Alagille Syndrome
Ellen Mitchell, Melissa Gilbert, and Kathleen M. Loomes

Alagille syndrome is a complex multisystem autosomal dominant disorder with a wide variability in penetrance of clinical features. Most patients have pathogenic mutations in either the \( JAG1 \) gene, encoding a Notch pathway ligand, or the receptor \( NOTCH2 \). No genotype-phenotype correlations have been found in any organ system. Liver disease is a major cause of morbidity in this population, whereas cardiac and vascular involvement accounts for most of the mortality. Current therapies are supportive, but the future is promising for the development of targeted interventions to augment Notch pathway signaling in involved tissues.

Alpha-1-Antitrypsin Deficiency Liver Disease
Dhiren Patel and Jeffrey H. Teckman

In homozygous ZZ alpha-1-antitrypsin (AAT) deficiency, the liver synthesizes large quantities of AAT mutant Z, which folds improperly during biogenesis and is retained within the hepatocytes and directed into intracellular proteolysis pathways. These intracellular polymers trigger an injury cascade, which can lead to liver injury. This process is highly variable, and not all patients develop liver disease. Although the injury cascade is not fully described, there is likely a strong influence of genetic and environmental modifiers of the injury cascade and of the fibrotic response. With improved understanding of liver injury mechanisms, new strategies for treatment are now being explored.

Progressive Familial Intrahepatic Cholestasis
Laura N. Bull and Richard J. Thompson

Genetic cholestasis has been dissected through genetic investigation. The major PFIC genes are now described. \( ATP8B1 \) encodes FIC1, \( ABCB11 \) encodes BSEP, \( ABCB4 \) encodes MDR3, \( TJP2 \) encodes TJP2, \( NR1H4 \) encodes FXR, and \( MYO5B \) encodes MYO5B. The full spectra of phenotypes associated with mutations in each gene are discussed, along with our understanding of the disease mechanisms. Differences in treatment response and targets for future treatment are emerging.

Inborn Errors of Bile Acid Metabolism
James E. Heubi, Kenneth D.R. Setchell, and Kevin E. Bove

Inborn errors of bile acid metabolism are rare causes of neonatal cholestasis and liver disease in older children and adults. The diagnosis should be considered in the context of hyperbilirubinemia with normal serum bile
acids and made by urinary liquid secondary ionization mass spectrometry or DNA testing. Cholic acid is an effective treatment of most single-enzyme defects and patients with Zellweger spectrum disorder with liver disease.

**Autoimmune Hepatitis, Sclerosing Cholangitis, and Autoimmune Sclerosing Cholangitis or Overlap Syndrome**

Nanda Kerkar and Albert Chan

Autoimmune hepatitis (AIH) is characterized by elevated serum aminotransferases, immunoglobulin G, autoantibodies, and interface hepatitis, in the absence of a known diagnosis. Presentation is varied. Therapy is with immunosuppression. There is inflammation of the intrahepatic and/or extrahepatic bile ducts in sclerosing cholangitis (SC), and when associated with inflammatory bowel disease, it is known as primary SC (PSC), with ursodeoxycholic acid used for therapy. The overlap of clinical, biochemical, and histologic features of AIH and PSC is known as autoimmune sclerosing cholangitis (ASC) or overlap syndrome. Liver transplant is performed when medical treatment fails, and both AIH and PSC may recur posttransplant.

**Hepatitis B and C**

Krupa R. Mysore and Daniel H. Leung

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections represent a major global public health and economic burden, with an estimated 257 million and 71 million people, respectively, having chronic infection worldwide. The natural history of HBV and HCV in children depends on the age at time of infection, mode of acquisition, ethnicity, and genotype. Most children infected perinatally or vertically remain asymptomatic but are at a uniquely higher risk of developing chronic viral hepatitis, progressing to liver cirrhosis and hepatocellular carcinoma, hence classifying HBV and HCV as oncoviruses. This article discusses the epidemiology, virology, immunobiology, prevention, clinical manifestations, evaluation, and advances in treatment of hepatitis B and C in children.

**Nonalcoholic Liver Disease in Children and Adolescents**

Sara Kathryn Smith and Emily R. Perito

Pediatric nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in children. The spectrum of NAFLD ranges from steatosis to nonalcoholic steatohepatitis (NASH) to fibrosis. Obesity rates in children continue to increase and, as a result, NAFLD in children is becoming more prevalent. The pathophysiology, natural history, and progression of disease are still being elucidated, but NAFLD/NASH in children may represent a more severe phenotype that will benefit from early identification and management.

**Cirrhosis and Portal Hypertension in the Pediatric Population**

Catherine A. Chapin and Lee M. Bass

Cirrhosis is a complex process in which the architecture of the liver is replaced by structurally abnormal nodules due to cirrhosis. Cirrhosis frequently leads to the development of portal hypertension. In children,
portal hypertension may have a wide range of causes, including extrahepatic portal vein obstruction, biliary atresia, alpha 1 antitrypsin deficiency, and autoimmune hepatitis. Gastroesophageal varices and ascites are two of the complications of portal hypertension likely to cause morbidity and mortality. This article also discusses extrahepatic manifestations of portal hypertension and treatment options.

**Pediatric Liver Tumors**

Kenneth Ng and Douglas B. Mogul

Although liver tumors are rare in the pediatric population, they are common in the setting of children with specific risk factors requiring increased awareness and, in some instances, screening. The evaluation of a liver mass in children is largely driven by the age at diagnosis, the presence of any medical comorbidities, and initial testing with alpha fetoprotein and imaging. Specific guidelines for the management of different tumors have been implemented in recent years such that a multidisciplinary approach is ideal and care should be provided by centers with experience in their management.

**Acute Liver Failure: An Update**

James E. Squires, Patrick McKiernan, and Robert H. Squires

Pediatric acute liver failure (PALF) is a dynamic, life-threatening condition of disparate etiology. Management of PALF is dependent on intensive collaborative clinical care and support. Proper recognition and treatment of common complications of liver failure are critical to optimizing outcomes. In parallel, investigations to identify the underlying cause and the implementation of timely, appropriate treatment can be lifesaving. Predicting patient outcome in the era of liver transplantation has been unfulfilling, and better predictive models must be developed for proper stewardship of the limited resource of organ availability.

**Liver Transplantation in Children**

Yen H. Pham and Tamir Miloh

Liver transplant (LT) for children has excellent short- and long-term patient and graft survival. LT is a lifesaving procedure in children with acute or chronic liver disease, hepatic tumors, and a few genetic metabolic diseases in which it can significantly improve quality of life. In this article, the authors discuss the unique aspects of pediatric LT, including the indications, patient selection and evaluation, allocation, transplant surgery and organ selection, posttransplant care, prognosis, adherence, and transition of care.