Roberto de Franchis
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Portal Hypertension VI

Proceedings of the Sixth Baveno Consensus Workshop: Stratifying Risk and Individualizing Care

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Editor
Roberto de Franchis
Gastroenterology Unit
Luigi Sacco University Hospital
Milan
Italy

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Andrew K. Burroughs, 26 May 1953–14 March 2014

Baveno VI was dedicated to the memory of Andrew K. Burroughs, hepatologist, clinical scientist, educator, mentor, and friend. Andy inspired the idea of the Baveno workshops and was one of the pillars upon which the Baveno history was built.

The early 1980s, with the introduction of beta-blockers and the rediscovery of endoscopic sclerotherapy, saw a dramatic change in the management of variceal hemorrhage in cirrhosis. The studies published in those years were difficult to interpret because of the lack of standard definitions. Andy was the first to understand that, in order to improve the quality and comparability of studies, the investigators should meet and compare methods and experiences.

For this reason, on 3 September 1986, Andy organized, in Groningen, an EASL premeeting in which representatives from 24 hepatology centers involved in the management of variceal hemorrhage participated.

The aims of the Groningen meeting were:

- *To analyze the differences in design, analysis, and reporting of trials in portal hypertension*
- *To agree on the intention of developing a consensus on various definitions and key descriptors of the treatment of portal hypertension*
- *To define the methods to improve the design and analysis of future clinical trials and to construct the basis for the conduct of multicenter trials*

The Groningen workshop made it clear that great differences among studies existed, especially concerning the methods and the reporting of data on patients' characteristics.

The need thus emerged to develop a uniform terminology, to reach a consensus in the definition of key events related to variceal bleeding, and to develop common guidelines for the design and conduct of future trials.

For these reasons, after Groningen, I contacted Andy and Jaime Bosch with the proposal of organizing a "consensus development workshop" on definitions, methodology, and therapeutic strategies in portal hypertension.

The first workshop of this kind took place in Baveno on 5–6 April 1990, and Andy chaired the session on definition of time events in variceal hemorrhage.
We were encouraged by the success of Baveno I and decided to keep organizing workshops of the same kind every 5 years, and thus, with the help of many other friends, we organized Baveno II in 1995, Baveno III in 2000, Baveno IV in 2005, and Baveno V in 2010 and are celebrating today at Baveno VI the silver Jubilee.
In each workshop Andy was a leading figure, not only as session chairman but also as a clear-headed and respected voice in the organization of the workshops and in the drafting, discussion, and finalization of the Baveno recommendations.
It was therefore only appropriate to dedicate Baveno VI to Andy's memory.

Roberto de Franchis
Baveno, 10 April 2015

Preface

Baveno VI was a sequel of the Baveno I–V workshops, which were held every 5 years from 1990 to 2010. All the previous workshops were successful, as proven by more than 1700 citations of the workshop reports in the medical literature.

After Baveno V, important advances have been made in understanding the pathophysiology of portal hypertension, as well as in developing new treatments and new strategies for the management of liver disease in general and of variceal bleeding in particular. For these reasons, we organized a sixth Baveno workshop, which took place on 10–11 April 2015.

As for the previous editions, the aim of the Baveno VI workshop was twofold: first, to review and put into perspective the changes in diagnostic and therapeutic strategies that had occurred in the past 5 years in the field of portal hypertension and, second, to continue the effort – which had begun in Baveno I 25 years ago – of producing updated definitions and guidelines aimed at improving the quality of our future studies and ultimately of patient management.

The workshop started with a brief introduction, followed by two lectures, one on the concept of risk stratification, the other on competing risks and prognostic stages in cirrhosis.

The structure of the workshop was similar to that of the previous ones – there were 6 sessions: each dealing with a key topic (screening and surveillance, the impact of etiologic and antifibrotic treatment, what to do after successful cure of the etiologic factor, management of the acute bleeding episode, prevention of further decompensation, and vascular diseases of the liver). According to the Baveno tradition, at the end of each session, updated consensus statements on the topic of the session were presented and discussed by the panels and the audience.

Between sessions, there were three more lectures, held by world experts: two dealing with the basic and clinical aspects of the relationship between the gut microbiome and cirrhosis and the third was an updated report on the controversies and challenges in pediatrics.

These proceedings follow closely the structure of the workshop. The consensus statements that were agreed upon in each session are reported at the end of the pertinent chapters. As was done in Baveno IV and Baveno V, the levels of available evidence and the strength of recommendations are graded according to the Oxford System: (http://www.cebm.net/ocebm-levels-of-evidence/).

We wish to warmly thank the friends who accepted to give the lectures and to serve as chairpersons and panelists of the sessions and who helped us by working hard during the past 2 years in the preparation of the workshop and the chapters.

We also wish to thank Annamaria Sorresso, Denise Santi, and the entire staff of ADB Eventi e Congressi, who managed brilliantly the organization of the workshop.

In addition, we are grateful to the European Association for the Study of the Liver (EASL), who supported and endorsed the workshop and to the following scientific societies who endorsed Baveno VI: American Association for the Study of Liver Disease (AASLD), Associazione Italiana Gastroenterologi ed Endoscopisti Digestivi Ospedalieri (AIGO), Associazione Italiana per lo Studio del Fegato (AISF), European Society for Gastrointestinal Endoscopy (ESGE), Società Italiana di Endoscopia Digestiva (SIED), and Società Italiana di Gastroenterologia (SIGE).

Finally, we wish to thank all the companies who sponsored the workshop and Catherine Mazars, Donatella Rizza, and Angela Schulze-Thoming of Springer for their encouragement and cooperation in this project and Springer for the timely and excellent production of this volume.

Milan, Italy Roberto de Franchis

Contents

Contributors

Lars Aabakken Department of Cancer, Surgery and Transplant Surgery, Oslo University Hospital, Oslo, Norway

Juan G. Abraldes Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada

Agustin Albillos Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain

Salvador Augustin, MD Liver Unit-Department of Internal Medicine, Hospital Universitari Vall d'Hebron-Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

CIBERehd, Juan Rodés Grant Researcher, Instituto de Salud Carlos III, Madrid, Spain

Jasmohan S. Bajaj, MD, MS, FACG, AGAF Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA

Rafael Bañares, MD, PhD Facultad de Medicina, Universidad Complutense, Madrid, Spain

Digestive Disease Department and Liver Unit, Hospital General Universitario Gregorio Marañón, IISGM CIBEREHD, Madrid, Spain

Annalisa Berzigotti, MD, PhD Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, University of Berne, Berne, Switzerland

Jaime Bosch, MD, PhD, FRCP Hepatic Hemodynamic Laboratory, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain

Inselspital-Bern University, Bern, Switzerland

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

Hepatic Hemodynamic Laboratory Hospital Clinic, Barcelona, Spain

Thomas D. Boyer, MD Liver Research Institute, University of Arizona, Tucson, AZ, USA

Christophe Bureau Service d'Hépato-Gastroentérologie, CHU de Toulouse, Toulouse, France

Laurent Castera, MD, PhD Department of Hepatology, Hôpital Beaujon, Assistance Publique –Hôpitaux de Paris, INSERM U773, University of Paris-VII, Clichy, France

Gennaro D'Amico UOC Gastroenterologia, Ospedale V Cervello, Palermo, Italy

Alessandra Dell'Era Department of Biomedical and Clinical Sciences, University of Milan, Gastroenterology Unit, Luigi Sacco University Hospital, Milan, Italy

Roberto de Franchis, MD, AGAF Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

Gastroenterology Unit, Luigi Sacco University Hospital, Milan, Italy

Andrea De Gottardi Department of Hepatology, Clinic of Visceral Surgery and Medicine, Berne, Switzerland

Àngels Escorsell ICU Liver Unit, Hospital Clinic, Barcelona, Spain

Juan Carlos Garcia-Pagàn Barcelona Hepatic Hemodynamic Lab, Liver Unit, Hospital Clinic, IDIBAPS and CIBERehd, University of Barcelona, Barcelona, Spain

Guadalupe Garcia-Tsao Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA

Joan Genescà, MD Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

Jordi Gracia-Sancho, PhD Hepatic Hemodynamic Laboratory, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain

Inselspital-Bern University, Bern, Switzerland

Ian M. Gralnek, MD, MSHS, FASGE Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Institute of Gastroenterology and Liver Diseases, Ha'Emek Medical Center, Afula, Israel

Roberto J. Groszmann Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA

Virginia Hernández-Gea Liver Unit, Hepatic Hemodynamic Unit, Hospital Clinic, Barcelona, Spain

Luis Ibáñez-Samaniego, MD Digestive Disease Department and Liver Unit, Hospital General Universitario Gregorio Marañón, IISGM CIBEREHD, Madrid, Spain

Maria Kalafateli UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK

Aleksander Krag Department of Gastroenterology and Hepatology, University of Southern Denmark and Odense University Hospital, Odense, Denmark

Vincenzo La Mura Department of Internal Medicine, IRCCS-San Donato, San Donato Milanese (MI), University of Milan, Milan, Italy

Wim Laleman, MD, PhD Department of Liver and Biliopancreatic Disorders, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Frank W.G. Leebeek, MD, PhD Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

Gin-Ho Lo Division of Gastroenterology, Department of Medical Research, E-DA Hospital, School of Medicine for International Students, Kaohsiung County 824, Taiwan

Avik Majumdar, MBBS (Hons), MPHTM, FRACP UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Centre Royal Free Hospital, London, UK

Carlo Merkel Department of Medicine, University of Padua, Padua, Italy

Manuela Merli Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy

Richard Moreau Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

Frederik Nevens, MD, PhD Division of Liver and Biliopancreatic Disorders, University Hospitals Leuven, KU Leuven – University of Leuven, Leuven, Belgium

James O'Beirne The Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK

Markus Peck-Radosavljevic Abteilung Gastroenterologie and Hepatologie, AKH & Medical University of Vienna, Vienna, Austria

Cyriac Abby Philips Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Massimo Pinzani, MD, PhD, FRCP UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Centre Royal Free Hospital, London, UK

Mónica Pons, MD Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Barcelona, Spain

Massimo Primignani, MD First Gastroenterology Unit, IRCCS Ca' Granda Policlinico Foundation, Milan, Italy

Bogdan Procopet, MD Hepatic Hemodynamic Laboratory, Liver Unit, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Hospital Clinic, Barcelona, Spain

Thomas Reiberger Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

Cristina Ripoll First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

Marika Rudler Department of Hepatogastroenterology, La Pitié-Salpêtrière Hospital, 47–80 boulevard de l'Hôpital, Assistance Publique-Hôpitaux de Paris, Pierre et Marie Curie University, Paris, France

Francesco Salerno Internal Medicine and Hepatology, Policlinico IRCCS San Donato, University of Milan, Milan, Italy

Begoña Santos Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

Shiv K. Sarin, MD, DM, DSc, FNA Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Susana Seijo Liver Unit, Hospital Clinic, Barcelona, Spain

Benjamin L. Shneider, MD Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Houston, TX, USA

Pediatric Gastroenterology, Hepatology and Nutrition,
Texas Children's Hospital, Houston, TX, USA

Jayant A. Talwalkar, MD, MPH Division of Gastroenterology and Hepatology,
Mayo Clinic, Rochester, MN, USA

Puneeta Tandon, MD, FRCP(C), MSc (Epi) Division of Gastroenterology,
Department of Medicine, Cirrhosis Care Clinic, Edmonton, AB, Canada

Dominique Thabut Liver ICU, Service d'Hépato-Gastroentérologie,
Hôpital de la Pitié-Salpétrière, APHP, UPMC, Paris, France

Jonel Trebicka Department of Internal Medicine I, University of Bonn, Bonn,
Germany

Emmanuel A. Tsochatzis UCL Institute for Liver and Digestive Health,
Royal Free Hospital and UCL, London, UK

Dominique-Charles Valla, MD Service d'hépatologie, DHU UNITY,
APHP Hôpital Beaujon, Clichy, France

Centre de recherche de l'inflammation, UMR 1149, Université Paris Diderot
and Inserm, Paris, France

Meritxell Ventura, MD Liver Unit, Department of Internal Medicine,
Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR),
Universitat Autònoma de Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas
y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

Càndid Villanueva Gastrointestinal Bleeding Unit,
Department of Gastroenterology, Hospital de Sant Pau, Barcelona,
Autonomous University, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas
y Digestivas (CIBERehd), Barcelona, Spain

Julio Vorobioff Associate Professor of Medicine, University of Rosario
Medical School, Rosario, Argentina

Reiner Wiest, MD Bauchzentrum, Gastroenterology, Freiburgstrasse, Inselspital,
University for Visceral Surgery and Medicine, Bern, Switzerland

Alexander Zipprich First Department of Internal Medicine,
Martin-Luther-University Halle-Wittenberg, Halle, Germany

Part I

Risk Stratification and Prognosis

Introduction: Baveno I to Baveno VI.... and Beyond

1

Roberto de Franchis

Since 1986, nine international consensus meeting on portal hypertension have been held. After the first organized in Groningen, the Netherlands, by Andrew Burroughs [1], the other eight took place in Baveno in 1990 (Baveno I) [2] and 1995 (Baveno II) [3, 4], in Milan in 1992 [5], in Reston, USA, in 1996 [6], in Stresa in 2000 (Baveno III) [7, 8], again in Baveno in 2005 (Baveno IV) [9, 10], in Atlanta, USA, in 2007 [11], and again in Stresa in 2010 (Baveno V) [12, 13]. This is the tenth meeting of this kind, the sixth with the name of Baveno.

Baveno I to VI

Topics Addressed at the Baveno I–V Workshops

- Definitions of key events
- Diagnostic evaluation of patients with portal hypertension
- Prognostic factors for first bleeding, rebleeding, and survival
- Therapeutic strategies in patients with portal hypertension
- Vascular diseases of the liver
- Methodological requirements of trials

R. de Franchis, MD, AGAF
Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

Gastroenterology Unit, Luigi Sacco University Hospital,
via G.B Grassi 74, Milan 20157, Italy
e-mail: Roberto.defranchis@unimi.it

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Attendance at the Baveno Workshops

The attendance to the Baveno workshops was 205 in Baveno I, 252 in Baveno II, 385 in Baveno III, 485 in Baveno IV, 314 in Baveno V, and 240 in Baveno VI. The proportion of international participants rose steadily from 19 % in Baveno I to 74 % in Baveno V. The countries represented were 18 in Baveno I and II, 29 in Baveno III, 40 in Baveno IV, 50 in Baveno V, and 46 in Baveno VI.

Publications Derived from the Baveno Workshops

Reports of the Baveno workshops have been published in the *Journal of Hepatology* in 1992 [2] (Baveno I), in 1996 [3] (Baveno II), in 2000 [7] (Baveno III), in 2005 [9] (Baveno IV), and in 2010 [12]. Proceeding books of the workshops were published by Blackwell Science in 1996 [4] (Baveno II) and 2001 [8] (Baveno III), by Blackwell Publications in 2006 [10] (Baveno IV), and by Wiley-Blackwell in 2011 [13] (Baveno V).

Impact of the Baveno Consensus on the Medical Literature

Figure 1.1 shows the number of citations of the Baveno I–V reports in the medical literature between January 1993 and April 2, 2015. Overall, the reports had 1724 citations. The number of citations more than doubled between 2010 and 2015.

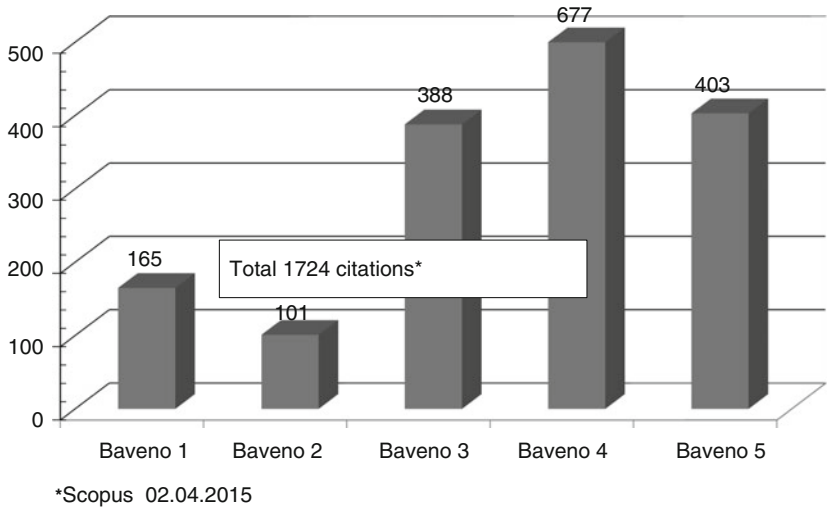

Fig. 1.1 Citations of the Baveno reports I to V (Data from Scopus 02.04.2015)

Validation of the Baveno Definitions

The success in producing high-quality trials in portal hypertension is largely attributable to the continued efforts to standardize trial design by agreeing on homogeneous definitions of study end points. In this respect, the most difficult area has been the definitions of key endpoints in acute variceal bleeding. In particular, the concept of "treatment failure," an endpoint aimed at evaluating the efficacy of hemostatic therapies, was developed, with the aim of homogenizing trial designs rather than to guide clinical practice. First proposed at Baveno II in 1995 [3], the criteria to define treatment failure have been discussed and redefined at each Baveno workshop thereafter, owing to the perceived difficulties in applying the criteria in real life. In all versions, treatment failure was used as a composite endpoint to evaluate efficacy, which included different criteria of failure to control bleeding, rebleeding, or death within 5 days of the index bleed. Both in Baveno IV and V, it was emphasized that the criteria for treatment failure required prospective validation. The continuing interest in this matter is witnessed by the publication, in the March 2015 issue of *Hepatology*, of two papers [14, 15] aimed at prospectively assessing the accuracy of the Baveno criteria to represent true treatment failure. These two studies provide excellent examples of the difficulties encountered in using the current criteria for treatment failure in acute variceal bleeding and provide the evidence-based starting point for redefining the key endpoints for the design of future trials.

