
Alcoholic and Non-Alcoholic Fatty Liver Disease

Naga Chalasani • Gyongyi Szabo
Editors

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Bench to Bedside

 Springer

Editors

Naga Chalasani, M.D.
Division of Gastroenterology
and Hepatology
Indiana University School of Medicine
Indianapolis, IN, USA

Gyongyi Szabo, M.D., Ph.D.
Department of Medicine
University of Massachusetts Medical
School
Worcester, MA, USA

ISBN 978-3-319-20537-3 ISBN 978-3-319-20538-0 (eBook)
DOI 10.1007/978-3-319-20538-0

Library of Congress Control Number: 2015958158

Springer Cham Heidelberg New York Dordrecht London
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Printed on acid-free paper

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(www.springer.com)

To my parents, Sujani and C.N. Rao, for their big dreams and sacrifices, and to my brother, Prasad, who is always there for me; To my wife, Satya, and to our son, Sai, who are the joy of my life; To my namesake, DWC, who is behind most of my major professional milestones.

Naga Chalasani

To my family, mentors, and friends.

Gyongyi Szabo

Preface

Alcoholic liver disease (ALD) and Nonalcoholic fatty liver disease (NAFLD) are among the most common causes of cirrhosis, liver failure, and liver cancer worldwide. Histologically, they resemble each other and they both share several common pathogenetic mechanisms. Over the last decade, steady progress has been made in almost all aspects of these two diseases, and this book reflects our attempt to integrate these new developments into existing disease pathogenesis and management paradigms. This book is developed as a state-of-the-art resource for medical students, clinicians, pathologists, clinical researchers, basic science investigators, and pharmaceutical industry worldwide. At the outset, we believed that a single book that includes both ALD and NAFLD would be highly desirable for various stakeholders, but organizing various chapters into a logical sequence turned out to be somewhat challenging. After much deliberation, we have decided to divide our book into multiple sections (e.g., epidemiology, pathogenesis, and clinical features) and then have both ALD and NAFLD chapters next to each other to make it easier for the readers. All contributors, who are experts in their respective areas, have done a masterful job with their chapters and we are indebted for their contributions.

Drs. Mariana Lazo and Mack Mitchell start the book with their review of the epidemiology and risk factors of ALD, followed by a detailed review of the epidemiology and risk factors of NAFLD by Drs. Zobair Younossi and Abhijit Chowdhury. These two chapters set the stage for two marvelous chapters on the pathogenesis of ALD (Drs. Gavin Arteel and David Crabb) and NAFLD (Dr. Jacquelyn Maher). Drs. Jun Xu and Hide Tsukamoto provide an outstanding review of various animal models for studying ALD, and Drs. Mariana Machado and Anna Mae Diehl have done an equally elegant job in describing a large number of animal models which have been developed in the recent past to investigate NAFLD. There have been several major developments in better understanding the genetic basis of these diseases (especially NAFLD), and Drs. Silvia Sookoian and Carlos Pirola have provided an in-depth review of the genetic basis of both ALD and NAFLD in a single chapter.

Moving to more clinical chapters, Dr. Craig McClain and colleagues review clinical features, disease modifiers, and natural history of ALD and alcoholic hepatitis, whereas Drs. Dawn Torres and Stephen Harrison describe in detail the clinical features, disease modifiers, and natural history of NAFLD. Currently, there are no approved therapies for either alcoholic hepatitis or nonalcoholic steatohepatitis (NASH), but there is tremendous interest among various stakeholders to develop novel and effective treatments

for these conditions. To conduct registration clinical trials that are needed for regulatory approval, we must have valid diagnostic criteria and therapeutic end points. The landscape in this area is rapidly evolving and Drs. Cheong, Stein, and Bataller describe state-of-the-art diagnostic criteria for various sub-phenotypes of ALD and therapeutic end points for various stages of clinical trials in individuals with various forms of ALD. The clinical trials' landscape for NAFLD and NASH has dramatically changed over the last 3 years, and there is an evolving consensus on "NASH without fibrosis" and "NASH with advanced fibrosis" as approvable indications from a regulatory standpoint. Also, clear-cut guidance from the regulatory agencies is becoming available with regard to primary end points for Phase 2 and Phase 3 clinical trials in NAFLD. Dr. Arun Sanyal, a pioneer in the field of NASH clinical trials, describes valid diagnostic approaches and clinical end points for treatment in NAFLD and NASH in Chap. 11.

