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Preface: Advances in Cholestatic Liver Diseases xiii

Cynthia Levy

The Gut-Liver Axis in Primary Sclerosing Cholangitis 1

Bertus Eksteen

Dysregulation of the key genetic, immunologic, and microbiome compounds of the gut-liver axis is the basis for inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC). This creates opportunities to accelerate therapies that have been traditionally developed for IBD to be used in PSC to the benefit of both diseases. Shared genetic susceptibility loci has yielded important clues into the pathogenesis of PSC-IBD. Understanding of the critical links between PSC and IBD are essential in designing clinical care pathways for these complex patients.

The Immunogenetics of Autoimmune Cholestasis 15

Palak J. Trivedi and Gideon M. Hirschfield

The immune-mediated hepatobiliary diseases, primary biliary cirrhosis and primary sclerosing cholangitis are relatively rare, and account for a significant amount of liver transplant activity and liver-related mortality globally. Precise disease mechanisms are yet to be described, although a contributory role of genetic predisposition is firmly established. In addition to links with the major histocompatibility complex, a number of associations outside this region harbor additional loci which underscore the fundamental role of breaks in immune tolerance and mucosal immunogenicity in the pathogenesis of autoimmune biliary disease. We provide an overview of these key discoveries before discussing putative avenues of therapeutic exploitation based on existing findings.

Making Sense of Autoantibodies in Cholestatic Liver Diseases 33

Simona Marzorati, Pietro Invernizzi, and Ana Lleo

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the most common chronic cholestatic liver diseases (CLD) in adults, and are associated with immune mechanisms. PBC is considered a model autoimmune disease, and more than 90% of patients present very specific autoantibodies against mitochondrial antigens. Whether PSC should be considered an autoimmune, or merely immune-mediated disease, is still under debate. This review addresses the clinical relevance of autoantibodies in CLD and their pathogenic mechanisms, and it illustrates the technology available for appropriate autoantibody detection.

New Thoughts on Immunoglobulin G4-Related Sclerosing Cholangitis

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Wouter L. Smit, Emma L. Culver, and Roger W. Chapman

Immunoglobulin G4 (IgG4)-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of the multisystem IgG4-related disease. IgG4-SC presents with biliary strictures and/or masses that can bear a striking similarity to other malignant and inflammatory diseases. Diagnosis is based on a combination of clinical, biochemical, radiological, and histologic findings with careful exclusion of malignant disease. Corticosteroids are the mainstay of treatment with good clinical, biochemical, and radiological responses. This review provides a comprehensive overview of the current knowledge of the prevalence, clinical features, radiology and histology findings, diagnosis, treatment, natural history, and pathophysiology of IgG4-SC.

Primary Sclerosing Cholangitis: Multiple Phenotypes, Multiple Approaches

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Souvik Sarkar and Christopher L. Bowlus

Primary sclerosing cholangitis (PSC) is a heterogeneous, idiopathic, inflammatory disorder frequently associated with inflammatory bowel diseases. PSC patients may be classified into several subphenotypes. Investigations of pediatric, nonwhite, and female PSC patients have revealed distinguishing features. The natural history of PSC is variable in progression with numerous possible clinical outcomes. PSC patients may suffer bacterial cholangitis, cholangiocarcinoma, or colorectal adenocarcinoma. Treatments focusing on bile acid therapy and immunosuppression have not proven beneficial. Interest in PSC and international collaboration has led to improved understanding of the heterogeneity and the genetic structure and introduced possible effective therapeutics.

Cancer Risk and Surveillance in Primary Sclerosing Cholangitis

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Trine Folseraas and Kirsten Muri Boberg

Primary sclerosing cholangitis (PSC) is a chronic, progressive disease characterized by inflammatory and fibrosing strictures of the biliary tree. PSC is associated with a high lifetime risk of hepatobiliary and colorectal cancers. The nature of the carcinogenic process in PSC is not well established. The lack of diagnostic methods for early detection and the limited therapeutic options for cholangiocarcinoma constitute a major challenge in the current handling of PSC patients. The article reviews the risk for cancer development in PSC and discusses surveillance strategies for PSC-associated cancers.