Application of the Baveno Recommendations in Clinical Practice

In a worldwide survey of practices for pharmacologic therapy in esophageal variceal hemorrhage published in 2014 [16], the recommendation of using vasoactive drugs before endoscopy in acute variceal hemorrhage was followed by 66 % of the physicians interviewed.

Need for Strategies to Increase the Use of the Baveno Definitions in Trials and the Adherence to the Recommendations in Clinical Practice

The number of citations of the Baveno reports in the literature has more than doubled between 2010 and 2015. However, the use of the Baveno definitions in trials and the adherence to the Baveno recommendations in clinical practice, especially outside specialized units, appear to be only fair. This suggests that the effort to refine the definitions should continue and that strategies should be developed to increase the awareness of the recommendations and their application in clinical practice, both by hepatologists and generalists.

Beyond Baveno VI

As was announced at Baveno V, awareness of the passage of time has led the founding members of the Baveno team to invite many young, brilliant investigators to join the Scientific Committee of Baveno VI. These younger colleagues have worked hard in the organization of the present workshop. As time goes by, the responsibility of carrying on the tradition of Baveno will rest more and more on the shoulders of these new Scientific Committee members. I am confident that these younger colleagues will continue to share the enthusiasm and the dedication they have shown until now and will be able to continue in the future the friendly collaboration that has always been the hallmark of the Baveno enterprise.

The Baveno I–VI Workshops Were a Concerted Effort of the Following

Speakers and Chairpersons

Argentina, J Vorobioff; *Austria*, G Krejs, M Peck, T Reiberger; *Belgium*, W Laleman, F Nevens; *Canada*, J Heathcote, S Ling, N Marcon, G Pomier Layrargues, P Tandon, I Wanless; *Denmark*, U Becker, F Bendtsen, E Christensen, C Gluud, A Krag, S Møller, TIA Sørensen; *Egypt*, G Shiha; *France*, B Bernard-Chabert, C Bureau, P Calès, L Castéra, D Lebrec, R Moreau, JP Pascal, M Rudler, C Silvain, D Thabut, D Valla, JP Vinel; *Germany*, K Binmøller, W Fleig, G Richter, M Rössle, T Sauerbruch, M Schepke, D Schuppan, M Staritz, J Trebicka, A Zipprich; *Great Britain*, AK Burroughs, E Elias, P Hayes, J O'Beirne, D Patch, S Seijo, E Tsochatzis, D Westaby; *India*, YC Chawla, A Kumar, SK Sarin; *Israel*, I Gralnek; *Italy*, E Ancona, M Angelico, G Balducci, G Barosi, G Battaglia, M Bolognesi, L. Bolondi, L Cestari, GC Caletti, F Cosentino, G D'Amico, R de Franchis, A Dell'Era, A Gatta, G Gerunda, V La Mura, A Liberati, A, Maffei Faccioli, PM Mannucci, C Merkel, M Merli, G Minoli, A Morabito, L Pagliaro, A Peracchia, M Pinzani, M Primignani, O Riggio, P Rossi, C Sabbà, D Sacerdoti, F Salerno, M Senzolo, F Schepis, GP Spina, F Tinè, A Tripodi, V Ziparo, M Zoli; *Norway*, L Aabakken; *Pakistan*, S Abid; *Portugal*, P Alexandrino; *Spain*, J Abraldes, A Albillos, S Augustin, R Bañares, A Berzigotti, J Bosch, A Escorsell, JC Garcia-Pagàn, J Genesca, P Ginés, V Hernandez-Gea, M Navasa, J Piqué, R Planas, C Ripoll, J Rodès, C Villanueva; *Switzerland*, A de Gottardi, A Hadengue, P Gertsch, C Sieber, R Wiest; *Sweden*, C Søderlund *Taiwan*, FY Lee, HC Lin, J H Lo; *the Netherlands*, H Janssen, F leebeek; H van Buuren; *USA*, J Bajaj, A Blei, T Boyer, N Chalasani, M Fallon, G Garcia-Tsao, N Grace, R Groszmann, JM Henderson, Y Iwakiri, P Kamath, WR Kim, D Kravetz, L Laine, B Mittman, A Sanyal, V Shah, B Shneider, J Talwalkar, G van Stiegmann.

Organization: S Covre, A M Sorresso, D Santi, Gaetano Sabattini, and ADB Eventi e Congressi.

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The Concept of Risk Stratification

2

Jayant A. Talwalkar

Abbreviations

AUROC	Area under the receiver operating characteristic curve
AVB	Acute variceal bleeding
CSPH	Clinically significant portal hypertension
EV	Esophageal varices
HCC	Hepatocellular carcinoma
LSM	Liver stiffness measurement
LSPS	Liver spleen platelet count score
MELD	Model for End-Stage Liver Disease
NIEC	North Italian Endoscopic Club

Introduction

Previous studies have indicated that subjective estimation of risk by physicians in the absence of scientifically based risk models is inaccurate, resulting in systematic underestimation and overestimation. In turn, there continues to be a substantial need to identify individuals at risk for potentially lethal clinical events before they occur. Over the past two decades, a number of risk stratification models have been created to identify groups of patients at risk for complications of portal hypertension. The growing availability of therapies for both portal hypertension and underlying liver disease etiologies have further raised interest in developing more rigorous models

J.A. Talwalkar, MD, MPH
Division of Gastroenterology and Hepatology, Mayo Clinic,
200 First Street Southwest, Rochester, MN 55905, USA
e-mail: talwalkar.jayant@mayo.edu

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using advanced methods of risk stratification [1, 2]. This chapter will discuss the evolution of methods for risk stratification model building in portal hypertension and address emerging concepts such as the incorporation of new tests into existing models, the economic impacts of risk attribution, and suggestions on how to prospectively validate consensus-driven models.

Definition of Risk Stratification

In the context of clinical medicine, risk stratification is defined as a statistical process to determine detectable characteristics associated with an increased chance of experiencing unwanted clinical outcomes. Said another way, risk stratification determines whether events in a local population are accounted for by the risk factors in that population. By identifying factors before the occurrence of an event, it may be possible to develop targeted interventions to mitigate their impact [3].

Dichotomization of Single Variables for Risk Stratification

The ability to estimate risk accurately for both individual patients and populations is a challenging concept. In clinical practice, the assessment of risk by physicians is usually based on the perception of a high or low probability for developing major clinical events over time. Furthermore, most indications for therapy are also dichotomous in nature which reinforces the decision-making process used in clinical practice [1, 2, 4]. In contrast, the syndrome of portal hypertension is a complex pathophysiological disease state where the biological and statistical basis for risk estimation certainly exceeds the limits of a dichotomous, single risk stratification variable [4, 5].

The use of variables in a dichotomous fashion is complicated by other issues. Reproducibility of variable measurement within an individual may vary by 10 % or more which is separate from the biological variation that causes additional error in measurement. Because the risk for clinical events is usually distributed across a spectrum versus being located at the extremes (high or low), a dichotomous variable alone lacks sufficient sensitivity and specificity to be a useful method of risk stratification [1, 2, 4, 6]. In general, odds ratios >15–20 are required to meaningfully affect prediction for an individual [4, 5]. However, such high odds ratios do not generally exist for individual predictors.

An example of using a single test result to assess risk comes from a recent systematic review and meta-analysis performed by Singh and colleagues [7] examining the association between quantitative liver stiffness measurement (LSM) and the future development of decompensated cirrhosis, hepatocellular carcinoma (HCC), and mortality. By pooling relevant studies for each outcome and the composite end point, a 7 % and 32 % increase in risk of liver-related event per unit of LSM was identified. The authors, however, cited heterogeneity of studies, variability in treatment and follow-up, and publication bias as potential limitations affecting precision of the results. The use of prospective cohort studies in patients at earlier stages of

chronic liver disease receiving similar treatment would be required to assess LSM as risk stratification tool for recognizing high- and low-risk patients for clinical events. Furthermore, a greater focus on assessing whether a prognostic model including measures of liver severity such as MELD is likely to provide better discriminative ability in predicting outcomes.

Clinical Prediction Models

Multivariable Models

An ideal approach should not only classify patients as high or low risk but also intermediate risk, so that the large majority of patients in a population can be assessed [4]. With the inception of risk stratification model development in most areas of clinical medicine, the predominant method used by many investigators was logistic regression analysis [1, 2, 6, 8]. In the literature, there are a multitude of publications using this approach in risk stratification of patients affected by portal hypertension. Current risk estimation systems, however, are now more commonly based on proportional hazards techniques with either Cox (semiparametric) or Weibull (parametric) approaches. In contrast to logistic regression, the proportional hazards techniques have the advantage of allowing for losses to follow-up and variable observation time among individuals within a cohort. The Cox proportional hazards method also has two additional distinct advantages : (1) no assumptions are required about the shape of the underlying survival function and (2) data is used more efficiently by allowing risk to be estimated for periods greater than the length of the study's follow-up [1, 2, 8].

The risk stratification of patients for determining the presence of esophageal varices has been a topic of great importance in the field of portal hypertension [9]. Over time, published studies have evolved from developing models in single center cohorts to examining multiple models in several validation cohorts. Berzigotti et al. [10] recently performed a cross-sectional study using a training set of 117 patients with compensated cirrhosis to determine the predictive ability of spleen diameter, platelet count, and LSM in detecting clinically significant portal hypertension (CSPH) and esophageal varices (EV). In this study, two unique statistical models generating CSPH and EV risk scores using multivariable backward stepwise logistic regression were developed. A composite score with LSM, spleen diameter, and platelet count (LSPS) was also examined. Subsequently, the models were assessed in an independent series of 56 patients from another center. The discriminative ability of the different models was assessed by area under the receiver operating characteristic curve (AUROC) analysis. Results were noted for an LSPS score above and below 3.2 correctly classifying 85 % of patients in the training set and 75 % in the validation set that was comparable to results from the EV risk score. The authors note that all of the patients had complete test results for all measurements, and thus model performance does not account for "real-life" situations where tests provide incomplete results in some patients.

Risk Scores

Risk scores have been developed from clinical prediction models in assessing risk. Their advantage is that risk stratification is most likely to define the spectrum of risk for complications among populations with the disease of interest [4, 6]. Risk scores are commonly used in cardiovascular medicine, with the Framingham risk score as the most well-known system assessing the risk of symptomatic heart disease in asymptomatic populations. Another advantage of using risk scores is their utility in clinical practice where clinicians faced with an individual patient can reliably identify low-risk patients who do not require potentially expensive or risky therapies without compromising the quality of care [1, 2, 6].

In contrast to logistic regression and some proportional hazards models, there are relatively fewer publications in populations with portal hypertension that examine risk scores across the spectrum of disease severity. An early notable example of risk stratification system development using PH methodology is the North Italian Endoscopic Club (NIEC) prognostic model for predicting a first bleeding episode in patients with cirrhosis and esophageal varices [11]. Subsequent validation of the NIEC index in multiple independent cohorts was also performed [12].

The most prominent example of risk stratification using PH techniques is the creation of the Model for End-Stage Liver Disease (MELD) score [13, 14]. With the idea of providing risk stratification for all patients in the spectrum of disease severity related to cirrhosis, Teh and colleagues [15] studied the ability of MELD score to predict short- and medium-term risks for mortality after common surgical procedures. By multivariable analysis, only MELD score, American Society of Anesthesiologists class, and age predicted mortality at 30 and 90 days, 1 year, and long-term, independently of type or year of surgery among 772 patients with cirrhosis. Thirty-day mortality ranged from 5.7 % with MELD scores <8 to more than 50 % for patients with MELD scores >20. Given the linear relationship with mortality risk and MELD score, patients across the entire range of disease severity could be assessed with an ordinal range of MELD scores corresponding to rising time-dependent probabilities for mortality. Subsequently, multiple validation studies in separate cohorts supported the initial study's results.

Other more complicated methods also exist, including cluster analysis, tree-structured analysis, and neural networks. These methods are particularly useful for selecting the most appropriate variables when a large number of potential predictors of risk are available. However, the main problem with all of these methods is model shrinkage—their predictive ability declines sharply once the model is applied to an external dataset which limits their utility in clinical practice [1, 2, 8].

Validation, Discrimination, and Calibration of Risk Stratification Models

Internal Validation

Internal validation describes how well a constructed model performs in the dataset from which it was derived. For the most part, risk estimation systems generally perform well when assessed in this way. However, when a proportion of the same

dataset from which the model was created is used to further demonstrate validity (i.e., split-set approach), assertions of model superiority require caution as prediction is made at the exact end point in the test dataset [2, 6, 8].

External Validation

In contrast to a spilt-set approach, the application of a risk model in an external dataset is more appropriate for assessing external validation. In general, risk models that demonstrate similar predictive ability in different cohorts suggest that the system may have good discrimination in identifying future cases and non-cases (see below) [2, 6, 8]. Model AUROCs or c-statistic values in external validation datasets >0.7 are generally considered satisfactory. Lower values may occur when population differences in an external dataset from the testing set are known or identified after cohort comparison [8, 16].

Discrimination

Several measures exist to assess the overall pattern of risk stratification model performance including sensitivity, specificity, AUROC, c-statistic, and clinical likelihood ratios [6, 8]. Although used for assessing diagnostic test performance, AUROC has increased in use for assessing the discrimination ability of a risk model (i.e., how well the model can identify future cases with clinical events and non-cases). AUROC technique using thresholds cut points provide sensitivity and specificity parameters which are better understood by physicians [16]. In turn, reporting the sensitivity and specificity at threshold cut points for distinguishing high from low risk is helpful. It is generally accepted that AUCROCs and c-statistic values $\geq$0.80 denote excellent discrimination [6, 8, 16, 17].

Calibration

Risk prediction models also require a high degree of calibration to fulfill the goals of internal and external validation. Calibration is defined by how well the predicted event rates correspond to the observed events. Models which can discriminate well but have marginal ability for calibration usually result in misclassifying high- and low-risk persons for clinical events [1, 2, 16, 17]. Risk estimation systems can also change how well calibrated they are based on different baseline rates for the event in question in different geographic regions. Methods to assess reclassification after modification of risk stratification models have been developed and are now beginning to be used more frequently in emerging literature. Of note, a system with perfect calibration will have a lower value of discrimination (between 0.8 and 0.9) as they are linked concepts [2, 8, 16, 17].

Despite mortality rates as high as 20 % following acute variceal bleeding (AVB), existing risk stratification models have seldom been used to determine prognosis given their lack of external validation. Recently, Reverter et al. [18] examined

multiple techniques to assess advanced performance metrics of risk stratification models for acute variceal bleeding (AVB). Among 178 patients with cirrhosis and esophageal AVB who received standard therapy from 2007 to 2010, several risk models including MELD and a modified version of MELD were assessed for the ability to predict mortality within 6 weeks of AVB presentation. In addition to discrimination and calibration assessment, the models were further examined in separate cohorts from Canada and Spain. With an observed 6-week mortality frequency of 16 %, MELD was the best model in terms of discrimination. Following recalibration by adding the use of a logistic regression model, a MELD score of 11 was associated with a 5 % risk of mortality (i.e., low-risk group), while a MELD score of 19 was associated with a 20 % mortality rate (i.e., high risk). The MELD-based model showed excellent discrimination (AUC 0.87) in both external cohorts, while calibration was excellent in the Canadian cohort. Overprediction of mortality risk in high MELD score patients within the Spain cohort suggested less robust calibration.

Integrating Current Tests into Existing Risk Stratification Models

Several novel markers for risk stratification have undergone evaluation as tools to assess prognosis in patients with portal hypertension. Elastography imaging has received the most attention recently, with serum fibrosis markers and genomic polymorphism analyses also examined as potential tests. As discussed earlier, no single test is likely to provide adequate risk stratification [1, 2, 4, 5]. In contrast, studies have been conducted to improve risk estimation through the incorporation of new risk factors into existing models. However, improving a model's AUC from 0.80 to 0.90 by adding a new marker requires the novel test result to have an independent odds ratio >3 which is highly uncommon given significant correlations with 1 or more risk factors for portal hypertension. Conversely, the absence of improved discrimination (as measured by the AUC or c-statistic) suggests the novel marker is unlikely to be useful as a screening test [5, 8, 16]. Additional challenges exist based on the strong correlation among parameters that address the same physiology. Choosing which tests to combine has also not been standardized to date [1, 2].

Asrani and colleagues [19] examined the contribution of LSM by magnetic resonance elastography in identifying patients at increased risk for hepatic decompensation among patients with cirrhosis. Among 430 subjects with varying stages of cirrhosis, the mean LSM value was independently associated with decompensated cirrhosis after adjustment for MELD score, age, gender, albumin, and platelet count at baseline. However, the odds ratio for LSM was only 1.13. In the follow-up cohort, the hazard rate of hepatic decompensation was 1.42 per unit increase in LSM over time. However, for subjects with compensated disease and mean LSM values >5.8 kPa (equivalent to roughly 18 kPa by transient elastography), the hazard rate of hepatic decompensation was 4.96 compared to an individual with compensated cirrhosis and lower mean LSM values. This study highlights the limitation of LSM alone for risk stratifying all patients with compensated cirrhosis.

Contemporary Issues in Risk Stratification Modeling

Competing Risks

The presence of competing risks for death in patients with portal hypertension modifies the relationship between risk stratification models and mortality. It is clear that many risk factors for portal hypertension are also significantly associated with death due to other liver-related causes such as hepatocellular carcinoma. Current risk stratification strategies do not typically account for competing risks, which limits some of their discrimination and calibration utilities. Risk stratification models examining short-term mortality risk will also be compromised when applied to populations with longer life expectancies [1, 2]. In the Asrani study, cause-specific Cox PH analysis adjusting for competing risks was utilized to determine the association between elevated LSM and development of decompensation [19].

