Primary biliary cholangitis (PBC) is a cholestatic liver disease with potential evolution to liver cirrhosis when left untreated. Despite being rare, PBC has a substantial impact on the quality of life and survival of affected patients. Women are the most diagnosed worldwide; however, male subjects seem to have more aggressive disease and worse prognosis. Changing epidemiologic trends are emerging in PBC, with increasing global prevalence and slight smoothing of sex differences. In this review we present available data on incidence rates and prevalence of PBC worldwide, highlighting geographic differences and factors impacting clinical outcomes.

Primary biliary cholangitis (PBC) is a rare disease of the liver characterized by an autoimmune attack on the small bile ducts. PBC is a complex trait, meaning that a large list of genetic factors interacts with environmental agents to determine its onset. Genome-wide association studies have had a huge impact in fostering research in PBC, but many steps need still to be done compared with other autoimmune diseases of similar prevalence. This review presents the state-of-the-art regarding the genetic architecture of PBC and provides some thoughtful reflections about possible future lines of research, which can be helpful to fill the missing heritability gap in PBC.

Primary biliary cholangitis (PBC) is an autoimmune liver disease with a female predisposition and selective destruction of intrahepatic small bile ducts leading to nonsuppurative destructive cholangitis. It is characterized by seropositivity of antimitochondrial antibodies or PBC-specific antinuclear antibodies, progressive cholestasis, and typical liver histologic manifestations. Destruction of the protective bicarbonate-rich umbrella is attributed to the decreased expression of membrane transporters in biliary epithelial cells (BECs), leading to the accumulation of hydrophobic bile acids and sensitizing BECs to apoptosis. A recent X-wide association study reveals a novel risk locus on the X chromosome, which reiterates the importance of Treg cells.
Autoantibodies in Primary Biliary Cholangitis
Kristel K. Leung and Gideon M. Hirschfield

Primary biliary cholangitis (PBC) is a chronic immune-mediated liver disease characterized by a lymphocytic cholangitis, with subsequent cholestasis, progressive liver fibrosis, and ultimately complications arising from end-stage liver disease. Testing for autoantibodies is important in the diagnosis of PBC, as well as stratifying prognosis. This review focuses on the role of autoantibodies in the diagnosis of PBC, as well as the relationship between autoantibodies with pathophysiology and prognostication, along with a discussion regarding novel and other related disease autoantibodies.

Prognostic Scoring Systems in Primary Biliary Cholangitis: An Update
Miki Scaravaglio and Marco Carbone

Primary biliary cholangitis (PBC) is a complex, chronic disease with a heterogeneous presentation, disease progression, and response to therapy. Several prognostic models based on disease stage and/or treatment response enhance risk stratification and therapeutic management. Recent work on disease modeling proposed early prediction of outcomes at PBC onset, yet this has not been implemented in clinical practice. Although early stratification of patients based on their individual risk of developing end-stage liver disease may prove cost-effective and actually become matter of medical deontology to timely offer the best therapeutic option, given the forthcoming availability of novel, disease-modifying drugs. This review outlines established and novel prognostic systems in PBC and provides some perspectives on the potential role of omics-derived biomarkers in developing reliable risk prediction models and promoting the implementation of personalized medicine in PBC.

Primary Biliary Cholangitis in Males: Pathogenesis, Clinical Presentation, and Prognosis
Mina Shaker, Natalie Mansour, and Binu V. John

Primary biliary cholangitis (PBC) is an immune-mediated chronic liver disease characterized by progressive cholestasis, bile duct destruction, biliary fibrosis, and cirrhosis. Patients who respond to ursodeoxycholic acid have an expected survival similar to the general population. Although PBC primarily affects females, the prevalence in males is higher than was previously believed, with contemporary studies suggesting a female-to-male ratio of 4–6:1. A diagnosis of PBC is often delayed among males because of the myth that PBC is rare in males.

The Inconvenient Truth of Primary Biliary Cholangitis/Autoimmune Hepatitis Overlap Syndrome
Nasir Hussain and Palak J. Trivedi

The term ‘PBC/AIH-overlap’ has been applied when features of autoimmune hepatitis (AIH), be they biochemical, serological or histological, coexist with primary biliary cholangitis (PBC), either at first presentation or sequentially during disease course. Several treatment paradigms have been proposed, extrapolated from those of the primary conditions.
However, there are no randomised studies showing improved survival with combination therapy compared to bile acid monotherapy. In the absence of high-quality evidence, multidisciplinary patient-specific approaches must be used to individualise treatment pathways, with appreciation that disease phenotypes are not always static, differ in treatment responses, and have the potential to evolve over time.

