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Jorge L. Herrera

The Liver and Celiac Disease  167
Alberto Rubio-Tapia and Joseph A. Murray

Celiac disease is a multisystem disorder. Celiac hepatitis characterized by gluten-responsive mild elevation of transaminases is the more common liver manifestation of celiac disease. Celiac disease may also be associated or coexist with other chronic liver disorders. Shared genetic risk and increased intestinal permeability have been suggested to be the most relevant events in the pathogenesis of liver injury in celiac disease. The aim of this article is to review the full spectrum of liver disorders in patients with celiac disease.

The Liver in Sickle Cell Disease  177
Eleni Theocharidou and Abid R. Suddle

Patients with sickle cell disease can develop liver disease as a result of intrahepatic sickling of erythrocytes, viral hepatitis and iron overload secondary to multiple blood transfusions, and gallstone disease as a result of chronic hemolysis. The spectrum of clinical liver disease is wide and often multifactorial. Some patients develop cirrhosis that may progress to end-stage liver failure. Limited evidence exists for medical treatments. Exchange blood transfusions may improve outcomes in the acute liver syndromes. Liver transplantation may be an option for chronic liver disease. The role for prophylactic cholecystectomy in preventing complications of gallstone disease is controversial.

Hepatic Complications of Inflammatory Bowel Disease  191
Mahmoud Mahfouz, Paul Martin, and Andres F. Carrion

Hepatobiliary disorders are commonly encountered in patients with inflammatory bowel disease (IBD). Although primary sclerosing cholangitis is the stereotypical hepatobiliary disorder associated with IBD, other diseases, including autoimmune hepatitis and nonalcoholic fatty liver disease, also are encountered in this population. Several agents used for treatment of IBD may cause drug-induced liver injury, although severe hepatotoxicity occurs infrequently. Furthermore, reactivation of hepatitis B virus infection may occur in patients with IBD treated with systemic corticosteroids and biologic agents.

The Liver in Circulatory Disturbances  209
Moira B. Hilscher and Patrick S. Kamath

Liver diseases frequently coexist with heart disease. The causes of coexistent heart and liver disease are categorized into four groups: (1) heart
disease affecting the liver, (2) liver disease affecting the heart, (3) cardiac and hepatic manifestations of a common cause, and (4) coexistent heart and liver disease with distinct causes. Discerning the cause of cardiac and liver dysfunction is important in the management of these conditions, particularly when considering surgical intervention or heart or liver transplantation.

Hepatobiliary Complications in Critically Ill Patients 221
Amanda Cheung and Steven Flamm

Critically ill patients frequently present with the systemic inflammatory response syndrome, which is largely a reflection of the liver’s response to injury. Underlying hepatic congestion is a major risk factor for hypoxic liver injury, the most common cause for hepatocellular injury. Cholestatic liver injury often occurs in critically ill patients due to inhibition of farnesoid X receptor (FXR), the main regulator of bile acid handling, particularly in the liver and intestines. Additional injury to the liver occurs due to alterations in the bile acid pool with increased cytotoxic forms and disturbance in the typical processing of xenobiotics in the liver.

Endocrine Diseases and the Liver: An Update 233
Miguel Malespin and Ammar Nassri

The endocrine system is a complex interconnected system of organs that control corporeal processes and function. Primary endocrine organs are involved in hormonal production and secretion but rely on a bevy of signals from the hypothalamic-pituitary axis and secondary endocrine organs, such as the liver. In turn, proper hepatic function is maintained through hormonal signaling. Thus, the endocrine system and liver are co-dependent, and diseases affecting either organs can lead to alterations in function within their counterparts. This article explores the hepato-endocrine relationship, including the effects on endocrine diseases on the liver.

Rheumatologic Diseases and the Liver 247
Agazi Gebreselassie, Farshad Aduli, and Charles D. Howell

A variety of rheumatologic disorders may affect the liver. There is a significant epidemiologic, genetic, and immunologic overlap between immune-mediated rheumatologic disorders and autoimmune liver diseases. There is an increased frequency of autoimmune liver diseases, such as primary biliary cholangitis, autoimmune hepatitis, primary sclerosing cholangitis, or overlap syndrome, in patients with systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, systemic sclerosis, vasculitis, and other immune-related diseases. Non-immune-mediated rheumatologic diseases such as gouty arthritis may also have hepatic manifestations. Furthermore, medications used to treat rheumatologic diseases occasionally cause liver dysfunction. Conversely, primary immune-mediated and non-immune-mediated liver disorders may present with rheumatologic manifestations.
Hepatic Manifestations of Cystic Fibrosis
Sasan Sakiani, David E. Kleiner, Theo Heller, and Christopher Koh

Cystic fibrosis liver disease (CFLD) remains the third leading cause of death in patients with cystic fibrosis. Although most patients with CFLD present in childhood, recent studies suggest a second wave of liver disease in adulthood. There are no clear guidelines for diagnosing CFLD. Treatment options for CFLD remain limited, and while UDCA is widely used, its long-term benefit is unclear. Those who develop hepatic decompensation or uncontrolled variceal bleeding may benefit from liver transplant, either alone, or in combination with lung transplant.