Dynamic Risk Profiling

Most risk stratification models incorporate variables as static entities when in most cases they are actually dynamic in nature. Continuous risk markers, such as liver stiffness, can vary within individuals when measured at different times or when repeated over time. Thus, the timing of risk assessment is important [1, 2]. Temporal variations in portal pressure including time of day [20, 21], season [22], and relationship with exertion [23, 24] have all been documented which affect timing of measurement as well. Finally, the frequency with which risk should be assessed is unknown because the duration of the predictive value of a test is rarely studied.

Economic Implications of Risk Stratification

One of the stated goals of risk stratification is to identify all individuals at high risk for major clinical events and to pursue treatments, when available, to prevent these events. However, for a randomized trial, this may require screening and evaluating 10–20 times as many patients to identify the 5–10 % of patients who are at high risk. Screening costs, therefore, could outpace costs of the study and its interventions and thus may prevent conduct of the study. Well-designed studies to improve risk stratification models could also incur costs that may be prohibitive as well. In clinical practice, a key goal of risk stratification is to identify those patients at low risk for clinical events who would not benefit from an expensive or invasive therapy. Notably, if an alternative therapy of equivalent efficacy and lower cost becomes available, the performance of risk stratification models could change. From a health economics perspective, recognizing high-risk groups that do not benefit from interventions due to competing risks (in addition to low-risk patients) also decreases the overall costs and increases effectiveness [1, 2, 25].

Unmet Needs

Despite advances in the approaches and techniques for developing risk stratification models over time, a number of unmet needs in this field remain. The majority of study designs used for model building are retrospective in nature given that the frequency of events is already known. In contrast, the conduct of prospective studies (observational or interventional) examining the efficacy of risk stratification models in predicting events would confirm excellent performance that is defined retrospectively. Developing consensus on strategies and evaluation plans for incorporating new tests into existing risk models is also needed as current approaches are nonsystematic. Assessing the robustness of risk stratification models in selected populations with portal hypertension is also needed with specific attention to the elderly, racial and ethnic minorities, populations with multiple comorbidities, and those residing in different geographic areas [1, 2, 6, 25].

Future Pathway for Risk Stratification

Recommendations have been proposed elsewhere [1, 2, 25] that define a pathway for improving the development and application of risk stratification models, which are relevant for populations with portal hypertension:

1. Establishing baseline risk models composed of important, readily available clinical variables for common patient groups
2. Generating a consensus list of currently available risk stratification techniques that should be assessed for improving performance of baseline model
3. Thorough evaluation of the added prognostic utility of novel risk markers, including assessment of interactions, discrimination, calibration, model fit, and reclassification
4. Evaluation of optimized risk stratification approaches in randomized clinical trials
5. Creation of a full and transparent process for promoting clinical trials supported by all stakeholders

Conclusion

Developing and validating risk stratification models in populations with portal hypertension remains a daunting process. While locating a simple algorithm or test for predicting mortality or major clinical events is ideal, this will not be realistic given that no single test result can adequately represent the pathophysiologic complexity of portal hypertension. As methodologies for risk model development have moved from logistic regression analysis to proportional hazards techniques, an increased emphasis on developing risk scores including patients at intermediate risk of adverse clinical events will improve the relevance of predictive models. Notably, the MELD score has been able to serve in this

capacity to date as compared to more traditional but categorical systems like Child-Pugh classification. There also need to be additional refinements which account for the dynamic nature of clinical variables and the knowledge of competing risks that can influence the risk for major clinical events. As risk stratification models are being developed using advanced statistical techniques in cooperation with biostatisticians, these strategies should be considered for testing in prospective randomized clinical trials to establish their utility and also to identify models where new tests can be incorporated to determine if risk stratification improves.

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Competing Risks and Prognostic Stages in Cirrhosis

3

Gennaro D'Amico

Introduction

Growing evidence has emerged in the last years suggesting that the clinical course of cirrhosis may be described by a multistate model. This evidence has been developed on the long-lasting knowledge that compensated cirrhosis has a much longer survival than decompensated cirrhosis [1]. Moreover, patients with compensated cirrhosis have an acceptable or at all good quality of life, do not usually experience symptoms, and may remain in this disease state for many years, if not indefinitely. By contrast, patients with decompensated cirrhosis not only have a significantly shorter survival but also a worse quality of life: they present clear evidence of clinically advanced disease, with bleeding and/or ascites, encephalopathy, or jaundice. These marked clinical differences have recently brought about the concept that compensated and decompensated cirrhosis are two different clinical disease states [2, 3].

Therefore, the basic model for cirrhosis is a three-state model: compensated disease, decompensated disease, and death. On this basis a more complex model has been proposed by introducing two disease states in compensated cirrhosis, defined by the presence or absence of esophageal varices, and three states in decompensated cirrhosis defined by variceal bleeding alone, first non-bleeding decompensation, and any second decompensation [4]. Sepsis and renal failure are events characteristic of the more advanced disease states and both are associated with a significant increase of death risk [5, 6]. Hepatocellular carcinoma may arise in any disease state and, whenever it develops, significantly worsens outcome.

To build up a multistate disease model, the risks of transition across the disease states have to be assessed. Since the transition toward a different state will compete

G. D'Amico
UOC Gastroenterologia, Ospedale V Cervello, Palermo, Italy
e-mail: gedamico@libero.it

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with the transition toward another state, a competing risks analysis has to be used to properly set the multistate model.

The concept of competing risks will be illustrated in this chapter by examples from liver cirrhosis.

Definition of Competing Risks

A competing risk is the risk of an event whose occurrence hampers the occurrence of another event and hence modifies the probability that it occurs.

To illustrate this definition, suppose that a group of patients with compensated cirrhosis is followed to observe the occurrence of decompensation. If, by the end of the observation period, each patient was decompensated or still alive and compensated, then one could conclude that all compensated patients will develop, earlier or later, decompensation without any competing event. This would imply that death would only occur after decompensation. However, this does not occur in real life because several patients do die before decompensation. Therefore, in some patients death precludes the occurrence of decompensation and hence modifies the risk of decompensation of the whole group (Fig. 3.1).

Recognizing competing risks is important because when assessing the risk of the event of interest in the presence of competing risks, specific analysis models are required. This is essentially because the survival analysis by the Kaplan-Meier model [7], usually extended to the analysis of the incidence of specific events, is only suitable for a two-state model, typically alive → dead. In the presence of competing events, the competing risks analysis should be used instead. This analysis is based on the cumulative incidence function (CIF) [8], which partitions the probability of any event in the probabilities of each event, in such a way that the probability of any event (or the sum of the probabilities of each event) ranges from 0 to 1.

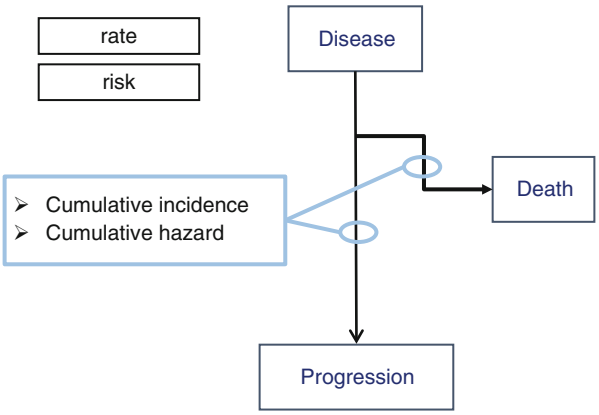

Fig. 3.1 Disease progression in a three-state disease model: disease, progression, and death. incidence and rate are both measures of the occurrence of each of the two events of interest

Rate and Risk

The reason why the Kaplan-Meier model may not be used in the presence of competing risks lies in the relationship between rate and risk, which in different ways measure the occurrence of the same event.

In epidemiology, risk is typically defined as the ratio D/N, where D is the number of subjects who develop the disease over a given time and N is the number of subjects disease-free at the beginning of that time [9]. The rate (or incidence rate) is the ratio D/Y where D is the number of subjects developing the disease and Y is the total amount of person-time at risk: it is essentially a measure of the speed of the occurrence of the event of interest. It is to note that while the risk necessarily increases along time (because D increases with time), the incidence may increase, remain unchanged, or decrease, according to the length of the follow-up.

Hazard (h) is the instantaneous risk of failing at each observation time t and is expressed by the ratio of the number of events to the number of patients exposed to the risk during the instantaneous time t. The hazard function, therefore, provides a dynamic description of how the instantaneous risk of failing varies along time; when the instantaneous risk is roughly constant, the cumulative hazard, $\hat{h}$, is equal to the rate, D/Y, and also estimates the instantaneous risk h. There is therefore a unique "one-to-one" correspondence between risk and rate. As a consequence of this correspondence, for a given hazard function, it is possible to compute the cumulative incidence function. The correspondence between the hazard function and the incidence rate allows to calculate the survival function in survival analysis models, like the Kaplan-Meier [8] and the Cox [10] models.

However, in the presence of competing risks, the correspondence between risk and rate is lost because the subjects experiencing the competing event are not any more at risk for the event of interest; therefore, the hazard function varies in a different way than the incidence rate function. The consequence of this lost relationship is that the Kaplan-Meier risk estimates are systematically upward biased in the presence of competing risks.

Censoring

Typically, in survival analysis or in analysis of time to an event of interest, the exact time to the event is known only for a part of the included subjects. For all the others, it is only known that at the time the analysis is performed, the event of interest had not yet occurred: the observation of these subjects has been truncated before the occurrence of the event. This condition is known as *censoring* (in this case, *right* censoring). Although the time to the event is not known for these patients, they provide an important information about the probability of remaining free of the event for at least the time period they were observed.

Clearly, if censoring is caused by some event related to the outcome of interest, as, for example, significant clinical deterioration or improvement, the analysis will be biased toward falsely pessimistic or optimistic conclusions. Therefore, censoring

must be *independent* of the outcome of interest. A second important requirement for censoring is that it must be *uninformative*, meaning that the events causing censoring must be unimportant for the clinical course of the disease [11, 12]. The end of the study period is typically such an event because the truncation of the observation is not at all informative with regard to the disease course.

In a competing risks situation, the competing event, which usually causes censoring in the Kaplan-Meier model, hardly fulfills the censoring requirements of being independent and uninformative. In fact, the competing event is frequently death, which in no way may be uninformative. Yet, when the competing event is not death, it is usually another clinically relevant event, likely informative for the course of the disease.

Because of these characteristics of censoring, in the presence of competing risks, the Kaplan-Meier model may not be used to assess the cumulative incidence. In this situation also the Cox proportional hazards model may lead to misleading results when the correspondence between rate and risk is lost. Both the Kaplan-Meier and the Cox models may however be used when the interest lies in the cumulative incidence of an outcome of interest or on the pure association between a covariate and the outcome, ignoring the competing risks. This is usually the case when looking for causal factors potentially involved in biological mechanisms of the outcome. In this situation the interest of the analysis lies in the incidence rate, i.e., in the total number of patients who will develop the outcome according to some given characteristics and not the in the real risk of the outcome occurrence observed in clinical practice, which may be affected by some competing risk.

Competing Risks Analysis

The Kaplan-Meier model computes the risk of only one event, the event of interest, and does not account for competing events, which are instead considered as censoring events. Since censored patients are treated as if they could experience the event of interest in the future [11], the Kaplan-Meier model, systematically overestimates the absolute risk. As a consequence of this overestimate, the sum of the probabilities of two competing events, each computed by the Kaplan-Meier model, may reach values greater than 1 [11], while by definition it should span between 0 and 1. The appropriate analysis for competing risks is based on the cumulative incidence function (CIF) [8] and the Nelson-Aalen estimator [12]. In this analysis the competing events are not censored but correctly counted as occurred events. Moreover, calculation of the risk is based on an additive approach, as compared to the multiplicative approach of the Kaplan-Meier model; this results in an overall probability of events ranging from 0 to 1, as expected. Details of the differences in calculation of risks between the Kaplan-Meier and the Nelson-Aalen estimators have been illustrated elsewhere [12, 13-14]. A visual example of how the Kaplan-Meier model overestimates the cumulative risks compared to the Nelson-Aalen estimator is provided in Fig. 3.2. The cumulative risk of death and of bleeding is computed by the two methods in a series of 402 patients

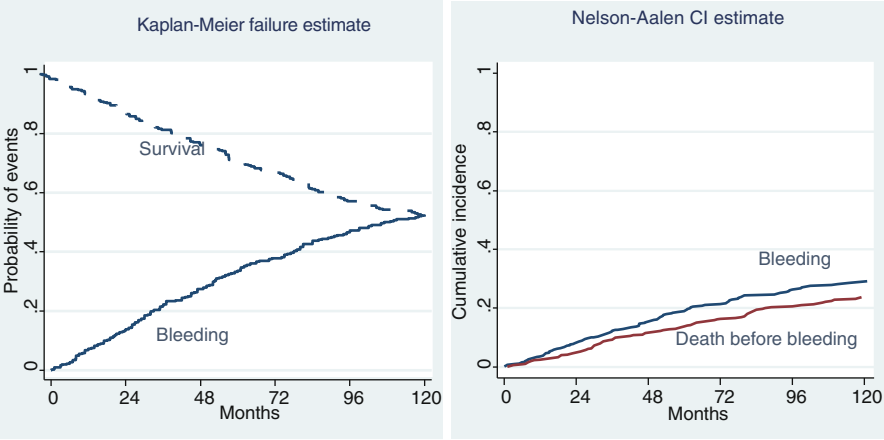

Fig. 3.2 *Left panel*: Kaplan-Meier plot of survival and incidence of variceal bleeding in a series of 402 patients with cirrhosis and newly diagnosed esophageal varices. *Right panel*: competing risks analysis of bleeding and death before bleeding by the Nelson-Aalen estimator in the same series of patients

with cirrhosis and newly diagnosed varices. Death is, of course, a competing risk for bleeding. By the Kaplan-Meier method (Fig. 3.2, left panel), the 10-year risk of bleeding is 0.54. The corresponding figure by the Nelson-Aalen estimator is 0.30 (Fig. 3.2, right panel). The explanation for the difference is that there is a 0.25 probability of death before bleeding which is not accounted for by Kaplan-Meier model, in which death before bleeding is a censoring event. On the other hand, the survival curve plotted by the Kaplan-Meier model does not account for bleeding and informs on overall survival.

Multistate Models and Competing Risks in Cirrhosis

There are no pre-definite multistate models in cirrhosis. Competing risk analysis should be applied whenever a competing risk may hamper correct risk assessment for an outcome of interest and the relevant multistate model should be appropriately built. Examples of this kind of situations are reported in Fig. 3.3. A typical situation where a multistate model is required is the assessment of liver specific mortality, where mortality for other causes is a competing outcome. Several applications of this kind of analysis may be appropriate when defining risks along the course of the disease. As outlined above, the assessment of the risk of decompensation for patients with compensated cirrhosis should account for the competing risk of death before decompensation. Likewise, a multistate model should be set to assess the risk of developing hepatocellular carcinoma, or the risk of resistant ascites or other major clinical events, to account for death before the event of interest as a competing outcome. The example of rebleeding after a first episode of variceal bleeding is reported

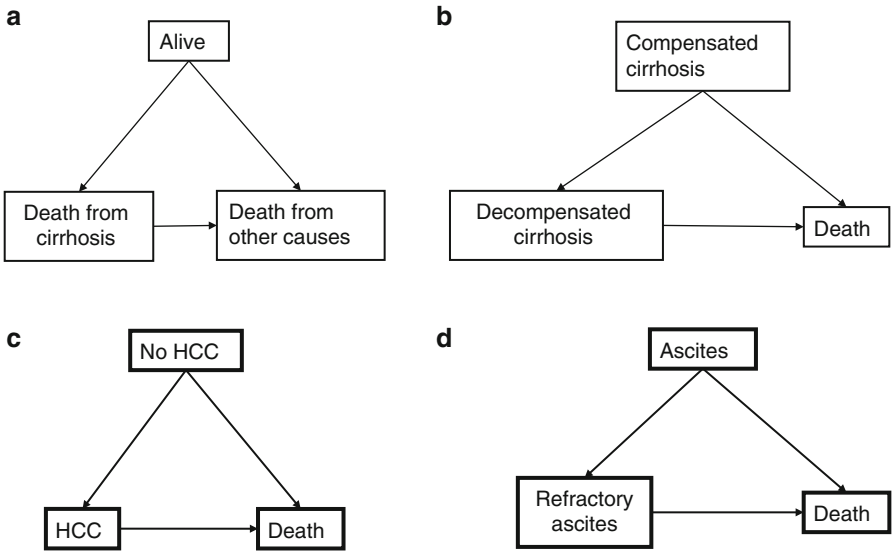

Fig. 3.3 Examples of multistate models to investigate risks in the clinical course of cirrhosis. (**a**) Cause specific death; (**b**) incidence of decompensation; (**c**) incidence of hepatocellular carcinoma (*HCC*); (**d**) incidence of refractory ascites

in Fig. 3.2. Many other similar situations may be recognized, along the clinical course of cirrhosis.

More complex multistate models may be built to fit the clinical course of cirrhosis [2]. For alcoholic cirrhosis a model has been proposed including compensated cirrhosis, variceal bleeding, ascites, ascites plus bleeding, and encephalopathy as disease states [15]. More recently a five-state model has been set for mostly viral and alcoholic cirrhosis [4]: compensated cirrhosis without esophageal varices, compensated cirrhosis with esophageal varices, variceal bleeding without other decompensating events, first non-bleeding decompensating event, and any second decompensating event. In this model, the probability of 5-year mortality increased from 0.015 in state 1 to 0.88 in state 5 (Fig. 3.4).

Competing risks analysis may be used also when assessing which is the next relevant clinical event to occur in a definite clinical condition. In this situation, several events may compete with each other to occur first. This kind of information is usually clinically relevant to plan the appropriate follow-up schedules and preventive interventions when available. As an example a competing risks analysis to assess the probability of the next clinical event in patients with compensated cirrhosis and without varices is reported in Fig. 3.5. The analysis shows that in this series of 202 consecutive patients, the probability of occurring as the first new event was 0.07 for death, 0.43 varices, 0.20 ascites, and 0.07 jaundice or encephalopathy, while the probability of remaining free of any event in the observation period was 0.23.