Sclerosing Cholangitis in Children and Adolescents

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Giorgina Mieli-Vergani and Diego Vergani

Sclerosing cholangitis in pediatric age is a severe disease, often associated with inflammatory bowel disease. It recognizes different etiologies. Management and prognosis depend on the underlying cause. A high proportion of patients have autoimmune features similar to those of autoimmune hepatitis and respond biochemically to immunosuppression, although bile duct disease progresses in half of them leading to liver transplant. The disease can recur after transplant. Severity of liver disease and

risk of recurrence after transplant are linked to the severity of bowel disease.

Novel Therapies on Primary Biliary Cirrhosis 113

Frank Czul and Cynthia Levy

All patients with primary biliary cirrhosis (PBC) and abnormal liver biochemistry should be considered for specific therapy. Ursodeoxycholic acid (UDCA) is the only FDA-approved drug for treating PBC. Approximately 40% of patients with PBC respond incompletely to treatment with UDCA, thus having increased risk of death or need for liver transplantation. No second-line therapies for patients with inadequate response to UDCA therapy have been approved. This review provides a current perspective on potential new approaches to treatment in PBC, and highlights some of the challenges we face in evaluating and effectively implementing those treatments.

Understanding and Treating Fatigue in Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis 131

Laura Jopson, Jessica K. Dyson, and David E.J. Jones

Fatigue is a significant problem for patients with primary biliary cirrhosis and although experienced less by patients with primary sclerosing cholangitis, a minority still report significant fatigue. Fatigue is the symptom with the greatest impact on quality of life, particularly when associated with social dysfunction. The pathogenesis of fatigue in cholestatic liver disease is complex, poorly understood, and probably has central and peripheral components. Managing fatigue in cholestatic liver disease presents a challenge for clinicians given the complexity and its numerous associations. This article presents a structured approach to managing fatigue in cholestatic liver disease to improve fatigue severity and quality of life.

Utility of Noninvasive Markers of Fibrosis in Cholestatic Liver Diseases 143

Christophe Corpechot

Methods of liver fibrosis assessment have changed considerably in the last 20 years, and noninvasive markers have now been recognized as major first-line tools in the management of patients with chronic viral hepatitis infection. But what about the efficiency and utility of these surrogate indices for the more uncommon chronic cholestatic liver diseases, namely primary biliary cirrhosis and primary sclerosing cholangitis? This article provides clinicians with a global overview of what is currently known in the field. Both diagnostic and prognostic aspects of noninvasive markers of fibrosis in cholestatic liver diseases are presented and discussed.

Total Parenteral Nutrition–Induced Cholestasis: Prevention and Management 159

Sue V. Beath and Deirdre A. Kelly

When cholestasis occurs in patients receiving total parenteral nutrition, it is the result of many pathogenic pathways converging on the hepatic acinus. The result may be a temporary rise in liver function tests. The resulting fibrosis, portal hypertension, and jaundice are hallmarks of type 3

intestinal-associated liver disease to which children are more susceptible than adults. The key to prevention is in identifying high-risk scenarios, meticulous monitoring, and personalized prescription of parenteral nutrition solutions combined with an active approach in reducing the impact of inflammatory events when they occur by prompt use of antibiotics and line locks.

New Insights on Intrahepatic Cholestasis of Pregnancy

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Annarosa Floreani and Maria Teresa Gervasi

Intrahepatic cholestasis of pregnancy (ICP) is characterized by maternal pruritus, and elevated serum transaminases and bile acids. Genetic defects in at least 6 canalicular transporters have been found. Association studies stress the variability of genotypes, different penetrance, and influence of environmental factors. Serum autotaxin is a sensitive, specific, and robust diagnostic marker. Elevated maternal bile acids correlate with fetal complications. Long-term sequelae for mothers include the gallstone risk and chronic liver disease. There is an association between ICP and hepatitis C. Current treatment is ursodeoxycholic acid, owing to benefits on pruritus, liver function, safety, and decreased rates of adverse effects.

Liver Transplantation for Cholestatic Liver Diseases in Adults

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Vandana Khungar and David Seth Goldberg

Liver transplantation (LT) is an established lifesaving therapy for patients with cholestatic liver diseases, including primary cholestatic diseases, namely primary sclerosing cholangitis and primary biliary cirrhosis, as well as secondary forms of cholestatic liver disease, including those with cholestatic complications of LT needing a retransplant. Patients with cholestatic liver diseases can be transplanted for complications of end-stage liver disease or for disease-specific symptoms before the onset of end-stage liver disease. These patients should be regularly assessed. Patient survival after LT for cholestatic liver diseases is generally better than for other indications.