observe the progression from early disease to liver failure, the criteria for entry into PALF were set relatively low, namely, coagulopathy secondary to acute liver disease with an INR of \( \geq 1.5 \) with hepatic encephalopathy or \( \geq 2.0 \) in the absence of encephalopathy. There was never an intention to liberalize the definition of acute liver failure, and yet more and more frequently, these study entry criteria are being quoted as the “definition” of acute liver failure which they patently are not.

Differentiating between the causes of acute liver failure can be challenging. Nonspecific

| Table 6.13 Causes of acute liver failure outside of infancy |
|----------------------------------------------------------|
| **Viral** | Hepatitis A |
|          | Hepatitis B |
|          | Hepatitis D |
|          | Hepatitis E |
|          | Herpes simplex |
|          | Epstein-Barr virus |
|          | Varicella-zoster |
|          | Paramyxovirus |
|          | Adenovirus |
|          | Parvovirus B19 |
|          | SARS |
|          | Hemorrhagic fever viruses |
| **Bacterial** | Septicemia |
|              | Leptospirosis |
|              | Salmonella typhi/paratyphi |
|              | Bartonella |
|              | Rocky Mountain spotted fever |
| **Metabolic** | Hereditary fructose intolerance |
|              | Urea cycle disorders |
|              | Organic acidemias |
|              | Fatty acid oxidation defects |
|              | Mitochondrial disorders |
|              | Carnitine defects |
|              | Wilson disease |
|              | Tyrosinemia type 1 |
|              | Acute fatty liver of pregnancy |
| **Immune** | Autoimmune hepatitis |
|             | Hemophagocytic lymphohistiocytosis |
| **Toxic** | Drugs/toxins/herbals |
|            | Amanita phalloides |
| **Vascular** | Budd-Chiari |
|              | Sinusoidal obstruction syndrome |
|              | Ischemic hepatitis/shock liver |
|              | Post-cardiac surgery |
|              | Liver trauma |
| **Neoplastic** | Leukemia |
|               | Lymphoma |
|               | Hepatocellular carcinoma |
| **Other** | Reye syndrome |
|            | Hypothermia |
|            | Heat stroke |
|            | Massive liver resection |
|            | Sickle-cell anemia |
metabolic derangement adds another level of complication to identifying a liver based-metabolic disease. Similar challenges to acute diagnosis exist with many other causes, and great care is required to not miss a potentially treatable cause of liver disease such as autoimmune hepatitis or Wilson disease. Although the single largest group of acute liver failure patients in childhood is those in whom a specific etiology is not identified, it does not negate the need for a full and detailed workup. Sadly, even in the context of a multicenter study with recommendations made for appropriate investigation, inadequate investigation of cause is frequently encountered [9].

There may be clues such as a history of medication or herbal ingestion (see chapter 19), encephalopathy that is fluctuating or out of proportion to the liver dysfunction may point towards a mitochondrial or other metabolic disease, hemolysis can suggest Wilson disease, or foreign travel increasing the likelihood of an infectious cause. Unfortunately these features are neither specific nor sensitive, and as much as we may like to narrow our differential diagnosis to address the most likely or most serious diagnoses first, in the situation of acute hepatic failure, all causes are life-threateningly serious, and therefore, an inclusive panel of investigation is the safest and most efficient approach. Clearly, investigations, especially for infectious causes, will be tempered by knowledge of local occurrence; we in Seattle do not, for example, routinely check for the flavivirus that causes yellow fever. For more details on the approach to acute liver failure, see chapter 23.

Other Phenotypes

Although singly or in combination jaundice, hepatitis, hepatomegaly, or liver mass account for the majority of new presentations of liver disease in childhood, occasionally none of these features are immediately obvious and in some cases absent completely (see Table 6.15). Pruritus in the absence of jaundice can rarely be due to cholestasis, although dermatological causes are far more prevalent. Gastrointestinal bleeding from esophageal varices or ascites usually occurs in the presence of recognized chronic liver disease but in some cases are the first overt signs of its presence. Variceal bleeding as a first presenting feature is seen not uncommonly in cavernous transformation of the portal vein secondary to temporally distant portal vein thrombosis. The child or teenager with isolate splenomegaly may be found to have developed cirrhosis with no past history of jaundice or other features of liver disease. Finally, a few infants and toddlers may manifest with hypocalcemic tetany or rickets and be found to have profound fat-soluble vitamin deficiency. If due to liver disease, other features almost always are