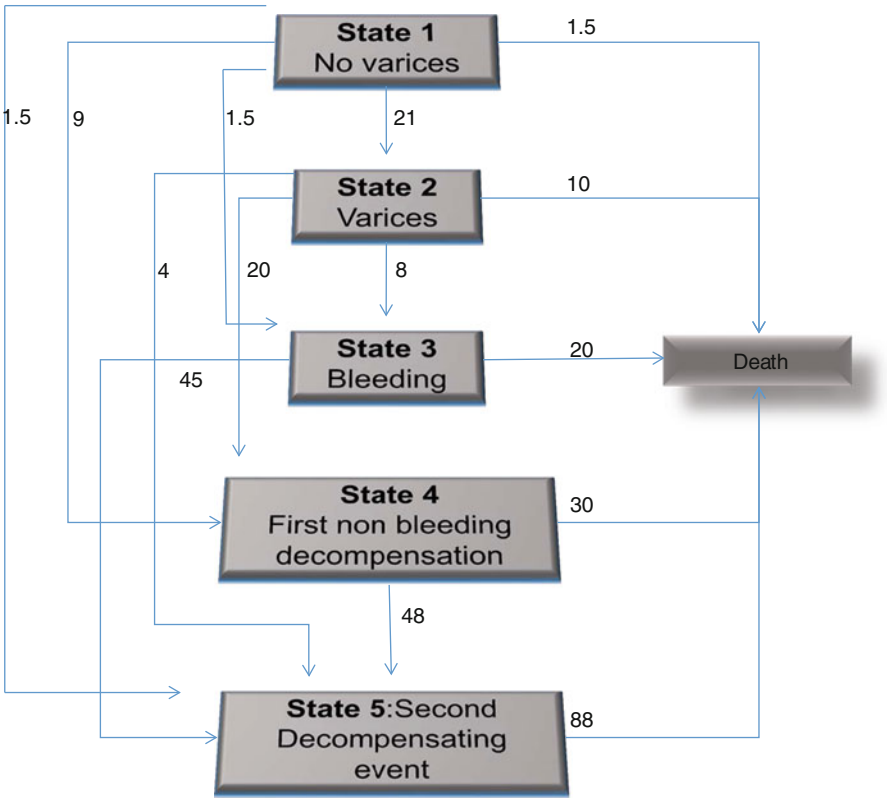

Fig. 3.4 Schematic representation of a five-state disease model for cirrhosis. Five-year transitioning rate across disease states and to death is shown for a series of 494 patients. *Arrows* represent transitions and the numbers close to each *arrow* are the relevant transition rates. A fairly steady increase in death rate was found across stages

Competing Risks and Prognosis Research

Prognosis research is aimed at assessing outcome probability and relevant predictors of outcome in a given time. By combining several predictors, prognosis research may also result in clinical prediction rules which, if appropriately validated, may assist physicians in clinical decision-making and in providing correct information to the patient [16, 17].

Predictors may be patient characteristics or biological or physiological disease characteristics and may be associated to the outcome either through a causal mechanism (causal factors) or without any causal relationship, simply as indicators of the risk (predictive factors). When the interest is on causal factors, the analysis should identify any significant association between the candidate factors and the event rate or incidence and not the risk. In this case, it is important to assess whether the outcome of interest did occur more frequently in patients presenting the candidate

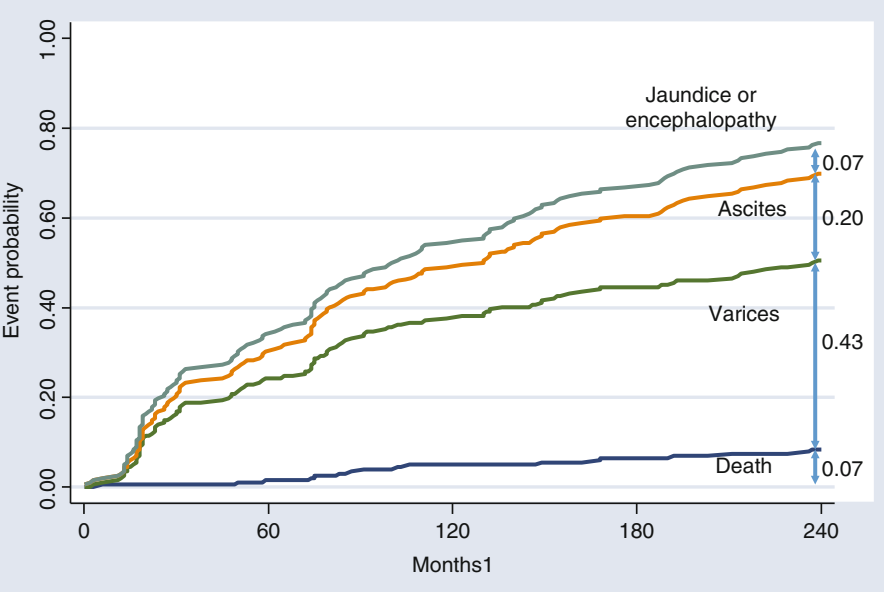

Fig. 3.5 Cumulative incidence of clinically relevant events in a series of 202 patients with compensated cirrhosis free of esophageal varices at diagnosis

causal factor compared to those without. Here, the measure of the risk observed in real practice or whether some competing event may alter the probability of occurrence of the event of interest is not important. In this situation a competing risks analysis is not required, and hence the Kaplan-Meier model may be used for incidence analysis and the proportional hazards Cox model may be safely used. By contrast, when the interest is in predictive factors, the analysis is centered on the cause specific risk: here, it is therefore essential to account also for competing risks, which may modify the risk of the event of interest. In this condition, neither the Kaplan-Meier nor the Cox models are appropriate, and an analysis properly accounting for competing risks should be used instead.

Prognostic Models with Competing Risks

Subgroup competing risks analysis of cumulative incidence allows to assess the association of candidate predictors with the outcome of interest in the presence of competing risks [18]. A multiple regression model has also been developed for competing risks [19]. The model allows to compute sub-hazard functions for prognostic indicators and provides regression coefficients which allow to calculate a prognostic score for individual patients to predict the probability of the outcome of interest at a given time. Comparing the predicted risk with the observed risk may inform on the calibration of the prediction. The standard Cox model, as expected,

usually overestimates the risk, while the Fine and Gray model provides reliable predictions [19].

Validity of prognostic models with competing risks may be assessed in groups of patients independent from the derivation sample, and statistical tools to assess discrimination, reclassification index, and calibration of the model are available [20].

Conclusions

Competing risks modify the probability that an event of interest occurs. In this situation the correspondence between risk and rate is lost, and the Kaplan-Meier model systematically results in upward biased risk estimation. Therefore, in the presence of competing risks, the specifically developed Nelson-Aalen estimator should be used to compute the cumulative incidence function (CIF) .

Competing risks analysis allows to build multistate models, which may satisfactorily represent typical clinical conditions in which it may be important to investigate the risk of a specific event. In cirrhosis, such models may provide reliable information on the probability of occurrence of major clinical events like hepatocellular carcinoma, bleeding, ascites, refractory ascites, and any other event of interest in the presence of competing risks.

Multistate models for cirrhosis have been proposed to fit the clinical course of the disease. These models are essentially based on compensated and decompensated disease and on the presence of esophageal varices and decompensating events.

Multiple regression analysis with competing risks may also be performed and allows to compute prognostic scores which may be validated by assessing discrimination, reclassification, and calibration by specific statistical approaches. A competing risk approach to prognostic research in cirrhosis may help to improve the performance of prediction rules.

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Part II

Screening and Surveillance: Invasive and Noninvasive Methods

Results of the Questionnaire

4

Bogdan Procopet and Annalisa Berzigotti

Introduction

In the previous Baveno consensus workshop, it was underlined that in any patient with compensated chronic liver disease, the identification of cirrhosis is crucial, since it marks the beginning of an increased risk of complications and death. On diagnosis, endoscopic screening of esophageal varices and ultrasound screening of hepatocellular carcinoma should be initiated, and patients should undergo an appropriate surveillance thereafter.

As will be explained in other chapters in this book, the term "cirrhosis" has been recently challenged [1]; it has been suggested that it should be replaced by the term "advanced chronic liver disease" or "compensated advanced chronic liver disease" (cACLD) that better responds to new concepts, among others those related to the difficulty of distinguishing between severe fibrosis and early cirrhosis in patients without previous decompensation of cirrhosis, and the potential reversibility of liver disease due to advances in treatment [2].

Independent of the terminology used, it is undoubtedly important to provide criteria to allow identification of this stage in asymptomatic, compensated patients, who should be referred to centers with expertise in liver diseases for confirmation and appropriate monitoring. In this group of patients, portal hypertension can be

B. Procopet, MD
Hepatic Hemodynamic Laboratory, Liver Unit, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Hospital Clinic, c/Villarroel 170, Barcelona 08036, Spain
e-mail: bogdanprocopet@gmail.com

A. Berzigotti, MD, PhD (✉)
Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, University of Berne, MEM F807, Murtenstrasse 35, Berne CH - 3010, Switzerland
e-mail: annalisa.berzigotti@insel.ch

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present and should be assessed as the next mandatory step due to its prognostic relevance.

Liver biopsy, despite several drawbacks (sampling errors, intra- and interobserver variability), is still considered as the standard reference method for staging fibrosis and diagnosing cirrhosis [3], while the gold standard method to assess portal hypertension is hepatic venous pressure gradient (HVPG) measurement obtained during hepatic vein catheterization [4]; upper gastrointestinal tract endoscopy is the reference method to assess the presence and severity of esophageal and gastric varices.

These invasive methods, however, are not available in all centers, require specific expertise, and hold a high cost and some potential risks. In the last Baveno consensus conference (Baveno V), it was underlined that there was a need to develop noninvasive methods to better select patients who should be referred to endoscopy [5, 6]. This implies that noninvasive tests should be able to identify or rule out (a) cACLD, (b) clinically significant portal hypertension, and (c) varices (or at least varices requiring treatment).

During the last years several noninvasive methods (Fig. 4.1), and in particular liver stiffness measurement (LSM) by transient elastography (TE) and serum

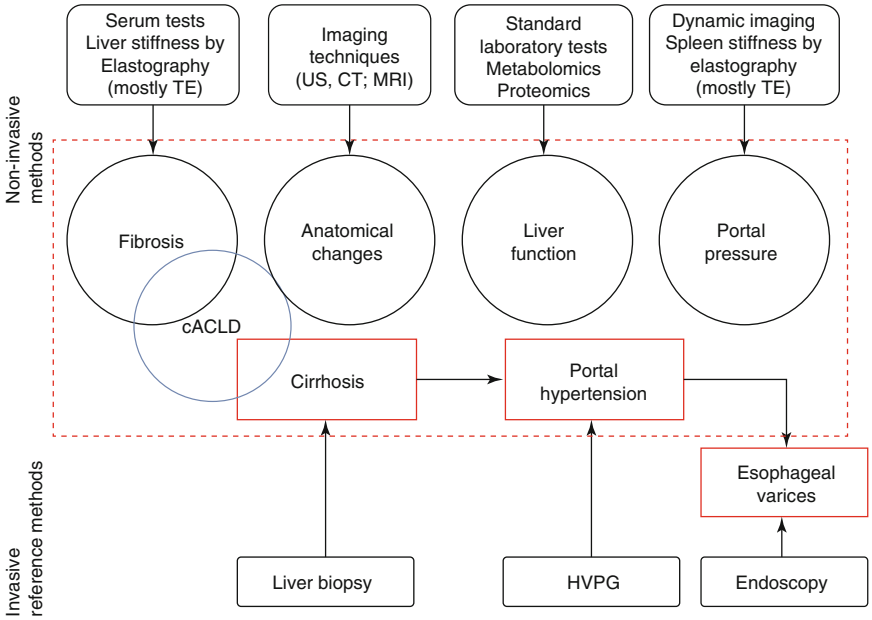

Fig. 4.1 Diagnostic methods currently used (or proposed) in patients with compensated liver disease. Liver stiffness by TE is a well-validated method that has changed clinical practice by allowing an early identification of patients in a pre-cirrhotic or early cirrhosis stage who are now grouped under the term "cACLD" that were previously often not detected due to the absence of other specific signs. These patients require further evaluation by invasive and noninvasive techniques to rule out or identify portal hypertension and varices

biomarkers, emerged as reliable surrogates of fibrosis [7]; in addition, LSM has been evaluated for diagnosing portal hypertension [4] and has been shown to hold prognostic significance for hard clinical endpoints such as clinical decompensation.

In this changing scenario, our panel is aimed at better understanding the opinion of the experts in the field of portal hypertension on the current practice and use of invasive and noninvasive methods in the following aspects:

(a) *When screening of varices should be initiated* or, in other words, how and when ACLD/cirrhosis is diagnosed
(b) *Screening of varices*
(c) *Surveillance of varices*

A questionnaire was sent to all Baveno experts faculty ($n=52$). The questionnaire obtained 48 answers (92 %) and was completely filled in by 47 respondents. The main results are presented in the following paragraphs.

Diagnosis of Compensated Advanced Chronic Liver Disease (cACLD)

Question 1 *Which parameters do you use to classify a patient as having compensated advanced chronic liver disease that requires initiation of HCC surveillance and evaluation of CSPH and varices*?

Respondents were allowed to choose more than one answer to summarize all the diagnostic methods they use. Eighty-three percent of experts use liver biopsy to diagnose cACLD; in addition, 81.3 % answered that they use the finding of varices on endoscopy, suggesting that, according to what is recommended by previous Baveno statements, once a clinical diagnosis/suspicion of cirrhosis was made, endoscopy was performed, and the observation of signs of portal hypertension was considered sufficient as a confirmatory sign.

Among noninvasive parameters, LSM by TE is the most widely accepted (83.3 % of experts), indicating that this is currently the most commonly used technique to rule out cACLD and to identify it even when no other sign is present. Cutoffs used varied among respondents (≥13.6 kPa, 60.4 % of respondents; ≥10 kPa, 16.6 %; other cutoffs, 6.3 %).

Imaging techniques (ultrasound, CT scan, or MRI) are the next most trusted; with these methods, respondents look for signs of definite cirrhosis (nodular liver surface, 75.9 % of respondents) and signs of portal hypertension (portosystemic collaterals, a pathognomonic sign of portal hypertension, 58.3 % of answers; splenomegaly, a sensitive but not a specific sign of cirrhosis and portal hypertension, 29.2 % of answers). Forty-eight percent of experts indicated an HVPG > 5 mmHg as confirmatory of cACLD.

Only 4 experts (8.3 %) considered liver stiffness by ARFI (with a cutoff of ≥1.75 m/s) as a diagnostic parameter, and no other newer elastographic techniques were specifically discussed. Laboratory tests and their combination with other

techniques obtained only a minority of answers (platelet count <150,000 mm^3, 18.7 %; platelet count <150,000 mm^3 + splenomegaly ≥13 cm, 37.5 %; platelet count/spleen diameter >909, 2 %; FibroTest ≥0.60, 4.1 %; FibroTest ≥0.75, 6.25 %).

The respondents had the possibility to insert comments to this question. Among them, some suggested that a stepwise approach is preferable; this approach would be based on identification of cACLD by LSM or multiple noninvasive tests as a first step, followed by invasive reference standard methods to be used in case of discordance of noninvasive methods, preferably in referral hospitals.

Screening of Varices

Question 2 *Do you perform screening endoscopy in patients with cACLD at the time of diagnosis to detect the presence of gastroesophageal varices*?
Question 3 *Do you use noninvasive methods to restrict the performance of endoscopy to the patients at higher risk of having varices*?
Question 4 *If you do*, *which method do you use*?

There is a clear consensus regarding the first two points: 95.8 % of the respondents confirmed that they use screening endoscopy once cirrhosis is diagnosed (Q2); according to the previous Baveno statements, this was done without any selection of higher-risk patients based on noninvasive methods (89.1 %) (Q3). Few respondents (10 %) use noninvasive methods to stratify patients before endoscopy; several methods were pointed out, but most answers indicated LSM by TE and ultrasound signs of portal hypertension.

Surveillance of Varices

According to the Baveno V consensus conference, patients should undergo surveillance by endoscopy to detect formation of varices when they were not present on first endoscopy and to detect growth of varices in patients with small varices at diagnosis. The intervals varied from 1–2 year to 2–3 years according to the first endoscopy findings and to the presence of clinical decompensation [8]. However, data suggest that the risk of developing varices is decreased in patients with alcoholic cirrhosis who stop drinking, in those with HBV-related cirrhosis who achieve a sustained suppression of HBV-DNA, and in those with HCV-related cirrhosis achieving a sustained virological response (SVR).

Question 5 *After performing screening endoscopy do you use any invasive or noninvasive method to follow up the portal hypertensive status in your patients*?
Question 6 *If you answered YES to the previous question*, *which method and what interval* (*e.g.*, *once a year*, *every 6 months*, *only when clinical changes appear*) *do you use to follow up portal hypertension in your patients*?
Question 7 *Do you always use the intervals for surveillance endoscopy suggested at the last Baveno consensus conference independent of any clinical/laboratory/imaging data*?

Question 8 *If you answered NO to the previous question, which are the data you consider to reduce the interval for surveillance endoscopy? Please tick all that apply.*

Question 9 *Similarly which are the data you consider to increase the interval for surveillance endoscopy? Tick all that apply.*

74.4 % of the responders reported that they are following the last Baveno consensus conference recommendations regarding surveillance endoscopy (Q7). However, about a half of respondents (53.2 %) also use noninvasive methods and/or HVPG during the follow-up to periodically reevaluate the portal hypertensive status of their patients; more than one answer was allowed. LSM by TE is the most frequently used method (60 %) [4, 9], followed by the HVPG measurement (44 %) and by the follow-up of ultrasound signs of portal hypertension/check of patency of the portal venous system (44 %). As for the frequency of controls, we received 15 answers; there was a large variability in methods and intervals used; most indicated US every 6 months (in the context of HCC screening) and LSM at an interval of 12 months.

