Contents

Preface: Cholestatic Liver Diseases  xiii
Cynthia Levy

Genetic Determinants of Cholestasis  147
Gideon M. Hirschfield

Cholestasis is an overarching term applied for conditions whereby biliary constituents are found in the circulation because of impairment to bile flow. A variety of processes can lead to cholestasis, be they acute or chronic injuries to hepatocytes, cholangiocytes, or the broader biliary tree itself. Such injuries may be driven by rare but highly informative primary genetic abnormalities, or may be seen in individuals with a prior genetic predisposition when confronted by specific environmental challenges such as drug exposure. This review provides a broad outline of some fundamental primary genetic cholestatic syndromes and an update on varying genetic predisposition underlying several acquired cholestatic processes.

Nuclear Receptors as Drug Targets in Cholestatic Liver Diseases  161
Emina Halilbasic, Anna Baghdasaryan, and Michael Trauner

Cholestatic liver diseases encompass a wide spectrum of disorders with different causes, resulting in impaired bile flow and accumulation of bile acids and other potentially hepatotoxic cholephils. The understanding of the molecular mechanisms of bile formation and cholestasis has recently improved significantly through new insights into nuclear receptor (patho)biology. Nuclear receptors are ligand-activated transcription factors, which act as central players in the regulation of genes responsible for elimination and detoxification of biliary constituents accumulating in cholestasis. They also control other pathophysiologic processes such as inflammation, fibrogenesis, and carcinogenesis involved in the pathogenesis and disease progression of cholestasis liver diseases.

Drug-Induced Cholestasis  191
Einar S. Bjornsson and Jon Gunnlaugur Jonasson

Cholestasis caused by drugs is an important differential diagnosis in patients presenting with a biochemical cholestatic pattern. The extent of serologic tests and radiological imaging depends on the clinical context. The underlying condition of the patient and detailed information on drug use, results of rechallenge, and the documented hepatotoxicity of the drug are important to establish a diagnosis of drug-induced liver injury (DILI). Most cases of cholestatic DILI are mild, but in rare cases, ductopenia and cholestatic cirrhosis can develop. Approximately 10% of patients with cholestatic jaundice caused by drugs develop liver failure.
Primary Sclerosing Cholangitis

Claudia O. Zein

Primary sclerosing cholangitis (PSC) is a chronic, progressive, cholestatic liver disease characterized by multifocal strictures of intra and extrahepatic bile ducts. PSC occurs more commonly in men and is often associated with inflammatory bowel disease. At present, there is no effective medical therapy for PSC. Current management of patients with PSC is centered on endoscopic therapy of biliary strictures, management of complications of chronic cholestasis and of progressive liver disease, and close clinical monitoring for development of cholangiocarcinoma, as well as for timely referral for liver transplantation.

Primary Biliary Cirrhosis: Therapeutic Advances

Frank Czul, Adam Peyton, and Cynthia Levy

Primary biliary cirrhosis (PBC) is a chronic and slowly progressive cholestatic liver disease characterized by destruction of the interlobular bile ducts, which, if untreated, leads to fibrosis, biliary cirrhosis, and liver failure. Because liver transplantation remains the only curative option for PBC, the goals of treatment are to slow the rate of progression, to alleviate related symptoms, and to prevent complications. Ursodeoxycholic acid is the only US Food and Drug Administration–approved medical treatment of PBC. Several agents are undergoing evaluation as monotherapy or as an adjuvant to ursodeoxycholic acid. This review summarizes current therapeutic advances in the care of patients with PBC.

Cholestatic Liver Disease Overlap Syndromes

Marilyn J. Mayo

Primary biliary cirrhosis and primary sclerosing cholangitis share some clinical features with autoimmune hepatitis, but when features of autoimmune hepatitis are present, prognosis can be affected and immunosuppressive treatment warranted. The presence of severe interface hepatitis in primary biliary cirrhosis portends a worse prognosis and should prompt evaluation for possible autoimmune hepatitis overlap and treatment with immunosuppression. Specific models to identify which subjects benefit most from the addition of immunosuppression need to be developed. Drug-induced liver injury and IgG4 disease may masquerade as autoimmune hepatitis or primary sclerosing cholangitis and are important to consider in the differential diagnosis of the overlap or variant syndromes.