Liver histology remains the gold standard for characterizing the severity of NAFLD and for diagnosing NASH, and there are recent studies showing the prognostic value of liver histology in individuals with alcoholic hepatitis. Drs. David Kleiner and Pierre Bedossa, two expert hepatopathologists, tackle the liver histology in ALD and NAFLD in a comprehensive fashion. NAFLD and ALD are strongly associated with hepatic and extrahepatic malignancies, and Drs. Vasilis Vasilou and Sam Zakhari thoroughly cover hepatic and extrahepatic malignancies in ALD, whereas Drs. Fabio Nascimbeni and Vlad Ratziu describe the putative mechanisms and risk factors of malignancies in NAFLD with a special emphasis on the risk of hepatocellular carcinoma in individuals with non-cirrhotic NAFLD.

Alcoholic hepatitis continues to carry significant morbidity and mortality and unfortunately no new effective therapies have been developed for this condition in nearly 3 decades. The role and timing of liver transplantation for individuals with acute alcoholic hepatitis remain controversial and geographically variable. Dr. Szabo and Dr. Jan Petrasek comprehensively describe existing and emerging therapies, novel targets, and the role of liver transplantation for individuals with various forms of ALD. As stated before, there is tremendous interest in developing effective pharmacological agents for NASH and there has been an explosion of Phase 2 and Phase 3 trials in this space. Drs. Samer Gawrieh and Naga Chalasani review various treatments including lifestyle modification, bariatric surgery, and new compounds to treat liver disease and coexisting comorbidities in individuals with NAFLD. Last but not the least, Drs. Hannah Awai and Jeffrey Schwimmer provide a comprehensive review of NAFLD in children, a growing problem with substantial disease burden.

As research is progressing rapidly in these two disorders, we suspect some important articles that have just been published may be missing in this book. Regrettably, such omissions are unavoidable due to lengthy editing and publishing process involved in developing a multiauthored textbook. Nonetheless, we hope this book provides an updated, broad, and practical review of all aspects of ALD and NAFLD.

Acknowledgments

We are indebted to all contributing authors as this book would have not been possible without their fantastic chapters. Despite their overwhelming responsibilities and competing demands, they graciously agreed to take yet another commitment and delivered their work in a timely fashion. There are important developments in the field almost on a daily basis and such developments are possible because of funding agencies across the world investing in biomedical research, emerging and established scientists and investigators continuing to pursue high-quality research, pharmaceutical industry exploring new therapeutic frontiers, and importantly, patients worldwide offering themselves through their participation in human investigations and early and late phase clinical trials. We are very thankful to all these stakeholders. We offer our sincere thanks to the publisher and to Ms. Tracy Marton who has done an outstanding job in developing this book.

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Contributors

Gavin E. Arteel, Ph.D. Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY, USA

Hannah I. Awai, B.A., M.D. Liver Imaging Group, Department of Radiology, University of California, San Diego School of Medicine, San Diego, CA, USA

Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego School of Medicine, San Diego, CA, USA

Department of Gastroenterology, Rady Children's Hospital San Diego, San Diego, CA, USA

Ramon Bataller, M.D., Ph.D. Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

Pierre Bedossa, M.D., Ph.D. Hôpitaux Universitaires Paris Nord Val de Seine, Département d'Anatomie Pathologique, Université Paris Diderot, Paris, France

Naga Chalasani, M.D. Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, USA

Jaeyoun Cheong, M.D. Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina Memorial Hospital, Chapel Hill, NC, USA

Abhijit Chowdhury, M.D. Department of Hepatology, School of Digestive and Liver Diseases, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India

David W. Crabb, Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
Department of Medicine, Eskenazi Health System, Indianapolis, IN, USA

Anna Mae Diehl, M.D. Division of Gastroenterology, Department of Medicine, Duke University Medical Center, Durham, NC, USA

Samer Gawrieh, M.D. Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, USA

Stephen A. Harrison, M.D. Division of Gastroenterology and Hepatology, Department of Medicine, San Antonio Military Medical Center, Fort Sam Houston, TX, USA

Ammar Hassan, M.D. University of Louisville, Louisville, KY, USA

David E. Kleiner, M.D., Ph.D. Laboratory of Pathology, NCI, Bethesda, MD, USA

Mariana Lazo, M.D., Ph.D., Sc.M. Division of General Internal Medicine, Johns Hopkins Hospital, Baltimore, MD, USA