The 12 experts (25 % of the respondents) who do not always follow Baveno recommendations mostly consider ongoing alcohol intake (66.6 %), lack of SVR in case of HCV cirrhosis (50 %), and appearance/worsening of ultrasound signs of portal hypertension (50 %) to reduce the interval of surveillance endoscopy. Conversely, most of these experts consider a longer interval for surveillance in case of alcohol abstinence (60 %) and achievement of SVR for HCV cirrhosis (50 %).

Endoscopic Surveillance Interval in Specific Conditions

Question 10 and 11 *What interval for surveillance endoscopy do you use for a patient with compensated alcoholic cirrhosis and ongoing drinking with no varices (Q10)/small varices (Q11) at screening endoscopy?*

Question 12 and 13 *What interval for surveillance endoscopy do you use for a patient with compensated HBV-related cirrhosis with no varices (Q12)/small varices (Q13) at screening endoscopy who has not achieved HBV-DNA suppression under antiviral treatment?*

Question 14 and 15 *What interval for surveillance endoscopy do you use for a patient with compensated HBV-related cirrhosis with no varices (Q14)/ small varices (Q15) at screening endoscopy who has achieved HBV-DNA suppression under antiviral treatment?*

Question 16 and 17 *What interval for surveillance endoscopy do you use for a patient with compensated HCV-related cirrhosis with no varices (Q16)/small varices (Q17) at screening endoscopy who has not achieved SVR under antiviral treatment?*

Question 18 and 19 *What interval for surveillance endoscopy do you use for a patient with compensated HCV-related cirrhosis with no varices (Q18)/small varices (Q19) at screening endoscopy who has achieved SVR under antiviral treatment?*

Table 4.1 Answers of the majority of the 48 responders regarding the appropriate interval between surveillance endoscopies in some specific clinical scenarios

		Result of first screening endoscopy	
		No EV	Small EV
Alcoholic cirrhosis	Ongoing alcohol intake	2 years (53.2 %)	1 year (86.6 %)
HBV cirrhosis	Achieved and maintained HBV-DNA suppression	3 years (51 %)	1 year (42.5 %) 2 years (42.5 %)
	Did not achieve/maintain HBV-DNA suppression	2 years (59.6 %)	1 year (73.3 %)
HCV cirrhosis	Achieved SVR	3 years (56.8 %)	1 year (52.1 %) 2 years (32.6 %) 3 years (10.9 %)
	Did not achieve SVR	2 years (60.8 %)	1 year (77.8 %)

In parenthesis are presented the percentage obtained by each answer from the total of responders

Correction of the underlying etiologic factor has been shown to favorably impact the natural history of cirrhosis. The questions posed to the audience were aimed at assessing whether published data on this topic changed the clinical practice of experts in the field regarding the intervals of surveillance endoscopy. The results are summarized in Table 4.1.

As shown, accordingly to the data of our survey, there is consensus among expert regarding the use of a shorter interval for surveillance endoscopies in patients with ongoing liver injury due to the persistence of the etiologic factor. Namely, respondents stated that they repeat endoscopy at 2-year intervals when no varices were seen on index endoscopy and at 1-year intervals when small varices were present at index endoscopy in patients who have ongoing drinking (alcoholic cirrhosis) or did not achieve HBV-DNA suppression (HBV-related cirrhosis) or did not achieve SVR (HCV-related cirrhosis). In patients in whom the causal factor was removed or under control, there is no clear consensus on the interval to be used, but the overall experts' opinion is that the upper limit of the recommended interval can be used (3-year intervals when no varices were seen on index endoscopy and at 2-year intervals when small varices were present at index endoscopy). Comments underlined that cofactors (e.g., obesity) should be always taken into consideration when assessing whether liver injury has been removed or not.

Conclusions

The results of this survey suggest that the experts agree on the use of noninvasive methods and in particular LSM to rule out/identify patients with cACLD (compensated patients with severe fibrosis/pre-cirrhosis or early cirrhosis). This is relevant, since patients without cACLD according to the most sensitive noninvasive method so far (LSM) do not require further work-up for CSPH and varices, while those who belong to this stage of CLD require further evaluation (preferably in referral centers which have invasive methods available). The questionnaire confirmed that screening endoscopy and surveillance are used by the experts according to the recommendations stated in previous Baveno workshops.

However, the results also indicated that the persistence or removal of the causal agent which led to cirrhosis seems to guide the choice of using the shortest or the longest interval among those recommended for surveillance endoscopies.

Finally, the answers and comments of the experts indicated that fields for future research regard: (a) the use of LSM and other noninvasive methods in the follow-up to tailor the interval of surveillance endoscopy or even to stop it in case of long-term stability after removal of the causal agent of CLD and (b) the relevance of cofactors of liver disease in the natural history of gastroesophageal varices, in particular in patients in whom the main cause of cirrhosis has been removed (e.g., SVR in HCV).

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5 Identifying Compensated Advanced Chronic Liver Disease: When (Not) to Start Screening for Varices and Clinically Significant Portal Hypertension

Salvador Augustin, Mónica Pons, Begoña Santos, Meritxell Ventura, and Joan Genescà

From Cirrhosis to Compensated Advanced Chronic Liver Disease

Chronic liver disease progresses through different stages as a consequence of increased liver fibrosis. As a result of continued liver injury, there is progressive accumulation of fibrous tissue in the liver. When accumulation exceeds degradation and remodeling, the process results in cirrhosis, the end stage of chronic liver disease. Cirrhosis is a histological diagnosis defined by the presence of regenerative nodules surrounded by fibrous tissue that leads to angioarchitectural distortion. Liver biopsy has been the "gold standard" in the assessment of the severity of fibrosis and in the diagnosis of cirrhosis. However, the limitations of the procedure are widely known (invasiveness, complications, sampling error, etc.), and in part due to these limitations, liver biopsy is not adequate for continuous monitoring of liver disease progression and does not provide a dynamic information of the process [1, 2].

In addition to liver biopsy, cirrhosis is also usually defined from a clinical point of view by the presence of a combination of clinical signs and biochemical (low platelets, liver dysfunction tests), imaging (nodular liver or signs of portal hypertension: splenomegaly and collateral circulation), and endoscopic parameters (varices). This practical definition has become popular among liver specialists, but the

S. Augustin, MD • M. Pons, MD • B. Santos, MD • M. Ventura, MD • J. Genescà, MD (✉)
Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain
e-mail: salva.augustin@gmail.com; monica_xina@hotmail.com; begosants@gmail.com; txell.ventura.cots@gmail.com; jgenesca@vhebron.net

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sensitivity and specificity of these clinical criteria are very variable and precisely defined criteria and consensus are lacking.

The development of portal hypertension is a crucial event in the evolution of cirrhosis. When the hepatic venous pressure gradient (HVPG) increases to 10 mmHg (clinically significant portal hypertension, CSPH), cirrhotic patients become at risk of developing varices and clinical decompensation [3–5]. HVPG is an accurate and reproducible method, although again invasive and, most importantly, only available in specialized centers. The reality is that HVPG has not entered universal routine clinical practice. In addition, detecting varices by endoscopy in cirrhotic patients with CSPH is an important hallmark in the natural history of cirrhosis, since it carries prognostic significance and sets the indication for primary prophylaxis of variceal bleeding [6, 7]. Therefore, international guidelines indicate that if possible, HVPG measurement should be used for diagnosis and therapeutic indications in cirrhotic patients and that all cirrhotic patients should be screened (by endoscopy) for varices at diagnosis [7, 8]. In addition to screening for portal hypertension, cirrhotic patients also should initiate surveillance for hepatocellular carcinoma [9].

For the reasons outlined before, in the last years, methods aimed at determining noninvasively the presence of liver fibrosis, cirrhosis, CSPH, and varices have been developed and extensively investigated. The appearance of such methods and their widespread use have somehow changed the clinical scenario of chronic liver disease, notably increasing the number of patients with significant chronic liver disease detected in the very early phases of the process. These previously undetected patients are now being labeled as cirrhotic patients, although we know that at least 10–15 % of them have no cirrhosis by histology [10]. In these patients also the decision to screen for varices and CSPH – which obviously has to be considered – may entail an important increase in the use of unnecessary procedures [11]. To adequately frame and describe this new clinical situation in chronic liver disease and provide recommendations, it might be helpful to use the term of compensated advanced chronic liver disease (cACLD), instead of liver cirrhosis that could be still used for patients with biopsy-proven cirrhosis, patients with evident signs of portal hypertension (varices), or decompensated patients. The incorporation of information from some noninvasive tests into the definition of cACLD might also be helpful and concur with current clinical practice in many centers.

Role of Elastography in Changing the Epidemiology of cACLD

Over the last years, several different approaches have explored the possibility of identifying by different noninvasive methods the degree of liver fibrosis and consequently recognizing cirrhosis, varices, or CSPH. Among the different modalities, including direct and indirect serum biomarkers of fibrosis and physical approaches that measure liver stiffness, transient elastography (TE) using FibroScan® (Echosens, Paris, France) has achieved wide acceptance, has been shown to possess excellent performance, and is currently incorporated as a valuable tool in the assessment of chronic liver disease in many centers, especially in Europe. Liver biopsy for

staging purposes has substantially been reduced in many hospitals. TE has very good performance in detecting cirrhosis and excluding significant fibrosis [10, 12].

The impact of TE in changing the epidemiology of chronic liver diseases can be illustrated by different approaches, but the most remarkable is the fact that TE is able to uncover cACLD in patients with chronic liver disease in whom the caring physician did not suspect it. This effect represents a substantial increase in the number of patients needing close follow-up and surveillance (Fig. 5.1). Prospective studies specifically aimed at identifying this occult cACLD among chronic liver disease patients are not available, but some information could be extracted from other studies.

Screening studies performed with TE in unselected healthy populations may help to understand what the prevalence of cACLD in general population is. In a French study carried out in more than 1000 normal subjects (general population), a 7.5 % prevalence of liver stiffness measurement (LSM) ≥8 kPa was found, among them 10 % with LSM >13 kPa (0.8 of the total population) [13]. In the Rotterdam cohort, with 1324 participants older than 65 years, the prevalence of LSM >9.5 kPa and >13 kPa was 4.2 % and 1.1 %, respectively [14]. Similar studies carried out in Asian populations, including more than 3000 individuals, have detected LSM values indicative of F3 fibrosis in 1–2 % of the individuals [15, 16, 17]. Nonalcoholic fatty liver disease (NAFLD) was the predominant etiology of liver disease in all studies.

A different way to analyze the importance of TE to uncover occult cACLD is by systematically studying series of patients with chronic liver disease without any

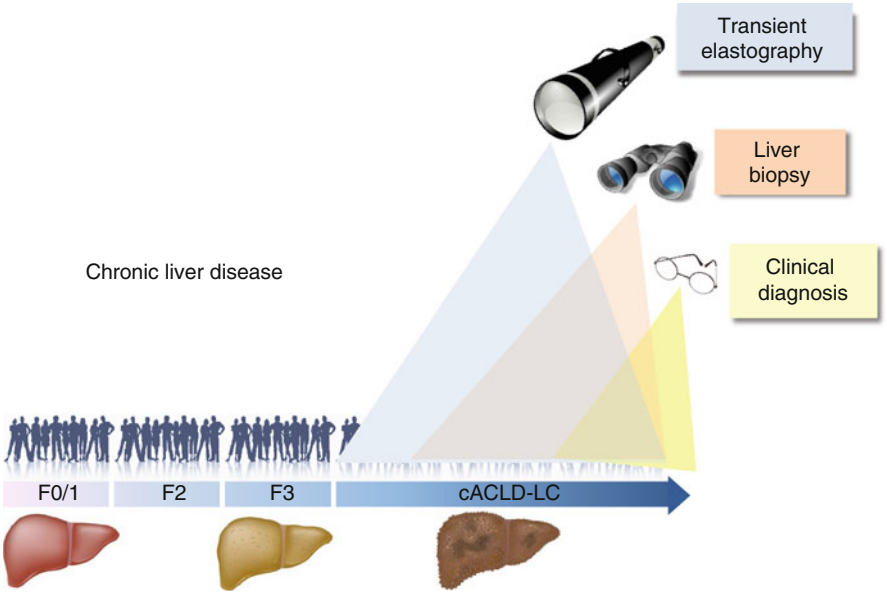

Fig. 5.1 Representation of the impact of transient elastography in uncovering advanced chronic liver disease/liver cirrhosis (*ACLD/LC*) in comparison to liver biopsy and clinical diagnosis of cirrhosis

clinical sign of cirrhosis (normal platelets and abdominal sonography). Results from Barcelona [18], Montreal [19], and Seoul [20] indicate a prevalence of 8–14 % of patients with LSM ≥13–13.6 kPa in these cohorts (Fig. 5.2. Panel a). These patients with occult cACLD represented 24–37 % of the total number of patients with LSM ≥13–13.6 kPa included in the first two prior cohorts, plus patients from the ANTICIPATE study [21] (Fig. 5.2. Panel b). The ANTICIPATE study is a cooperative study (Edmonton, Barcelona, Toulouse, Cluj-Napoca) aimed at assessing noninvasive tools to identify the risk of CSPH and varices in patients with presumed or confirmed compensated liver cirrhosis. Therefore, patients with occult cACLD account for a substantial portion of patients in the different studies.

Finally, it is also worth to mention that in the study by Chen et al. [19], patients with occult cACLD received significant less surveillance than patients with clinically evident liver cirrhosis, and this resulted in a higher rate of late diagnosis (advanced hepatocellular carcinoma, variceal bleeding). The results of this

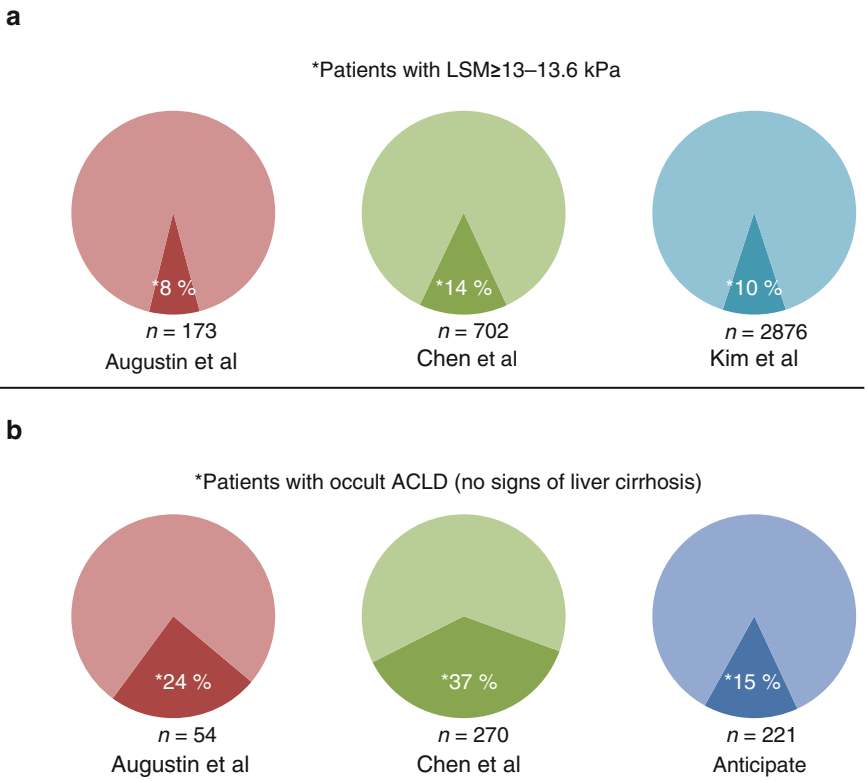

Fig. 5.2 Prevalence of patients with LSM ≥13–13.6 kPa in three series of patients with chronic liver disease without any clinical sign of cirrhosis (normal platelets and abdominal sonography) (Panel **a**). Prevalence of occult ACLD (normal platelets and abdominal sonography) in three series of patients with LSM ≥13–13.6 kPa (Panel **b**)

observational study suggest that patients with occult cACLD are frequently underdiagnosed and under-monitored compared to patients with evident liver cirrhosis.

Why Compensated Advanced Chronic Liver Disease?

When a patient with chronic liver disease develops clinical decompensation, there is no doubt that liver cirrhosis is present, and the same could be applied to a patient in whom varices are detected by endoscopy or CSPH by HVPG. However, the presence or not of cirrhosis in its early stages might be challenging, and since the spectrum of severe fibrosis and cirrhosis is actually a continuum that is difficult to be distinguished without liver histology, the new term of what we have called cACLD might be helpful in this setting. The new definition would be useful for several reasons: (1) to select patients for clinical and therapeutic studies; (2) to adequately frame a clinical situation; and (3) to provide recommendations for screening of hepatocellular carcinoma, varices, and CSPH.

The grounds for this new term of cACLD that would include both patients with severe fibrosis and patients with compensated cirrhosis, especially in the earliest stages, could be the following:

1. Liver cirrhosis is a histological diagnosis.
2. Cirrhosis is not histologically present in every patient classified as F4 by noninvasive methods.
3. There is no consensus in a clinical definition of liver cirrhosis.
4. Patients in pre-cirrhotic stages may have portal hypertension [22, 23].
5. Hepatocellular carcinoma surveillance might be indicated in pre-cirrhotic stages [9, 24].
6. Noninvasive tests have changed the clinical scenario of chronic liver disease.

A patient with cACLD would be a patient with chronic liver disease with signs of severe liver fibrosis or compensated liver cirrhosis with or without signs of portal hypertension. The identification of a patient with cACLD would imply referral by primary care physicians to a liver disease specialist for follow-up and treatment. Considerations for closer follow-up and hepatocellular carcinoma surveillance, and CSPH and varices evaluation should be made at this point by the liver disease specialist.

