Primary biliary cholangitis (PBC) is considered a model autoimmune disease, characterized by circulating antimitochondrial antibodies and a selective autoimmune destruction of intrahepatic cholangiocytes. PBC is heterogeneous in its presentation, symptomatology, disease progression, and response to therapy. The pathogenesis is still largely unknown, and epidemiologic studies have facilitated the identification of risk factors and the understanding of disease prevalence, geographic variations, heterogeneity, and differences in sex ratio. Recent studies from large international cohorts have better identified prognostic factors, suggesting a change in patient management based on risk-stratification tools to identify subgroups at greatest potential benefit from second-line therapies.

Both genetic background and environmental factors contribute to primary biliary cholangitis (PBC). Recent innovative technologies, such as genome-wide association studies, identified a remarkable number of susceptible nonhuman leukocyte antigen genes contributing to the development of PBC; however, they are primarily indicators of active immunologic responses commonly involved in autoimmune reactions. Thus, recent studies have focused on epigenetic mechanisms that would link genetic predisposition and environmental triggering factors. In PBC, methylation profiling and altered X chromosome architecture have been intensively explored in conjunction with a striking female predominance. Furthermore, microRNAs have been found to be associated with the etiology of PBC.

The biliary HCO$_3^-$ umbrella hypothesis states that human cholangiocytes and hepatocytes create a protective apical alkaline barrier against millimolar concentrations of potentially toxic glycine-conjugated bile salts in bile by secreting HCO$_3^-$ into the bile duct lumen. This alkaline barrier may retain bile salts in their polar, deprotonated, and membrane-impermeant state to avoid uncontrolled invasion of apolar toxic bile acids, which initiate apoptosis, autophagy, and senescence. In primary biliary cholangitis, defects of the biliary HCO$_3^-$ umbrella, leading to impaired biliary HCO$_3^-$ secretion, have been identified. Current medical therapies stabilize the putatively defective biliary HCO$_3^-$ umbrella and improve long-term prognosis.
Current Treatment Options for Primary Biliary Cholangitis

Kimberly A. Wong, Runalia Bahar, Chung H. Liu, and Christopher L. Bowlus

Primary biliary cholangitis is a progressive, autoimmune disease of the interlobular bile ducts, leading to secondary damage of hepatocytes that may progress to cirrhosis and liver failure. Until recently, the only approved treatment was ursodeoxycholic acid. However, 40% of patients do not have an adequate response. Obeticholic acid was approved for treatment as add-on therapy in this group of patients. Off-label use of fibrates has also been reported to be effective. Several new therapies are in development and may further add to the treatment options available to patients with primary biliary cholangitis.

Work in Progress: Drugs in Development

Gwilym J. Webb and Gideon M. Hirschfield

Primary biliary cholangitis is an archetypal autoimmune disease that causes cholestasis, fibrosis, and liver failure. Ursodeoxycholic acid and obeticholic acid are approved for its treatment. Not all patients respond, some are intolerant, many have ongoing symptoms, and new therapies are required. Herein the authors describe drugs in development and potential future biological targets. They consider compounds acting on the farnesoid X receptor/fibroblast growth factor 19 pathway, fibrates, and other agonists of the peroxisome proliferator-activated receptor family, transmembrane-G-protein-receptor-5 agonists, and several immunologic agents. They also consider the roles of bile acid reuptake inhibitors, nalfurafine, and fibrates in pruritus management.

Understanding and Treating Pruritus in Primary Biliary Cholangitis

Andres F. Carrion, Jordan D. Rosen, and Cynthia Levy

Pruritus is a common symptom with primary biliary cholangitis. Research has focused on refining understanding of the neurohumoral pathways involved in the transduction of pruritus from peripheral cutaneous receptors to the central nervous system and identifying modulating drugs. Current treatments have variable efficacy and safety. Because of the deleterious effects on the quality of life or debilitation, many patients necessitate individualized therapeutic approaches; clinicians may need to consider invasive treatment options. This article highlights various therapeutic interventions, from general measures to invasive strategies, and novel agents under investigation, providing clinicians with the management tricks of the trade.

Chronic Complications of Cholestasis: Evaluation and Management

David N. Assis

Patients with primary biliary cholangitis (PBC) are at risk for various harmful consequences of chronic cholestasis. These include fat-soluble vitamin deficiency, even in the setting of macronutrient sufficiency, as well as metabolic bone disease, including osteoporosis with fractures. Hyperlipidemia is often present and less commonly associated with risk of cardiovascular event; however, the long-term effect of new emerging therapies for PBC remains to be determined. Patients with PBC also have infrequent but notable risk of portal hypertension despite early-stage disease. This
article discusses the background, evaluation, and practical management of these complications of chronic cholestasis.