Mariana Luisa Verdelho Moutinho Machado, Division of Gastroenterology, Department of Medicine, Duke University Medical Center, Durham, NC, USA

Gastroenterology Department, Hospital de Santa Maria, CHLN, Lisbon, Portugal

Jacquelyn J. Maher, M.D. Liver Center, University of California, San Francisco, San Francisco, CA, USA

Liver Center Laboratory, UCSF/San Francisco General Hospital, San Francisco, CA, USA

Luis S. Marsano, M.D. Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Louisville, Louisville, KY, USA

Robley Rex Veterans Affairs Medical Center, Louisville, KY, USA

Craig J. McClain, M.D. Division of Gastroenterology, Hepatology and Nutrition, University of Louisville, Louisville, KY, USA

Department of Medicine, University of Louisville, Louisville, KY, USA

Department of Pharmacology & Toxicology, University of Louisville School of Medicine, Louisville, KY, USA

Robley Rex Veterans Affairs Medical Center, Louisville, KY, USA

Mack C. Mitchell, M.D. Department of Internal Medicine, U.T. Southwestern Medical Center, Dallas, TX, USA

Fabio Nascimbeni, M.D., Ph.D. Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

Division of Internal Medicine, Nuovo Ospedale Civile Sant'Agostino Estense, Modena, Italy

Department of Hepatogastroenterology, Hospital Pitié-Salpêtrière, Université Pierre et Marie Curie, Paris, France

Kimberly P. Newton, M.D. Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego School of Medicine, San Diego, CA, USA

Department of Gastroenterology, Rady Children's Hospital San Diego, San Diego, CA, USA

Jan Petrasek, M.D. Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Carlos Jose Pirola, Ph.D. Department of Molecular Genetics and Biology of Complex Diseases, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires—National Scientific and Technical Research Council (CONICET), Combatiente de Malvinas, Buenos Aires, Argentina

Svetlana Radaeva, Ph.D. Division of Metabolism and Health Effects, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA

Vlad Ratziu, M.D. Department of Hepatogastroenterology, Pitié-Salpêtrière Hospital, Paris, France

Jeffrey B. Schwimmer, M.D. Division of Gastroenterology, Department of Pediatrics, Hepatology, and Nutrition, University of California, San Diego School of Medicine, San Diego, CA, USA

Department of Gastroenterology, Rady Children's Hospital San Diego, San Diego, CA, USA

Department of Radiology, Liver Imaging Group, University of California, San Diego School of Medicine, San Diego, CA, USA

Arun J. Sanyal, M.B.B.S., M.D. Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Commonwealth University School of Medicine, Richmond, VA, USA

Silvia Sookoian, M.D., Ph.D. Department of Clinical and Molecular Hepatology, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires—National Scientific and Technical Research Council (CONICET), Combatiente de Malvinas, Buenos Aires, Argentina

Eva Stein, B.S. Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

Gyongyi Szabo, M.D., Ph.D. Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Dawn M. Torres, Division of Gastroenterology, Department of Medicine, Walter Reed National Military Medical Center, Bethesda, MD, USA

Hidekazu Tsukamoto, D.V.M., Ph.D. Keck School of Medicine of the University of Southern California, Southern California Research Center for ALPD & Cirrhosis, Los Angeles, CA, USA

Department of Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

Greater Los Angeles VA Healthcare System, Los Angeles, CA, USA

Vasilis Vasilou, Ph.D. Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT, USA

Division of Gastroenterology, Hepatology and Nutrition, University of Louisville, Louisville, KY, USA

Vatsalya Vatsalya, M.D., Department of Medicine, University of Louisville, Louisville, KY, USA

Division of Gastroenterology, Hepatology and Nutrition, University of Louisville, Louisville, KY, USA

Jun Xu, M.D., Ph.D. Keck School of Medicine of the University of Southern California, Southern California Research Center for ALPD and Cirrhosis, Los Angeles, CA, USA

Department of Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

Greater Los Angeles VA Healthcare System, Los Angeles, CA, USA

Zobair M. Younossi, M.D., M.P.H. Department of Medicine, Inova Fairfax Hospital, Center for Liver Diseases, Falls Church, VA, USA

Betty and Guy Beatty Center for Integrated Research, Falls Church, VA, USA

Samir Zakhari, Ph.D. Office of Science, DISCUS, Washington, DC, USA