Different parameters that liver specialists with experience in cACLD and cirrhosis use to classify patients as having or suspecting cACLD are shown in the results of the questionnaire answered by the panelists of the present consensus workshop (Table 5.1). Two aspects are worth to mention from this survey: (1) Many of the parameters are the ones we have been using for years with different performance for the clinical diagnosis of liver cirrhosis, and (2) experts consider now noninvasive tests useful for classifying patients as cACLD patients, and among them only TE possesses wide acceptance. In consequence, recommendations for ruling out and ruling in cACLD based on TE results are now included in the final statements of the

Table 5.1 Parameters used by the panelists of the consensus workshop to classify a patient as suspecting/having compensated advanced chronic liver disease (cACLD)

Options	Response percent
Liver biopsy showing cirrhosis	83.3
Varices on endoscopy	81.3
Imaging studies: Nodular liver surface	72.9
Liver stiffness by transient elastography ≥13.6 kPa	60.4
Imaging studies: Collateral circulation	58.3
HVPG > 5 mmHg	47.9
Platelet count <150,000 mm^3 + splenomegaly ≥13 cm	37.5
Imaging studies: splenomegaly ≥13 cm	29.2
Child-Pugh score >5	29.2
Platelet count <150,000 mm^3	18.8
Liver stiffness by transient elastography ≥10 kPa	16.7
Liver stiffness by ARFI ≥1.75 m/s	8.3
Liver stiffness using other cutoff	6.3
Fibrotest ≥0.75	6.3
Fibrotest ≥0.60	4.2
Platelet count/spleen diameter >909	2.1
Liver stiffness by ARFI ≥1.72 m/s	0.0
Liver stiffness by ARFI using other cutoff	0.0
Fibrotest using other cutoff	0.0

Parameters are ordered by the percentage of positive responses

consensus workshop. In essence, an LSM below 10 kPa (high negative predictive value) will exclude cACLD, and values above 15 kPa (high positive predictive value) will be highly indicative of cACLD; for the rest of TE results between these two points, additional work-up would be needed.

What Patients with cACLD Could Avoid Screening Endoscopy?

One of the main challenges of detecting cACLD by noninvasive methods is the large number of unnecessary endoscopies that would potentially be performed in patients with a very low risk of varices [11]. TE has been evaluated as a predictor of varices in several studies. In general, studies show that TE performs better in ruling out (high sensitivity and negative predictive value) than in ruling in (high specificity and positive predictive value) the presence of varices [12, 18, 25, 26]. However, heterogeneity in the results and cutoffs, and overall low predictability has impeded translation into clinical practice. Since TE seems to work better to rule out varices, it is

important to decide what would be an acceptable risk when using this technique for prescreening purposes. For all varices a 20 % risk of missing might be acceptable, but for varices needing treatment (VNT: medium-large varices or small with red signs), it should be near 0 or 5 % at the most.

Diagnostic performance for varices seems to improve when LSM is combined with simple clinical parameters, mainly including platelets and spleen size. The LSPS (LSM-spleen diameter to platelet ratio) [27, 28] and the VRS (variceal risk score) [29] are very good examples of this strategy, and both perform better than LSM alone for varices prediction. Also in the ANTICIPATE study cohort, LSPS was the best predictor for varices and VNT in a risk prediction modeling analysis [21].

However, these combined noninvasive tests require more or less complex calculation and threshold memorization to be applied to daily clinical practice. Simple, visual, practical clinical rules using these parameters could be equally useful and easily implementable. Three studies using just a combination of LSM and platelets are summarized in Table 5.2 [18, 30, 31]. In addition, the validation of the classification rules of these studies in the ANTICIPATE cohort is also shown. Results indicate that using a combination of LSM with a cutoff of 25 kPa and platelet count with cutoffs between 100 and 150 $\times 10^3$ mm^3, 20–40 % of screening endoscopies could be avoided in these patients, with an acceptable risk of missing VNT (5 % in the worst case). The simplicity and readiness-to-use of the classification rule could allow doctors to easily defer endoscopy while visiting the patient and consequently contribute to the incorporation of the classification rule into clinical practice.

What Patients with cACLD Could Be Classified as Having CSPH?

Similarly to varices detection, TE has also been utilized to predict CSPH. Detecting patients at very high risk of having CSPH could be useful to select patients for clinical studies and indicate empiric prophylactic therapy for decompensation (provided future studies show its usefulness). However, it is quite clear that TE will never be capable of predicting the numerical value of HVPG and it is probably not suitable for monitoring HVPG changes. TE seems to be a good predictor of CSPH and in general, tends to perform better in ruling in (high specificity and positive predictive value) than in ruling out (high sensitivity and negative predictive value) the presence of CSPH [12, 18, 25, 26]. In terms of selecting patients with CSPH, positive predictive values (ruling in) higher than 90 % can be achieved with an LSM cutoff of 25 kPa; these numbers decrease slightly to 85–90 % if LSM cutoff is lowered to 20–21 kPa. Again data from the ANTICIPATE study [21] shown in Fig. 5.3 indicates that with an LSM ≥25 kPa (37 % of the cohort), 96 % of these patients can be assumed as having CSPH.

The ability of TE to rule in CSPH is not substantially improved by adding simple clinical information (platelets and spleen size), as in the LSPS or the PH (portal hypertension) risk scores [28, 29]. Also in the ANTICIPATE study cohort, LSPS was only slightly better than LSM alone to predict CSPH in a risk prediction modeling analysis [21]. By contrast and although TE is not very accurate in ruling out

Table 5.2 Summary of performance for excluding varices of studies using a combination of liver stiffness measurement (LSM in kPa) and platelets

	No.	All varices	VNT	Classification rule	All varices NPV	VNT NPV	Varices missed	VNT missed	Endoscopies avoided
Augustin et al. [18]	49	10 %	0	LSM<25 LSM<25+Pla≥150	93 % 100 %	100 % 100 %	7 % 0	0 0	61 % 20 %
Montes et al. [30]	85	45 %[a]	20 %	LSM<20 LSM<20 and/or Pla>120	90 % 100 %	– 100 %	9.5 % 0	– 0	25 % 15 %
Ding et al. [31]	272	–	–	LSM<25+Pla≥100	–	100 %	–	0	42 %
ANTICIPATE [20]	379	42 %	15 %	LSM<25+Pla≥100 LSM<25+Pla≥150	79 % 86 %	95 % 96.5 %	21 % 14 %	5 % 3.5 %	45 % 23 %

VNT varices needing treatment, *NPV* negative predictive value, *Pla* platelets ($\times 10^3$ mm^3)

[a]Includes varices and portal hypertensive gastropathy

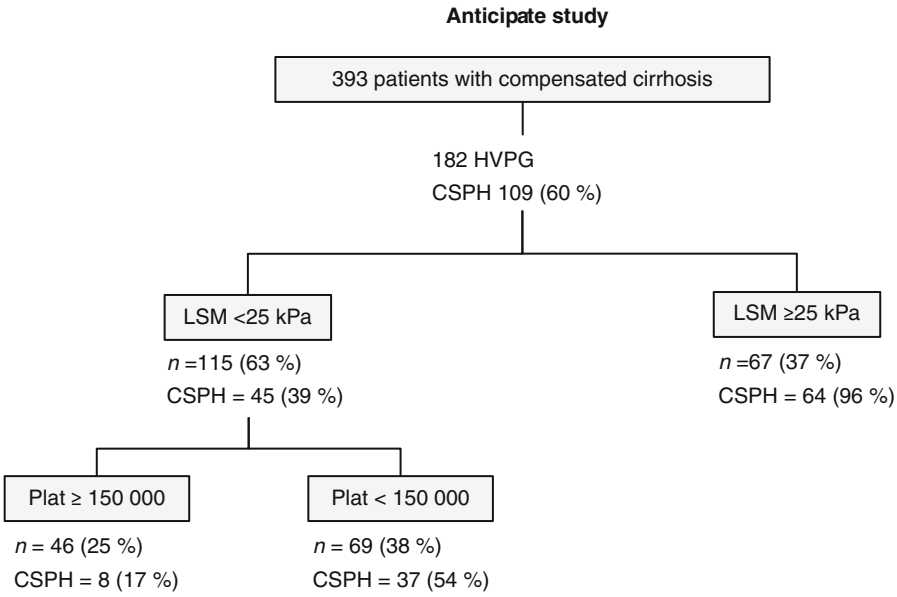

Fig. 5.3 Assessment of clinical significant portal hypertension (*CSPH*) in the ANTICIPATE cohort by using liver stiffness measurement (*LSM*) and platelet count (*Plat*). *HVPG* hepatic venous pressure gradient

CSPH, a subgroup of patients with less than 20 % risk of having CSPH can be detected combining LSM and platelet count. As shown in Fig. 5.3, patients with LSM <25 kPa and normal platelets have a risk of CSPH of 17 %. These patients, representing 25 % of the total cohort, can probably be monitored and safely avoid immediate CSPH evaluation. Other studies [18, 32] with lower number of patients have revealed very similar results. The study by Kitson et al. [32] found a 90 % negative predictive value (10 % risk) of CSPH with the same classification rule, LSM <25 kPa and platelet count >150 $\times 10^3$ mm^3. As for the rest of patients positioned in the gray zone, patients with LSM <25 kPa and low platelets, representing 35–40 % of the population (Fig. 5.3), the prevalence of CSPH ranges from 40 to 60 %, and if CSPH is to be diagnosed, an HVPG should be performed.

Summary

A new term of cACLD defining patients in the early phases of severe chronic liver disease has been proposed, including both patients with severe fibrosis or pre-cirrhotic patients and patients with compensated cirrhosis. The term will be helpful for both clinical practice and research purposes. Simple clinical rules to avoid unnecessary endoscopies and HVPG in these cACLD patients are also provided. With the combination of LSM <25 kPa and platelet count $\geq 100 \times 10^3$ mm^3, 40–45 %

of screening endoscopies could be avoided in these patients, with an acceptable risk of missing 5 % VNT. Similarly, patients with LSM ≥25 kPa can be safely considered as having CSPH, and patients with LSM <25 kPa and normal platelets can be classified as not having CSPH; 60 % of unnecessary procedures might be avoided . These recommendations will definitely decrease the number of unneeded procedures in these patients.

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How to Screen?

6

Laurent Castera

Introduction

The Baveno V consensus conference recommended 5 years ago that all patients with newly diagnosed cirrhosis should undergo screening endoscopy for assessing gastroesophageal varices in order to begin primary prophylaxis, if required, and hepatic vein pressure gradient (HVPG) measurement should be obtained for prognostic aims whenever available [1]. However, in the meantime noninvasive methods have been increasingly validated and used not only for staging liver fibrosis but also to predict complications of cirrhosis including those related to portal hypertension [2]. Among noninvasive methods, transient elastography (TE) (FibroScan™, Echosens, Paris, France) has reached an established role in clinical practice, particularly in viral hepatitis-induced chronic liver diseases and is now routinely used worldwide [3]. Several meta-analyses [4–8] have confirmed the excellent performance of liver stiffness (LS) measurement using TE for diagnosing cirrhosis in patients with chronic liver disease, with mean AUROC values of 0.94 and a suggested optimal cut-off of 13 kPa [6]. In clinical practice, TE is better at ruling out than ruling in cirrhosis with negative and positive predictive values of 96 % and 74 %, respectively [9]. Although different cut-offs have been proposed for cirrhosis according to etiologies (ranging, for instance, from 11 kPa in chronic hepatitis B [10] to 22.6 kPa in alcoholic liver disease [11]), it should be kept in mind that these cut-off values have been defined in a single population using ROC curves in order to maximize sensitivity and specificity – and not applied to a validation cohort. Difference between cut-offs may be simply related to difference in cirrhosis

L. Castera, MD, PhD
Department of Hepatology, Hôpital Beaujon, Assistance Publique –Hôpitaux de Paris,
INSERM U773, University of Paris-VII,
100 boulevard du General Leclerc, Clichy 92110, France
e-mail: laurent.castera@bjn.aphp.fr

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prevalence in the studied populations, known as the spectrum bias [12]. Finally, the cut-off choice should also consider the pretest probability of cirrhosis in the target population (varying from less than 1 % in the general population to 10–20 % in tertiary referral centers). For instance, it has been shown that in a population with a pretest probability of 13.8 %, at a cut-off <7 kPa, cirrhosis postestprobability ranged from 0 to 3 %, whereas at a cut-off >17 kPa cirrhosis probability was 72 % [13]. Interestingly, several recent studies have shown that in patients with chronic liver disease, LS could also predict clinical decompensation as well as survival [14–17]. For instance, Robic et al. [15] found that TE was as effective as HVPG measurement in predicting clinical decompensation in 100 patients with chronic liver disease with a 2 years follow-up. Both HVPG $\leq$ 10 mmHg and liver stiffness $\leq$21.1 kPa had 100 % negative predictive value for portal-hypertensive complications. However in clinical practice, TE results should always be interpreted being aware of the risk of overestimating liver stiffness values with confounding factors such as ALT flares, food intake, extrahepatic cholestasis, congestive heart failure, and excessive alcohol intake [18].

Thanks to the improvements in the noninvasive methods, most patients are currently diagnosed in a very initial stage of cirrhosis, in which CSPH and esophageal varices (EV) are often absent. In this new scenario, a large proportion of HVPG measurements and screening endoscopies may be unnecessary. Therefore, efforts should be directed at limiting these procedures to those patients at higher risk of CSPH and varices, so as to reducing healthcare cost and lessen patients' discomfort [19]. There are two clinically relevant questions when screening for portal hypertension: first, identification of patients at high risk for clinically significant portal hypertension (CSPH) defined by an HVPG $\geq$ 10 mmHg [20]; second, identification of patients at high risk for EV.

Detection of Patients at High Risk for CSPH

Among available noninvasive tests, LS measurement using TE has been the most extensively studied. There is substantial evidence indicating that TE can be quite effective in detecting patients with a high risk of having (or not having) developed CSPH. Several studies have shown that there is a good correlation between liver stiffness values and HVPG in patients with advanced liver diseases [21–24]. According to a recent meta-analysis (based on 5 studies including 420 patients), the diagnostic performance of TE for predicting CSPH in the setting of patients with compensated chronic liver disease/cirrhosis is excellent, with an AUROC of 0.93 [25]. TE was very informative with 81 % probability of correctly detecting significant portal hypertension following a "positive" measurement (over the threshold value) and lowering the probability of disease to as low as 11 % when "negative" measurement (below the threshold value) was found when the pretest probability was 50 %. However, it should be noted that when the pretest probability of significant portal hypertension was as low as 25 %, the probability of correctly identifying significant portal hypertension decreased markedly. The studies addressing the

diagnostic performances of TE for the detection of CSPH [22–24, 26–31] are summarized in Table 6.1. The results of these studies deserve several comments: most if not all of them have been conducted in European expert centers where HVPG is available with a likely referral bias. Indeed, studied populations are heterogeneous in terms of etiologies and Child-Pugh classes (ranging from 20 to 100 % for Child-Pugh class A) with small sample size (<100 patients) and high prevalence of CSPH (51–86 %). These are limitations that are inherent to the HVPG technique and thus will be difficult to overcome but that hamper the applicability of these results to the target population of patients with early cirrhosis eligible for screening. Finally, TE cut-offs vary from 13.6 to 34.9 kPa, making the optimal TE cut-offs for prediction of CSPH difficult to be defined. In the largest studied population ($n = 502$), Reiberger et al. [29] have shown that at a cut-off of 18 kPa, TE was better at ruling in than ruling out CSPH (positive and negative predictive values of 86 and 81 %) [29]. Other authors [27] have proposed a dual cut-off strategy (<13.6 kPa with a 90 % sensitivity for CSPH diagnosis and ≥21 kPa with a 90 % specificity), allowing a correct stratification of presence/absence of CSPH in patients with compensated cirrhosis and potentially resectable hepatocellular carcinoma, reducing the need for invasive hemodynamic assessment in around 50 % of patients. However, while the correlation is excellent for HVPG values between 5 and 10–12 mmHg (typical of cirrhosis without evident clinical manifestations related to portal hypertension), it hardly reaches statistical significance for values above 12 mmHg [22]. This is because,

Table 6.1 Diagnostic performance of transient elastography for the detection of clinically significant portal hypertension (HVPG ≥10 mmHg)

Authors	Year	Patients (*n*)	Etiologies	CP A (%)	CSPH (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Vizzutti et al. [22]	2007	61	HCV	46	77	13.6	0.99	97	92	95
Lemoine et al. [24]	2008	44 48	HCV alcohol	100	77 83	20.5 34.9	0.76 0.94	63 90	70 88	98 98
Bureau et al. [23]	2008	150	CLD	20	51	21.0	0.94	90	93	83
Sanchez-Condé et al. [26]	2011	38	HIV-HCV	71	74	14.0	0.80	93	50	81
Llop et al. [27]	2011	79	CLD	100	40	13.6/21	0.84	91/58	57/91	53
Reiberger et al. [29]	2012	502	CLD	NA	55	18.0	0.82	83	82	72
Colecchia et al. [28]	2012	100	HCV	68	65	16.0 / 24.2	0.92	95/52	69/92	65
Berzigotti et al. [30]	2013	117 56	CLD CLD	88 70	67 86	13.6 / 21.1 13.6 / 21.1	0.88 0.91	91/65 NA	56/92 NA	62 70
Kitson et al. [31]	2015	95	CLD	91	74	29.0	0.90	72	100	-

with the progression of cirrhosis, the mechanisms of portal hypertension (PH) become less and less dependent on the intrahepatic resistance to portal flow due to tissue fibrosis and progressively more dependent on extrahepatic factors (i.e., hyperdynamic circulation, splanchnic vasodilatation) [32]. This observation sets a key limitation to the use of liver stiffness measurements as a noninvasive surrogate of HVPG beyond the prediction of clinically significant (HVPG ≥ 10 mmHg) and severe (HVPG ≥ 12 mmHg) PH, and, accordingly, TE of the liver is unlikely to be useful in monitoring the hemodynamic response to the administration of beta-blockers or disease progression in the decompensated phase.