Noninvasive Evaluation of Fibrosis and Portal Hypertension in Primary Biliary Cholangitis

Christophe Corpechot

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that, if left untreated or insufficiently treated, inexorably progresses toward cirrhosis and its potentially fatal complications. Alongside with the biochemical response to ursodeoxycholic acid therapy, advanced liver fibrosis and portal hypertension (PH) were shown to be major prognostic determinants in PBC. Therefore, one of the goals of noninvasive PBC evaluation should be to early diagnose compensated advanced disease and/or clinically significant PH. In this article, the main methods of noninvasive assessment of liver fibrosis and PH in PBC, and their clinical relevance, will be reviewed.

Hepatocellular Carcinoma in Primary Biliary Cholangitis

Alexander M. Sy, Raphaella D. Ferreira, and Binu V. John

Hepatocellular carcinoma (HCC) is potentially fatal complication affecting patients with primary biliary cholangitis (PBC). The incidence of HCC is 13 per 1000 person-years in patients with PBC cirrhosis, but much lower at 2.7 per 1000 person-years among patients with PBC without cirrhosis. Risk factors for the development of HCC in PBC include the presence of advanced fibrosis or cirrhosis and male sex, with some studies suggesting that treatment with ursodeoxycholic acid (UDCA) and UDCA response may reduce risk.

Treatment of Primary Biliary Cholangitis: First-Line and Second-Line Therapies

Chung-Heng Liu and Christopher L. Bowlus

Primary biliary cholangitis (PBC) is an autoimmune disease of the interlobular bile ducts leading to secondary damage of hepatocytes and may progress to cirrhosis and liver failure. The first-line treatment is ursodeoxycholic acid; up to 40% of patients do not have an adequate response and remain at risk of disease progression. Obeticholic acid has been conditionally approved for the treatment of PBC as add-on therapy and bezafibrate has shown similar efficacy in this group of patients. Several new therapies are in development and may further add to the treatment options available to patients with PBC.

Evaluation and Management of Pruritus in Primary Biliary Cholangitis

Miriam M. Düll and Andreas E. Kremer

Chronic pruritus is a classic symptom in patients with primary biliary cholangitis. It affects up to two-thirds of patients in the course of the disease.
Efficient therapy consists of topical treatment combined with systemic options such as anion exchangers, rifampicin, bezafibrate, μ-opioid receptor antagonists, selective-serotonin receptor uptake inhibitors, and gabapentinoids. Future therapeutic approaches may contain the selective blockade of the enterohepatic cycle by inhibiting the ileal bile acid transporter, the agonism at κ-opioid receptors, and antagonism of the mas-related G protein–coupled receptor X4. As nondrug treatment, ultraviolet B therapy, albumin dialysis, and biliary drainage are available at specialized centers.

**Novel Therapies in Primary Biliary Cholangitis: What Is in the Pipeline?**

Keri-Ann Buchanan-Peart and Cynthia Levy

Primary biliary cholangitis is a chronic autoimmune disease characterized by inflammation and the progressive destruction of small intrahepatic bile ducts. Current first-line treatment includes ursodeoxycholic acid; however, a significant number of patients have an inadequate response to therapy. These patients are at risk of liver failure requiring liver transplantation and experience a poor quality of life due to refractory symptoms. This manuscript aims to shed light on the current and prospective treatment options that may slow disease progression and improve these patients' symptoms.

**Liver Transplantation for Primary Biliary Cholangitis**

Eric F. Martin

Despite a significant increase in the total number of liver transplants (LTs) performed over the last 3 decades, primary biliary cholangitis (PBC) has become an uncommon indication for LT, which likely reflects the benefits of earlier diagnosis and available treatment, such as ursodeoxycholic acid (UDCA). Nonetheless, LT remains the only cure for patients with progressive PBC despite medical therapy with survival rates that are among the highest of all indications for LT. Post-LT PBC patients, however, are at increased risk of rejection and disease recurrence.