IgG4-Associated Cholangitis

Marina G. Silveira

IgG4-associated cholangitis is the hepatobiliary manifestation of a recently characterized inflammatory systemic disease, associated with increased IgG4 serum levels and IgG4-positive lymphoplasmacytic infiltration. Often, patients present with obstructive jaundice, and imaging reveals stenoses of the extrahepatic or intrahepatic bile ducts, often in association with parenchymal pancreatic findings and irregularities of the pancreatic duct. The histologic findings include lymphoplasmacytic infiltrates, on
occasion resulting in tumefactive lesions (which can mimic malignancy), obliteratorive phlebitis, and fibrotic changes. Steroid treatment is the mainstay of management, but relapse is common after discontinuation of therapy or during tapering of steroids and may require further treatment.

Secondary Sclerosing Cholangitis: Pathogenesis, Diagnosis, and Management 269
Mohamad H. Imam, Jayant A. Talwalkar, and Keith D. Lindor

Secondary sclerosing cholangitis (SSC) is an aggressive and rare disease with intricate pathogenesis and multiple causes. Understanding the specific cause underlying each case of SSC is crucial in the clinical management of the disease. Radiologic imaging can help diagnose SSC and hence institute management in a timely manner. Management may encompass simple interventions, such as supportive therapy, antibiotics, and monitoring, or more serious measures, such as surgery, endoscopic intervention, or liver transplantation. Patients with AIDS cholangiopathy have limited therapeutic options and worsened survival. The disease should always be highly suspected in patients with primary sclerosing cholangitis with questionable diagnosis.

Alagille Syndrome and Other Hereditary Causes of Cholestasis 279
Jane L. Hartley, Paul Gissen, and Deirdre A. Kelly

Neonatal conjugated jaundice is a common presentation of hereditary liver diseases, which, although rare, are important to recognize early. Developments in molecular genetic techniques have enabled the identification of causative genes, which has improved diagnostic accuracy for patients and has led to a greater understanding of the molecular pathways involved in liver biology and pathogenesis of liver diseases. This review provides an update of the current understanding of clinical and molecular features of the inherited liver diseases that cause neonatal conjugated jaundice.

Systemic Causes of Cholestasis 301
Andrew S. deLemos and Lawrence S. Friedman

Systemic causes of cholestasis constitute a diverse group of diseases across organ systems. The pathophysiology of cholestasis in systemic disease can be a consequence of direct involvement of a disease process within the liver or extrahepatic biliary system or secondary to immune-mediated changes in bile flow. Evaluating a patient with cholestasis for a systemic cause requires an understanding of the patient’s risk factors, clinical setting (eg, hospitalized or immunosuppressed patient), clinical features, and pattern of laboratory abnormalities.

Advances in Pathogenesis and Treatment of Pruritus 319
Ruth Bolier, Ronald P.J. Oude Elferink, and Ulrich Beuers

The pathogenesis of itch during cholestasis is largely unknown and treatment options are limited. Lysophosphatidate, female steroid hormones, and endogenous opioids are among the agents discussed as potential pruritogens in cholestasis. The itch-alleviating action of guideline-based therapeutic interventions with anion exchanger resins, rifampicin, opioid
antagonists, and serotonin reuptake inhibitors are studied to unravel the molecular pathogenesis of itch. Still, a considerable part of the patients is in need of alternative experimental therapeutic approaches (eg, UV-B phototherapy, extracorporeal albumin dialysis, nasobiliary drainage), providing additional information about the enigmatic pathophysiology of cholestatic pruritus.

**Care of the Cholestatic Patient**  
Andrea A. Gossard

Cholestasis is defined as impairment of bile formation or bile flow. Care of the patient with cholestatic features is dependent on identifying the cause of the cholestasis, initiating appropriate treatment of reversible conditions, and the recognition and management of cholestatic-specific complications. Cholestasis may include extrahepatic ducts and intrahepatic bile ducts, or may be limited to one or the other. Jaundice and pruritus are the hallmarks of cholestasis clinically but biochemical evidence may, and often does, precede the clinical manifestations.

**Liver Transplant for Cholestatic Liver Diseases**  
Andres F. Carrion and Kalyan Ram Bhamidimarri

Cholestatic liver diseases include a group of diverse disorders with different epidemiology, pathophysiology, clinical course, and prognosis. Despite significant advances in the clinical care of patients with cholestatic liver diseases, liver transplant (LT) remains the only definitive therapy for end-stage liver disease, regardless of the underlying cause. As per the United Network for Organ Sharing database, the rate of cadaveric LT for cholestatic liver disease was 18% in 1991, 10% in 2000, and 7.8% in 2008. This review summarizes the available evidence on various common and rare cholestatic liver diseases, disease-specific issues, and pertinent aspects of LT.