Several biological parameters have been proposed for the noninvasive detection of clinically significant portal hypertension including prothrombin time [23], a score combining platelet count and total bilirubin [33], and FibroTest® [34]. In particular, a score combining platelet count with total bilirubin had an AUROC of 0.91 for predicting clinically significant portal hypertension with 88 % sensitivity and 86 % specificity at a cut-off of −1.0.

Finally, in order to increase diagnostic accuracy, some authors have proposed scores combining LS with platelet count and spleen diameter by ultrasound, referred as LSPS for LSM-spleen diameter to Platelet ratio score [35] or PH risk score [30]. For instance, in a population of 117 patients with compensated cirrhosis, more than 80 % of patients were accurately classified for CSPH using LSPS and PH risk score. These promising results require further external validation but could represent an attractive strategy for screening patients for CSPH as proposed by some authors [36].

Detection of Patients at High Risk for GOV

More uncertain and controversial is the possibility of predicting the presence and the size of OV based on LS measurements (LSM). In a recent meta-analysis [25] (based on 18 studies and 3644 patients), the diagnostic performance of TE for predicting OV and large OV (LOV) was not as good as for CSPH with AUROCS of 0.84 and 0.78, respectively. The studies addressing the performance of TE for prediction of OV [22–24, 28, 37–52] are summarized in Table 6.2. AUROCs range from 0.62 to 0.90 and cut-offs from 13.9 to 48.0 kPa. Although the sensitivity for the prediction of the presence of OV was high (56–100 %), specificity was much lower (32–87 %) and less satisfactory. Regardless, the general features of these studies, i.e., single-center retrospective, heterogeneous etiology of cirrhosis and stages of disease progression, and subjective assessment of OV size, do not allow any sound conclusion on the utility of liver stiffness assessment in predicting the presence of OV and to screen cirrhotic patients without endoscopy [54].

Similarly, several biomarkers have been proposed for the detection of OV including routine biological parameters [55], FibroTest® [56], and combination of simple biological and ultrasound parameters [57]. In the largest study to date comparing retrospectively a panel of serum markers (platelet count, AST/ALT ratio, APRI, Forns index, Lok index, FIB-4, and Fibroindex) in more than 500 patients with

Table 6.2 Diagnostic performance of transient elastography for the detection of esophageal varices (OV and LOV) in cirrhotic patients

Authors	Year	Patients (*n*)	Etiologies	CP A (%)	Endpoint	OV (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Kazemi et al. [37]	2006	165	CLD	NA	OV LOV	45 38	13.9 19.0	0.83 0.84	95 91	43 60	66 69
Foucher et al. [38]	2006	144	CLD	NA	LOV	29	27.5	0.73	88	53	NA
Vizzutti et al. [22]	2007	47	HCV	60	OV	66	17.6	0.76	90	43	74
Bureau et al. [23]	2008	89	CLD	34	OV LOV	72 48	21.1 29.3	0.85 0.76	84 81	71 61	81 71
Castera et al. [39]	2009	70	HCV	100	OV LOV	36 19	21.5 30.5	0.84 0.87	76 77	78 85	73 79
Pineda et al. [40]	2009	102°	HIV-HCV	76	LOV	13	21.0	0.71	100	32	44
Nguyen et al. [41]	2010	183	CLD	63	LOV	22	48.0	0.76	73	73	73
Malik et al. [42]	2010	124	CLD	NA	OV	51	20.0	0.85	NA	NA	NA
Pritchett et al. [43]	2011	211	CLD	NA	OV LOV	NA 37	19.5 19.8	0.74 0.76	76 91	66 56	NA 69
Sporea et al. [44]	2011	1000	CLD	NA	LOV	35	31.0	0.78	83	62	NA
Stefanescu et al. [45]	2011	231	HCV/ALD	76	OV LOV	68 29	19.0 38.0	0.66 0.69	84 56	32 75	67 68
Colecchia et al. [28]	2012	100	HCV	68	OV	53	16.4 / 25.0	0.90	96/57	60/98	NA
Chen et al. [46]	2012	222	HBV	49	OV	37	17.1	0.73	90	44	NA
Wang et al. [53]	2012	126	HBV	NA	OV LOV	38 10	12.0 21.0	0.79 0.86	67 77	77 87	73 86
Calvaruso et al. [48]	2013	96	HCV	100	OV LOV	57 27	17.0 19.0	0.70 0.71	71 72	57 55	63 56
Sharma et al. [51]	2013	174	CLD	31	OV	71	27.3	0.91	91	72	86

(continued)

Table 6.2 (continued)

Authors	Year	Patients (*n*)	Etiologies	CP A (%)	Endpoint	OV (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Fraquelli et al. [49]	2014	110	HCV/HBV	NA	OV	10	19.0	0.62	73	47	NA
Hu et al. [50]	2015	200	HBV	NA	OV LOV	55 34	20.2 25.2	0.85 0.84	84 86	72 72	NA NA
Stefanescu et al. [52]	2015	90	CLD	62	LOV	52	38.0	0.70	60	71	65

chronic liver diseases, the combination of Lok index (cut-off = 1.5) and Forns index (cut-off = 8.8) had the best diagnostic performance (AUROC of 0.80 and negative predictive value of 90 %) for predicting clinically relevant OV [55]. Finally, as mentioned before for CSPH, scores combining LS with platelet count and spleen diameter by ultrasound such as LSPS or variceal risk score have been proposed [30, 35]. For instance, in 401 Korean patients with HVB cirrhosis (280 in the training set and 121 in the validation set), the LSPS had a significantly better AUROC than TE alone for prediction of high-risk OV (0.95 vs. 0.88 in the training set, respectively, $p < 0.001$) [35]. At a cut-off < 3.5, LSPS had a 94.0 % negative predictive value and a 94.2 % positive predictive value at a cut-off > 5.5. Overall, upper GI endoscopy could be saved in 90.3 % patients. Interestingly, LSPS appeared as a reliable predictor of OV bleeding risk [58]. The performance of LSPS has also been confirmed externally [28, 30]. Using a similar strategy in 173 patients, Berzigotti et al. [30] have shown that only 3 of 70 with varices (4 %; all with small varices) would have been missed if endoscopy was delayed using the varices risk score. These scores appear thus as an attractive strategy in clinical decision making for detecting patients with high-risk OV.

Spleen Stiffness: A New Surrogate of Portal Hypertension?

Recently, studies employing different technical approaches have highlighted the potential utility of spleen stiffness (SS) assessment for the prediction of the presence of OV and the degree of portal hypertension in cirrhotic patients [28, 51, 59]. Colecchia et al. measured SS and LS by TE in 100 consecutive patients with hepatitis C virus-induced cirrhosis patients who underwent measurement of HVPG and upper GI endoscopy [28]. The ability of both SS and LS to predict CSPH and the presence of OV was compared to that of the previously proposed methods, i.e., LSPS and platelet count to spleen diameter [35, 57, 60]. SS and LS were more accurate than other noninvasive parameters in identifying patients with OV and different degrees of portal hypertension. However, TE may not be the most appropriate tool for SS measurement, as ultrasound examination of the spleen was mandatory before performing TE to ensure that the ultrasound beam remained within the spleen parenchyma. Indeed, SS could not be measured in 13 % of patients particularly those with an anteroposterior spleen diameter measuring <4 cm. Alternative ultrasound-based elastography techniques such as acoustic radiation force impulse imaging (ARFI) (Virtual touch tissue quantification™, Siemens) or 2D-shear-wave elastography (2D-SWE) (Aixplorer™, Supersonic Imagine, France) have been proposed for measuring SS with much lower failure rates of 4.5 % [61] and 3 % [62], respectively. Another technical advantage of ARFI and 2D-SWE over TE is that they can be performed using a regular ultrasound machine, allowing during a single procedure to choose the region of interest where the shear-wave velocity is measured under direct visualization of the spleen [63]. Although not clearly demonstrated in the study by Colecchia et al. [28], the study by Takuma et al. [61] in 340 patients showed that SS was better than LS measurement, particularly for ruling out

the presence of OV. Finally, there may be a ceiling effect with TE that showed significantly higher kPa values (up to 70 kPa) with SS values compared with LS at any given HVPG level, suggesting that even an upper detection limit of 75 kPa could be too restrictive for a satisfactory SS measurement and would need to be extended as proposed by some authors [48]. Thus, SS is not ready yet for "prime time," and further validation is needed before its exact place in clinical practice can be defined.

Conclusions and Perspectives

In conclusion, the evidence accumulated so far indicates that noninvasive methods cannot replace HVPG for a detailed portal hypertension evaluation and upper GI endoscopy for detecting OV. However, in settings where HVPG is not available, TE could be considered to stratify the risk of CSPH. Similarly, strategies combining LS measurement with platelet count and spleen diameter could be useful to rule out OV in patients at low risk of having portal hypertension. One would foresee different levels of invasiveness, starting with simple laboratory tests, followed by measurements of LS and, only in a minority of patients, would we need to perform an invasive test.

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When and How to Perform Surveillance

7

Avik Majumdar and Massimo Pinzani

Introduction

The distinction between medical screening and surveillance was comprehensively described in 1968 by Wilson and Jungner. Screening refers to the cross-sectional collection of data from a population at risk of disease resulting in separation of high- and low-risk groups. Alternatively, surveillance conveys the idea of a long-term process where screening examinations are repeated at intervals for early disease detection in individuals or a population [1]. In the context of chronic liver diseases, surveillance for the complications of portal hypertension and hepatocellular carcinoma has become a tenet in the model of care for those with an established diagnosis of cirrhosis.

The onset of clinically significant portal hypertension (CSPH), as defined by a hepatic venous pressure gradient (HVPG) of greater than or equal to 10 mmHg, is a critical event in the clinical course of chronic liver disease as it heralds the development of oesophageal varices and the potential for clinical decompensation. Gastro-oesophageal varices develop at a rate of approximately 7 % per year, with a 1-year bleeding risk of 12 % [2]. Upper gastrointestinal endoscopy (UGIE) has traditionally been the mainstay of diagnostic, surveillance and therapeutic algorithms for oesophageal varices, while HVPG remains the gold standard in assessment for CSPH. Both have the disadvantages of being invasive, costly and in the case of HVPG, available only in specialised centres.

Since Baveno V, there have been a number of developments in the evaluation of non-invasive markers of CSPH; however, these are yet to find their place in consensus guidelines. Current algorithms have many unresolved issues, particularly

A. Majumdar, MBBS (Hons), MPHTM, FRACP • M. Pinzani, MD, PhD, FRCP (✉)
UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Centre Royal Free Hospital, London, UK
e-mail: avik.majumdar@nhs.net; m.pinzani@ucl.ac.uk

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agreement on surveillance intervals, consensus on endoscopic criteria, the economic impact of surveillance and whether currently available non-invasive tests can reduce unnecessary procedures. This chapter aims to "fill the gap" between the preceding Baveno consensus meeting by summarising the literature to date.

Is Surveillance Needed?

The benefits of endoscopic surveillance have translated to improved clinical outcomes with a decline in both the mortality and incidence of variceal haemorrhage in population-based studies. A recent national database analysis of patients who presented to acute care hospitals in the USA with upper gastrointestinal bleeding from 1989 to 2009 demonstrated a reduction in the annual incidence of variceal haemorrhage from 2.9 cases to 1.3 cases per 100,000 over the study period. In-hospital mortality decreased from 10.7 to 5.6 % during this time [3]. A decline in mortality has also been demonstrated in other countries [4, 5]. A previous analysis of US national databases found that the outpatient diagnosis of non-bleeding oesophageal varices had increased from 5.5 to 6.6 per 100,000 from 1997 to 2003, respectively [6]. This increase in detection and reduction in overall mortality rates cannot be solely explained by improvements in the acute management and secondary prophylaxis of variceal haemorrhage, indicating that screening, surveillance and prophylaxis algorithms are likely contributors.

Despite the improvements in short-term outcomes, the mortality rate associated with variceal haemorrhage is still unacceptably high and particularly so when considering longer-term survival after the bleeding event. Mortality at 6 weeks is estimated at 10–20 %, while 1-year mortality is estimated at 50–60 % [2, 7–9]. Optimising preventative and surveillance strategies is therefore of paramount importance if these outcomes are to be improved.

However, the economic burden of these interventions is significant, with one Markov model estimating a total cost of $37,300 (US dollars in the year 2000) per patient for an endoscopic surveillance strategy [10]. Further modelling studies have had conflicting conclusions regarding the most cost-effective strategy for prevention, with universal beta-blocker prophylaxis without endoscopy being suggested in certain simulated models [10–14]. The idea of universal beta-blocker prophylaxis has been controversial in the real-world setting for a variety of reasons, and thus endoscopic surveillance is still recommended in consensus guidelines [15–17].

The issue of financial costs associated with endoscopy may be addressed through better risk-stratification of patients who are at risk of progression of liver disease, thereby limiting the number of patients entering into surveillance programmes. The potential for currently available non-invasive tests of CSPH to function in this role is discussed in detail below. Additionally, current surveillance strategies have more to improve upon, particularly regarding the standardisation of endoscopic criteria, surveillance intervals and whether surveillance can be withdrawn.

Available Tools for Surveillance

Hepatic Venous Pressure Gradient

HVPG measurement has been the reference standard for the diagnosis and prognosis of patients with CSPH. However, it has not been widely adopted outside specialised centres due to its invasive nature, cost and the technical expertise required to perform the procedure. HVPG measurement is safe, with a minor complication rate reported between 0 and 1 % and a negligible risk of major complications [18, 19]. In cost-effectiveness models, HVPG appears to be more expensive than endoscopic screening strategies [20, 21]. For these reasons, HVPG does not have a role in surveillance directly but should be used as a reference in validating other non-invasive modalities of detecting CSPH.

Upper Gastrointestinal Endoscopy (UGIE)

UGIE continues to be the ideal screening and surveillance tool as it is widely available and the risk of variceal haemorrhage can be estimated by endoscopically assessable criteria. Specifically, bleeding risk has been correlated with the presence of high-risk endoscopic stigmata such as red signs and variceal size [22, 23]. Furthermore, endoscopic assessment also provides information regarding other causes of portal hypertension-associated bleeding such as portal hypertensive gastropathy, gastric or duodenal varices and gastric antral vascular ectasia. Primary prophylaxis with endoscopic band ligation can also be administered during the diagnostic procedure. However, a universal standard for the endoscopic classification of oesophageal varices is yet to be adopted. Currently, two major classification systems are commonly used: the two-stage Italian Liver Cirrhosis Project [24] and the three-stage Japanese Research Society of Portal Hypertension [25]. Both classification systems rely on subjective criteria, which carry an inherent risk of interobserver variability. Endoscopic assessment has a number of other disadvantages, including being invasive and as aforementioned, expensive. Furthermore, certain patient groups may never develop high-risk endoscopic features despite regular surveillance, which confers an unnecessary burden on patients and endoscopy services.

Wireless Capsule Endoscopy

Wireless capsule endoscopy (WCE) has recently been investigated as a screening and surveillance tool, but lacks the diagnostic capability to be used as a first-line investigation. A Cochrane review with a pooled study population of 936 from 15 studies, including patients with portal vein thrombosis, found that both the sensitivity and specificity of WCE for the detection of varices were approximately 84 % [26]. A more recent prospective multicentre trial yielded sensitivities of 76 % and

64 %, to diagnose and stage oesophageal varices, respectively. The specificity of diagnosis and staging were reported as 91 % and 93 %, respectively [27]. Thus, WCE could be used where UGIE is contraindicated or not possible but lacks the sensitivity to be used routinely in this setting.

Conventional Imaging

Conventional imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound scanning (USS) also do not have the accuracy to be used as primary screening tools for the presence of CSPH and oesophageal varices. Splenomegaly can be easily identified as a marker of CSPH using imaging modalities, but is a non-specific sign. Conversely, the finding of abdominal portosystemic collaterals on cross-sectional imaging or USS lacks sensitivity, but has a specificity approaching 100 % [28, 29]. USS has been proposed to have the potential to avoid screening endoscopy for varices in compensated cirrhosis; however the data are conflicting [30–32]. CT scanning is reliable in detecting large oesophageal varices with a sensitivity of 84–100 % and specificity of 90–100 % and has been suggested to be more cost-effective than endoscopy. Alternatively, the sensitivity of diagnosing small varices is lower and with moderate interobserver variability [33]. Other modifications to standard imaging techniques that have been recently investigated to predict oesophageal varices are the presence of Gamna-Gandy bodies on splenic MRI [34] and the use of effervescent powder to enhance multi-detector CT scanning [35]; however, these require further study and are unlikely to be used as stand-alone surveillance tools.

Liver Stiffness Measurement

Liver stiffness measurement techniques such as transient elastography (TE), acoustic resonance force impulse imaging (ARFI), real-time shear wave elastography (SWE) or magnetic resonance elastography (MRE) have all been shown to correlate with HVPG with varying accuracy [36–40]. Transient elastography, as measured by FibroScan® (Echosens, Paris, France), is the most widely studied and adopted modality in clinical practice for the non-invasive detection of liver fibrosis. However, the correlation between liver stiffness measurements and portal pressure is less robust once HVPG exceeds 10–12 mmHg. This results in poor prediction of the development and stratification of oesophageal varices and CSPH [36, 41, 42]. Furthermore, interobserver variability has been demonstrated to occur when TE is used as a screening tool for oesophageal varices [43]. As a result, liver stiffness alone is not suitable for surveillance strategies, but has been shown to be more effective in combination algorithms, which will be discussed in detail below.

