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Hepatitis C Genotype 3 Infection: Pathogenesis and Treatment Horizons  645
Haripriya Maddur and Steven L. Flamm

Genotype 3 hepatitis C infection is the second most common genotype worldwide and accounts for most infections in Southeast Asia. It is a particularly ominous genotype because it has been linked to increased mortality, specifically increased late-stage liver events, accelerated development of hepatic fibrosis, and an increased risk of hepatocellular carcinoma. As new treatment regimens for hepatitis C have been emerging, treatment of genotype 3 often requires longer treatment duration with decreased response rates as compared with other genotypes.

Primer on Hepatitis C Virus Resistance to Direct-Acting Antiviral Treatment: A Practical Approach for the Treating Physician  659
Ilan S. Weisberg and Ira M. Jacobson

Treatment of hepatitis C virus has been vastly transformed by the arrival of all-oral, interferon-free, direct-acting antiviral regimens. Despite the high rate of success with these agents, a small portion of treated patients fail therapy and the emergence of viral resistance is the most common cause of treatment failure. Given the error-prone hepatitis C virus polymerase, baseline resistance-associated substitutions (RASs) may be present before direct-acting antiviral exposure. Clinicians need to understand the role of baseline RAS testing and the settings and manner in which the treatment regimens need to be customized based on the presence of RASs.

Genetic Testing in Liver Disease: What to Order, in Whom, and When  673
Emily A. Schonfeld and Robert S. Brown Jr

Genetic causes of liver disease lead to a wide range of presentations, from mildly abnormal liver tests to acute liver failure. This article discusses the indications for testing and what to test for in hereditary hemochromatosis, progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis, lysosomal acid lipase deficiency, Gilbert syndrome, alpha-1 antitrypsin deficiency, and Wilson disease.

Liver Disease in Patients on Total Parenteral Nutrition  687
Arnab Mitra and Joseph Ahn

Parenteral nutrition–associated liver disease (PNALD) spectrum ranges from liver enzyme abnormalities to steatosis to fibrosis, and, eventually, cirrhosis from total parenteral nutrition (TPN). The pathophysiology is
postulated to be multifactorial. Diagnosis in adults is primarily by exclusion, eliminating other causes of chronic liver disease or cirrhosis, and other factors seen in critically ill or postoperative patients on TPN. Principal treatment is avoiding TPN. If this is not feasible, research supports fish oil–based lipid emulsions in TPN formulations to reduce risk and progression of PNALD. With liver and intestinal failure, liver and intestine transplantation is an option.

The Liver in Oncology 697
Renu Dhanasekaran and Paul Y. Kwo

Gastroenterologists and hepatologists will encounter oncology patients who develop abnormal liver tests, patients with hepatic malignancies, and patients with acute and chronic liver disease who require chemotherapy or immediate evaluation. Chemotherapy can cause liver injury owing to toxic effects or idiosyncratic reactions. Immune checkpoint inhibitors may be associated with autoimmune-mediated liver toxicities. Veno-occlusive disease requires immediate evaluation. Nodular regenerative hyperplasia is a chronic progressive disorder. Screening and prophylaxis for reactivation of hepatitis B is important to minimize complications in patients receiving chemotherapy. Patients with metastatic lesions can undergo resection or ablation. Hepatic injury may occur in those receiving radiation-based therapies.

An Update on the Treatment and Follow-up of Patients with Primary Biliary Cholangitis 709
Blaire E. Burman, Manan A. Jhaveri, and Kris V. Kowdley

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by chronic granulomatous lymphocytic cholangitis of the small bile ducts. PBC was a leading indication for liver transplantation in the United States; with early diagnosis and treatment, most patients with PBC have a normal life expectancy. Pathogenesis involves inflammatory damage of bile duct epithelium secondary to innate and adaptive immune responses, and toxicity from accumulated bile acids. Cholestasis and disease progression can lead to cirrhosis. Extrahepatic complications include dyslipidemia, metabolic bone disease, and fat-soluble vitamin deficiency. Ursodeoxycholic acid is a well-established therapy. Novel targeted therapeutics are being developed.

Primary Sclerosing Cholangitis: What the Gastroenterologist and Hepatologist Need to Know 725
Andrea A. Gossard and Gregory J. Gores

Primary sclerosing cholangitis (PSC) is a chronic, idiopathic biliary tract disease characterized by segmental strictures. The disease is progressive with no proven treatments and may eventually lead to cirrhosis and end-stage liver disease. Abrupt changes in liver biochemistries, pain, and/or cholangitis may suggest a dominant stricture amenable to endoscopic therapy or the development of cholangiocarcinoma. Patients with PSC are at increased risk of cholangiocarcinoma. There is a strong association
with inflammatory bowel disease, and an associated increased risk of colorectal cancer. Colonoscopy every 1 to 2 years is appropriate.

Treatment Strategies for Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Pegah Golabi, Haley Bush, and Zobair M. Younossi

Nonalcoholic fatty liver disease is recognized as a global health problem and as a common cause of chronic liver disease. Nonalcoholic steatohepatitis (NASH) carries an increased risk for development of advanced liver disease. Lifestyle modifications with diet and exercise have been the initial management recommendation. However, these changes are difficult to achieve and sustain over time. There are pharmacologic agents being considered for treatment of NASH. Some target insulin resistance and others focus on oxidative stress, inflammation, apoptosis, and fibrosis. There is a great deal of effort to develop therapeutic regimens for patients with NASH and NASH with significant fibrosis.

Wilson Disease: Diagnosis, Treatment, and Follow-up

Michael L. Schilsky

Consideration of a diagnosis of Wilson disease is still the critical factor in testing for and establishing disease diagnosis. In association with other clinical and biochemical tests, liver biopsy results and molecular genetic testing also can be used to generate a score for diagnosing Wilson disease. Medical therapy is effective for most patients; liver transplantation can rescue those with acute liver failure or those with advanced liver disease who fail to respond to or discontinue medical therapy. Treatment monitoring must be done at regular intervals and includes clinical evaluation, liver tests and blood counts, and copper metabolic parameters.

Acute Liver Failure

Chalermrat Bunchorntavakul and K. Rajender Reddy

Acute liver failure is a life-threatening condition of heterogeneous etiology. Outcomes are better with early recognition and prompt initiation of etiology-specific therapy, intensive care protocols, and liver transplantation (LT). Prognostic scoring systems include the King’s College Criteria and Model for End-stage Liver Disease score. Cerebral edema and intracranial hypertension are reasons for high morbidity and mortality; hypertonic saline is suggested for patients with a high risk for developing intracranial hypertension, and when it does, mannitol is recommended as first-line therapy. Extracorporeal liver support system may serve as a bridge to LT and may increase LT-free survival in select cases.

Follow-up of the Post-Liver Transplantation Patient: A Primer for the Practicing Gastroenterologist

Amanda Cheung and Josh Levitsky

The focus in liver transplantation in the next 10 years will likely change from preventing viral disease recurrence to minimizing the toll of rejection and fatty liver disease, minimizing the complications from immunosuppression
with withdrawal strategies, and more optimal management of long-term risks, such as malignancy, cardiovascular disease, and renal failure. In addition, now that short-term results (<1 year) have improved significantly, there will be a shift toward improving long-term patient and graft survival, as well as a focus on primary care preventive strategies.