Consult from Other Services with Liver Dysfunction in Association with Known Disease

When a consult comes in from another specialist service, there is always the possibility that the liver disease has nothing to do with the condition that the specialist has been managing. This is essentially a caution because the referral from cardiology of the child with Eisenmenger syndrome, abnormal transaminases, and mild splenomegaly may automatically become hepatic congestion and portal hypertension secondary to right heart failure, while their autoimmune hepatitis goes unrecognized and untreated! Therefore, no matter who the originator of the referral is, the approach to differential diagnosis should be based on the child themselves as outlined in the sections above. Having said this, there is probably a different weighting of the diagnostic possibilities in patients with non-liver diseases with known hepatic pathological associations. Table 6.14 lists some of the particular diagnostic considerations based on the specialty team requesting a hepatological consultation on one of their patients.
| Organs System | Conditions Associated with Recognized Patterns of Liver Involvement |
|---------------|---------------------------------------------------------------|
| **Gastroenterology** | |
|   (i)  | Inflammatory bowel disease associated with sclerosing cholangitis or autoimmune hepatitis |
|   (ii) | Celiac disease associated with autoimmune hepatitis |
|   (iii) | Parenteral nutrition-associated liver disease in patients with intestinal failure |
|   (iv) | Shwachman-Diamond syndrome – pancreatic insufficiency and neutropenia often associated with hepatomegaly and transaminitis |
| **Cardiology** | |
|   (i)  | Fontan circulation with ascites |
|   (ii) | Heart failure associated with hepatosplenomegaly, hepatic fibrosis, and sinusoidal dilation |
|   (iii) | Cardiac surgery leading to shock liver (ischemic hepatitis) and acute liver failure |
|   (iv) | Alagille syndrome |
|   (v)  | Constrictive pericarditis |
|   (vi) | Cardiomyopathy |
| **Hematology/oncology** | |
|   (i)  | Sinusoidal obstruction syndrome |
|   (ii) | Drug effect |
|   (iii) | Hemolysis leading to biliary inspissation/sludge/stones |
|   (iv) | Sickle liver |
|   (v)  | Transfusion-related iron overload |
|   (vi) | Transfusion-related infectious hepatitis |
|   (vii) | Budd-Chiari |
|       | (a) Hypercoagulable states |
|       | (b) Myeloproliferative disorders |
|       | (c) Paroxysmal nocturnal hemoglobinuria |
|   (viii) | Leukemia and lymphoma |
|   (ix) | Langerhans cell histiocytosis |
|   (x)  | Liver tumors |
|   (xi) | Stem cell transplantation |
|       | (a) Graft versus host disease |
|       | (b) Sinusoidal obstruction syndrome |
|       | (c) Opportunistic liver infections |
| **Pulmonology** | |
|   (i)  | Cystic fibrosis liver disease |
|   (ii) | Sarcoidosis |
|   (iii) | Tuberculosis |
| **Nephrology** | |
|   (i)  | Polycystic kidney disease, nephronophthisis |
|   (ii) | Alagille syndrome |
|   (iii) | Membranoproliferative glomerulonephritis associated with portal hypertension |
| **Endocrine** | |
|   (i)  | Nonalcoholic steatohepatitis |
|   (ii) | Diabetic glycogen hepatopathy (Mauriac syndrome) |
|   (iii) | Hypopituitarism |
|   (iv) | Autoimmune polyendocrine syndrome type 1 |
|   (v)  | McCune-Albright syndrome |
|   (vi) | Generalized lipodystrophy (Berardinelli-Seip syndrome) |
| **Immunology** | |
|   (i)  | Immunodeficiencies associated with sclerosing cholangitis or hepatic abscess |
|   (ii) | Granulomatous hepatitis in chronic granulomatous disease (CDG) |
present with the notable exception of defects of bile acid amidation (see chapter 8).

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