**Individualizing Care: Management Beyond Medical Therapy**
Laura Cristoferi, Alessandra Nardi, Pietro Invernizzi, George Mells, and Marco Carbone

The evolving research landscape, with advances in the omics technologies, availability of large-scale patient cohorts, and forthcoming availability of novel drugs in primary biliary cholangitis (PBC), is creating a unique opportunity for developing a precision medicine (PM) program. PM has potential to change the paradigm of management. The diagnostic workup of patients with PBC may include information on genetic variants and molecular signature to define a particular subtype of disease and provide an estimate of treatment response and survival. To reach this point, specific interventions, such as sequencing more genomes, creating bigger bio-banks, and linking biological information to health data, are needed.

**Natural History of Primary Biliary Cholangitis in the Ursodeoxycholic Acid Era: Role of Scoring Systems**
Aparna Goel and Woong Ray Kim

Primary biliary cholangitis (PBC) is a chronic disease that progresses to end-stage liver disease. Ursodeoxycholic acid (UDCA), the standard treatment for PBC for several decades, is associated with improved survival without liver transplant. Approximately 40% of patients do not respond to UDCA. Because of disease variability, there exist several prognostic models that incorporate various factors including biochemical response to UDCA. These models are useful for patient care and counseling as well as risk stratification for research and clinical trials, and the role of these models in the pre-UDCA and UDCA eras is discussed.

**Liver Biopsy in Primary Biliary Cholangitis: Indications and Interpretation**
Daisong Tan and Zachary D. Goodman

Primary biliary cholangitis is a disease characterized by immune-mediated bile duct destruction, followed by inflammation, scarring, and the development of chronic cholestasis and a slow progression to cirrhosis over the course of years. Liver biopsy has traditionally been used in conjunction with clinical evaluation and serologic autoantibody testing to establish the diagnosis, but it is no longer required in typical cases with positive antimitochondrial antibodies. Biopsy remains essential, however, in antimitochondrial antibody-negative patients or suspected overlap syndrome with autoimmune hepatitis, and if an adequate biopsy is performed, precise staging is possible for the assessment of prognosis.

**Antimitochondrial Antibody–Negative Primary Biliary Cholangitis: Is It Really the Same Disease?**
David M. Chascsa and Keith D. Lindor

Antimitochondrial antibody (AMA)-negative primary biliary cholangitis (PBC) is a term reserved for the condition with clinical and histopathologic
findings consistent with PBC but without positive AMA. There does not seem to be a natural progression from AMA negativity to positivity. Antinuclear and anti-smooth muscle antibodies are frequently found in the absence of histologic autoimmune hepatitis features. The disease course may be more severe than that of AMA-positive PBC. Response to standard therapy for PBC and autoimmune hepatitis varies. Nevertheless, there is insufficient evidence to suggest that AMA-negative PBC is different enough to warrant classification as a separate disease from AMA-positive PBC.

Overlap Syndrome of Autoimmune Hepatitis and Primary Biliary Cholangitis 603

Uyen To and Marina Silveira

Overlap syndrome of autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) is typically defined as concomitant or serial presentation with clinical features of both these distinct diseases. The Paris criteria and variations of the International Autoimmune Hepatitis group scoring systems for the diagnosis of AIH have been used to diagnose overlap syndrome. If left untreated, patients with overlap syndrome will have higher rates of portal hypertension, gastrointestinal bleeding, ascites, death, and need for liver transplant. Therefore, early identification is essential in providing appropriate therapy to potentially prevent long-term adverse outcomes in patients with overlap syndrome.

Current Status of Liver Transplantation for Primary Biliary Cholangitis 613

Maria T. Aguilar and Elizabeth J. Carey

Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease diagnosed with elevated alkaline phosphatase in the presence of antimitochondrial antibody. With the introduction and widespread use of ursodeoxycholic acid the proportion of patients with PBC undergoing liver transplant (LT) has decreased. However, up to 40% of patients are ursodeoxycholic acid nonresponders and require second-line treatment or progress to end-stage liver disease requiring LT. Several scoring systems have been developed and validated to assess treatment response and transplant-free survival in patients. Although PBC is a favorable indication for LT, recurrence of PBC may occur and requires biopsy for diagnosis.