Intestinal Failure-Associated Liver Disease
Loris Pironi and Anna Simona Sasdelli

Intestinal failure-associated liver disease (IFALD) is characterized by either liver steatosis or cholestasis and may develop in patients on long-term home parenteral nutrition for chronic intestinal failure. The pathogenesis of IFALD is multifactorial and includes gastrointestinal disease-related, parenteral nutrition-related, and systemic-related factors. Alteration of bile acid enterohepatic circulation, gut microbiome, and intestinal permeability, seem to be the main mechanisms. Patients forced to a total oral fasting regimen are at greater risk. Parenteral nutrition overfeeding and/or of soybean-based lipid emulsion may be contributing factors. Prevention and treatment are based on avoiding and promptly treating all the risk factors.

Hepatic Manifestations of Lymphoproliferative Disorders
Chalermrat Bunchorntavakul and K. Rajender Reddy

Hepatic abnormalities in patients with lymphoproliferative disorders are common and can occur from direct infiltration by abnormal cells, bile duct obstruction, paraneoplastic syndrome, hemophagocytic syndrome, drug-induced liver injury, opportunistic infections, and reactivation of viral hepatitis. Hepatic involvement by lymphoma is often in association with systemic disease and rarely seen as a primary hepatic lymphoma. Vanishing bile duct syndrome is a well-known complication of Hodgkin disease. Antiviral prophylaxis for hepatitis B virus (HBV) reactivation is recommended for all HBsAg\(^+\) patients undergoing chemotherapy and all resolved HBV patients undergoing rituximab therapy and stem cell transplantation.

Liver Disease in Human Immunodeficiency Virus Infection
Katerina G. Oikonomou, Eugenia Tsai, Dost Sarpel, and Douglas T. Dieterich

Liver disease in human immunodeficiency virus (HIV) remains a main cause of morbidity and mortality. Liver-related morbidity and mortality can be caused by multiple etiologic factors, including opportunistic infections, direct and indirect effects of antiretrovirals, direct and indirect effects of HIV, and viral hepatitis. These factors present with varied liver pathophysiologic mechanisms that lead to abnormalities in liver enzymes and synthetic function test, followed by distinct clinical presentations. This article elucidates the direct effects on HIV in the liver and explores the

**Sarcoidosis and the Liver** 331
Manoj Kumar and Jorge L. Herrera

Hepatic granulomas are a common finding in systemic sarcoidosis, but most patients remain asymptomatic. Elevated alkaline phosphatase is the most common sign of hepatic sarcoidosis (HS). Lacking a specific diagnostic test, the diagnosis of HS is one of exclusion. Therapy may be indicated in a minority of patients to control symptoms, but the effects of therapy in the natural history of HS are unknown.

**Liver Diseases During Pregnancy** 345
Karen Ma, Daniel Berger, and Nancy Reau

Liver diseases during pregnancy pose a unique clinical challenge because they can affect the lives of both the mother and unborn child. Although severe liver disease is rare, pregnancy-related liver disease affects approximately 3% of pregnancies and can be fatal. Timely recognition and diagnosis are essential in order to institute appropriate management strategies. This article provides an overview of liver diseases during pregnancy and is divided into 2 sections: (1) liver diseases specific to pregnancy, and (2) preexisting or coincident liver diseases during pregnancy.

**Obstructive Sleep Apnea and the Liver** 363
Malav P. Parikh, Niyati M. Gupta, and Arthur J. McCullough

Nonalcoholic fatty liver disease (NAFLD), a disorder of altered metabolic pathways, is increasing worldwide. Recent studies established obstructive sleep apnea (OSA) and chronic intermittent hypoxia (CIH) as NAFLD risk factors. Studies have ascertained that CIH is independently related to NAFLD. Continuous positive airway pressure (CPAP) shows inconsistent results regarding its efficacy in improving NAFLD. Observational, longer duration CPAP therapy studies have shown positive outcomes, whereas shorter duration, randomized controlled trials have shown no benefit. A multifaceted approach to NAFLD management with sufficiently longer duration of CPAP therapy may be beneficial in patients with moderate to severe OSA.