Spleen Stiffness Measurement

Since Baveno V, there has been a concerted effort to investigate the spleen as a marker of CSPH. Spleen stiffness (SS) measurement with TE was initially shown to be superior to liver stiffness measurement when correlated with HVPG in 100 patients with hepatitis C cirrhosis ($R^2 = 0.78$ and 0.70, respectively) [41]. Measurement of SS with ARFI to determine the presence of oesophageal varices has also been investigated and has a sensitivity of up to 98.5 %, but has a suboptimal specificity of 60.1 % [44]. A subsequent meta-analysis of 12 studies measuring SS using TE, ARFI, real-time tissue elastography or virtual touch tissue quantification found lower sensitivity and higher specificity in the detection of varices at 78 % and 76 %, respectively. Nine studies were included in the meta-analysis for clinically significant varices, which yielded 81 % sensitivity and 66 % specificity [45]. More recently, there has been a suggestion that SWE may have a higher technical success rate and diagnostic accuracy than TE in predicting CSPH with a sensitivity and specificity of 81 % and 88 %, respectively [40]. MRE has been used to measure SS and correlated with HVPG as well as the presence of varices in a cohort of 36 patients but requires further study [39]. The overall diagnostic capability of SS as a single modality is still insufficient to be an adequate surveillance tool.

Combined Algorithms

Varying combinations of non-invasive markers for the detection of CSPH have been developed in an effort to improve accuracy. The platelet count/spleen diameter ratio (PSR) is determined by dividing the platelet count by the maximum bipolar splenic diameter on conventional ultrasound. A meta-analysis of 20 studies found the sensitivity and specificity for detecting oesophageal varices were 92 % and 87 %, respectively; however, there was statistically significant heterogeneity across studies indicating that further prospective evaluation is required [46]. The LSPS index (liver stiffness platelet spleen index = LS × spleen diameter/platelet count) showed promising results in the detection of oesophageal varices with an AUROC (area under the receiver operating characteristic curve) of 0.954 in 280 patients with hepatitis B cirrhosis. However, two cut-off values were established to delineate those who may avoid endoscopy (LSPS < 3.5) and those who should be considered for prophylactic intervention (LSPS > 5.5), which results in ambiguity for those who fall between these values [47]. Additional parameters were added to the LSPS in a prospective cohort of 117 compensated cirrhotics, resulting in the development of the PH (portal hypertension) risk score and VRS (variceal risk score), which resulted in AUROCs of 0.935 and 0.909 for the detection of CSPH and varices, respectively [48]. SS has also been combined with LS and most recently Lok Score plus LS, which all have resulted in similar data [45, 49]. Finally, SS and the Model for End-Stage Liver Disease (MELD) score have been combined to predict clinical decompensation with compelling results that are similar to the predictive ability of HVPG [50].

Combined algorithms have resulted in improved diagnostic accuracy, but still require further validation before widespread use can be recommended for surveillance.

Others

Other emerging non-invasive tools to detect CSPH that have been described are indocyanine green (ICG) clearance, von Willebrand factor antigen and CT esophagography. The ICG 15-min retention (ICG-r15) parameter demonstrated sensitivity and specificity of 97.8 % and 90 %, respectively, for the detection of oesophageal varices in 96 compensated cirrhotic patients using the cut-off values of <10 % (rule out) or >22.9 % [51]. A von Willebrand factor antigen cut-off of >241 % has been correlated with HVPG ($r = 0.69$) and clinical decompensation using a second cut-off of >315 % [52]. Dedicated multi-detector CT oesophagography using air insufflation has been described in a study of 90 patients and differentiated low- and high-risk oesophageal varices with an AUROC 0.931–0.958, depending on the radiologist [53]. Needless to say, these emerging modalities will need ongoing evaluation to determine their clinical utility.

Current Surveillance Algorithms

The majority of international variceal surveillance strategies are largely based on the consensus reached at the Baveno meetings. Most guidelines advise annual surveillance for patients with decompensated cirrhosis and between 2 and 3 yearly for those with compensated disease. The established threshold for initiating primary prophylaxis with non-selective beta-blockade or band ligation is the presence of large varices or high-risk endoscopic stigmata. Adequate beta-blockade should ameliorate the need for ongoing surveillance, while endoscopic follow-up at 6–12 monthly intervals has been suggested once a band ligation course has been completed [15–17].

A number of issues exist with these guidelines: the reliance on subjective endoscopic criteria, the cost of endoscopic surveillance, the lack of consensus on surveillance intervals and the lack of provision for gastric or ectopic varices. Current guidelines risk "over-surveillance" of those with compensated liver disease that are at low probability of progression. Moreover, surveillance strategies have omitted the impact of the persistence, or the removal, of the cause of liver injury. For example, viral eradication in chronic hepatitis C infection has been associated with a reduction in HVPG and the development of varices [54–56]. Similarly, abstinence in alcoholic liver disease or directed weight loss in non-alcoholic fatty liver disease are factors that are more likely to reduce the progression of portal hypertension. Conversely, the removal of the aetiological factor does not infallibly halt the clinical trajectory, especially in decompensated disease. However, stratifying patients who are at a lower risk of disease progression once their aetiological factor is

controlled may be another component in reducing the burden of endoscopic variceal surveillance.

Non-invasive markers have the potential to fill the void and address these issues pertaining to surveillance for both CSPH and varices. Additionally, the assessment of response and adequacy of non-selective beta-blockade is another potential application. However, as discussed, a more extensive evidence base is required before these tools can be adopted into consensus guidelines.

Conclusions

Surveillance for the development of both CSPH and oesophageal varices is a necessary intervention that has led to improvements in clinical outcomes. Despite the many advances in the 5 years since the previous Baveno meeting, the ideal non-invasive portal venous "manometer" that can be used in surveillance strategies is regrettably yet to be found. Combination algorithms involving spleen stiffness hold the most promise and required further validation. In the interim, however, there is still much to be done. The endoscopic classification of varices should be simplified into a single system, minimising interobserver and intraobserver variability. Further study is needed to investigate the impact of aetiologically specific treatments on the natural history of different chronic liver diseases, enabling better risk stratification. Emerging tools, such as ICG clearance, require ongoing development and evaluation. Cost-effectiveness models should be encouraged to assess the effect of implementation of non-invasive surveillance. Surveillance strategies for gastric and ectopic varices also need to be developed. The ideal surveillance algorithm should involve non-invasive markers that are widely available, easily reproducible, economically viable, have excellent diagnostic capability and that provide objective data. The momentum to achieve this is increasing and will only be aided by international collaboration.

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Cost Considerations

8

Thomas D. Boyer

Introduction

Bleeding from esophageal or gastric varices is a life-threatening complication of cirrhosis, and the endoscopic appearance of the varices has been shown to be predictive of bleeding risk. Screening is based on upper endoscopy, and current guidelines recommended a screening endoscopy be performed on all cirrhotics to document the presence or absence of varices and to define therapy [1]. However, as technology has advanced, a number of tests, from the simple CBC to new technologies such as elastography, have been proposed as the best way to screen for varices [2]. The difficulty with all of the reports on the new approaches to the diagnosis of portal hypertension is the lack of a common end point. When using endoscopy, the most important end point is the finding of high-risk varices. In contrast, in most studies which use noninvasive tests, the end point has been the presence of varices irrespective of size or clinically significant portal hypertension with or without varices. One can question whether or not this is appropriate as it is the large varices with or without red signs that are associated with the greatest risk of bleeding and are the current targets of treatment [1]. How to manage those with small varices or with portal hypertension without varices is unclear given the uncertain benefit from beta blockers on variceal growth and risk of bleeding [3, 4]. The purpose of this review is to look at cost and see if it should be a factor in determining how we screen for varices. The relative costs of each screening test are shown in Table 8.1.

The first question is whether or not screening is even necessary. Perhaps the best approach would be to place all patients with cirrhosis on beta blockers given their proven efficacy in reducing the risk of bleeding. This approach has been examined

T.D. Boyer, MD
Liver Research Institute, University of Arizona, AHSC 245136, Tucson, AZ 85724, USA
e-mail: tboyer@deptofmed.arizona.edu

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Table 8.1 Relative cost of tests used to screen for varices

Test	Relative cost (least to most)
Platelet count	+
Ultrasound	+++
Elastography	++++
CT scan	+++++
Upper endoscopy	+++++
Pill endoscopy	++++
WHVP	+++++

in two separate reports using Markov modeling. Firstly, not screening or treating was an unacceptable option as it was not expensive or effective. Placing all patients on beta blockers was the most cost-effective approach with an incremental cost of $12,408 per additional variceal bleed prevented. Adding screening endoscopy with a beta blocker or variceal band ligation (VBL) to follow added ~$170,000 to the cost of preventing a variceal bleed [5]. The analysis also suggested that using pre-screening tests, such as platelet counts or splenomegaly, was not cost-effective as well. In a second report looking at cost/life saved, universal screening was the most cost-effective in compensated cirrhotics, but in decompensated cirrhotics, primary prophylaxis without screening was the most cost-effective [6]. For all of these studies, the incidence of large varices in the patient population and cost of drugs and upper endoscopy affected the results of the modeling. Other important factors that make the treat all approach less appealing include the fact that the incidence of varices in cirrhotic populations is quite variable and perhaps only 12–20 % will have high-risk varices which is the target population. Also, 70 % of patients will have no varices [6–8]. Beta blockers also cause a clinically significant fall in the hepatic venous pressure gradient (HVPG) in ~50 % of patients [9, 10] leaving the other 50 % at risk for bleeding. Thus, if one treats 100 cirrhotics with beta blockers, the 65 patients with no varices will have no benefit. The 20 patients with small varices may or may not have a benefit [3, 4]. Thus, only 7 of the 15 with large varices will have a therapeutic benefit from treatment. That is not an acceptable number considering the side effects of beta-blocker therapy. We need better noninvasive tests to help direct who should be screened for varices in a cost-effective manner.

Instead of the treat all or scope all strategy, we need to define the population at risk for having high-risk varices or variceal progression in order to improve the cost-effectiveness of our approach. One approach is to screen all patients initially placing those with high-risk varices on beta blockers. In addition, those with small varices can be placed on a beta blocker as well. This approach was modeled using variceal progression, bleeding, and death as a composite end point. Treating those with small varices with beta blockers was more cost-effective as compared to repeated screening endoscopies waiting for the varices to grow before initiating treatment [11].

The least expensive approach is the use of the platelet count in combination with the size of the spleen. Using the platelet count alone or the spleen diameter/platelet count ratio (SDPC) has a modest sensitivity (0.8) in identifying clinically significant portal hypertension (CSPH-HVPG $\geq$10 mmHg) and/or varices.

Somewhat more expensive is measuring liver stiffness (LS) which is more sensitive than the platelet count/spleen diameter in identifying patients with varices. When LS and SDPC are combined, the sensitivity approaches 0.9 for the diagnosis of varices and in one report the negative predictive value for high-risk varices was almost 100 % [2, 7]

Based on the above data, if upper endoscopy was only performed on those with CSPH, 54 % would have no varices, 28 % small varices, and 18 % large varices. In those not reaching the screening threshold, only 2.5 % would have varices, none of which would be large [7]. Thus, one could reduce the number of patients with cirrhosis who need screening. Could this selective approach be cost-effective? In one report platelet counts of <88,000 or the presence of splenomegaly were associated with the presence of large varices. The incremental cost of averting each variceal bleed was $3533 for the selective approach (endoscoping only those with low platelet counts or splenomegaly) and $15,160 for the scope all approach. The risk of large varices in those lacking either risk factor was 7.2 %. However, the difference in the predicted number of variceal bleeds between the two groups was small, 12.9 vs. 12.4, for selective versus scope all strategy, respectively [8]. These studies suggest that we should be more selective in the patients we screen for varices. Establishing thresholds of platelet counts and presence or absence of splenomegaly as indications for screening endoscopy would reduce the number of endoscopies performed, improve the benefits of screening endoscopy, and most likely save money as well.

One alternative to endoscopy is using the computed tomography (CT) scan to detect varices. In one series screening with CT and treating those patients with large varices with beta blockers was more cost-effective than was screening endoscopy. The cost using CT to screen was $232 to prevent one variceal bleed vs. $35,000 using screening endoscopy to prevent one variceal bleed [12]. When screening with CT vs. endoscopy was compared in a managed care environment using modeling, CT was again more cost-effective [13]. Ultrasound (US) has also been used to screen for varices. The finding of increased thickness of the esophageal wall is associated with the presence of varices but the cost-effectiveness of this approach is unknown [14]. Lastly, is the performance of PillCam esophagoscopy more cost-effective than EGD to screen for varices? Using Markov modeling PillCam was more cost-effective, but the results were influenced by the ability of PillCam to distinguish between large and small varices as well as cost and prevalence of large varices. The authors concluded that they are equivalent strategies based on cost [15].

In conclusion, although giving beta blockers to all cirrhotics may be cost-effective in the prevention of variceal bleeding, it is not clinically practical to take this approach. Alternatively, the scope all strategy also is not practical as it is the most costly approach for variceal screening. Clearly using noninvasive tests allows for the prediction of which cirrhotics are and perhaps more importantly are not at risk for varices [7]. In a limited number of studies, these noninvasive tests are more cost-effective than screening endoscopy as discussed above. We need to develop cost-sensitive recommendations about which patients need endoscopic screening for varices.

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Consensus Statements: Session 1—Screening and Surveillance

9

Annalisa Berzigotti, Thomas D. Boyer, Laurent Castera, Massimo Pinzani, Roberto de Franchis, and Joan Genescà

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A. Berzigotti, MD, PhD
Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, University of Berne, MEM F807, Murtenstrasse 35, Berne CH – 3010, Switzerland
e-mail: Annalisa.berzigotti@insel.ch

T.D. Boyer, MD
Liver Research Institute, University of Arizona, AHSC 245136, Tucson, AZ 85724, USA
e-mail: tboyer@deptofmed.arizona.edu

L. Castera
Department of Hepatology, Hôpital Beaujon, Assistance Publique –Hôpitaux de Paris, INSERM U773, University of Paris-VII, Clichy, France
e-mail: laurent.d.castera@gmail.com

M. Pinzani, MD, PhD, FRCP
UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Centre
Royal Free Hospital, London, UK
e-mail: m.pinzani@ucl.ac.uk

R. de Franchis, MD, AGAF (✉)
Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

Gastroenterology Unit, Luigi Sacco University Hospital, via G.B Grassi 74, Milan 20157, Italy
e-mail: Roberto.defranchis@unimi.it

J. Genescà, MD
Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain
e-mail: jgenesca@vhebron.net

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Definition of Compensated Advanced Chronic Liver Disease (cACLD)

- The introduction of transient elastography in clinical practice has allowed the early identification of patients with chronic liver disease (CLD) at risk of developing clinically significant portal hypertension (CSPH) (1b;A).
- For these patients, the alternative term "compensated advanced chronic liver disease (cACLD)" has been proposed to better reflect that the spectrum of severe fibrosis and cirrhosis is a continuum in asymptomatic patients and that distinguishing between the two is often not possible on clinical grounds (5; D).
  - Currently, both terms "cACLD" and "compensated cirrhosis" are acceptable (5; D).
  - Patients with suspicion of cACLD should be referred to a liver disease specialist for confirmation, follow-up, and treatment (5;D).

Criteria to Suspect cACLD

- Liver stiffness by transient elastography is sufficient to suspect cACLD in asymptomatic subjects with known causes of CLD (1b;A).
- Transient elastography often has false-positive results; hence, 2 measurements on different days are recommended in fasting conditions (5;D).
- TE values <10 kPa in the absence of other known clinical signs rule out cACLD; values between 10 and 15 kPa are suggestive of cACLD but need further test for confirmation; values >15 kPa are highly suggestive of cACLD (1b;A).

Criteria to Confirm cACLD

- Invasive methods are employed in referral centers in a stepwise approach when the diagnosis is in doubt or as confirmatory tests.
- Methods and findings that confirm the diagnosis of cACLD are:
  - Liver biopsy showing severe fibrosis or established cirrhosis (1a;A); collagen proportionate area (CPA) measurement on histology provides quantitative data on the amount of fibrosis and holds prognostic value (2b;B), and its assessment is recommended (5;D).
  - Upper GI endoscopy showing gastroesophageal varices (1b;A).
  - Hepatic venous pressure gradient (HVPG) measurement; values >5 mmHg indicate sinusoidal portal hypertension (1b;A).

Diagnosis of Clinically Significant Portal Hypertension (CSPH) in Patients with cACLD

- HVPG measurement is the gold-standard method to assess the presence of clinically significant portal hypertension, which is defined as HVPG ≥10 mmHg (1b;A).
- By definition, patients without CSPH have no gastroesophageal varices and have a low 5-year risk of developing them (1b;A).
- In patients with virus-related cACLD, noninvasive methods are sufficient to rule in CSPH, defining the group of patients at risk of having endoscopic signs of PH. The following can be used (2b; B):
  - Liver stiffness by TE (≥20–25 kPa; at least two measurements on different days in fasting condition; caution should be paid to flares of ALT; refer to EASL guidelines for correct interpretation criteria), alone or combined to Plt and spleen size.
- The diagnostic value of TE for CSPH in other etiologies remains to be ascertained (5;D).
- Imaging showing collateral circulation is sufficient to rule in CSPH in patients with cACLD of all etiologies (2b;B).

Identification of Patients with cACLD Who Can Safely Avoid Screening Endoscopy

- Patients with a liver stiffness <20 kPa and with a platelet count >150,000 have a very low risk of having varices requiring treatment and can avoid screening endoscopy (1b;A).
- These patients can be followed up by yearly repetition of TE and platelet count (5;D).
- If liver stiffness increases or platelet count declines, these patients should undergo screening EGD (5;D).

Surveillance of Esophageal Varices

- In compensated patients with no varices at screening endoscopy and with ongoing liver injury (e.g., active drinking in alcoholics, lack of SVR in HCV), surveillance endoscopy should be repeated at 2-year intervals (5;D).
- In compensated patients with small varices and with ongoing liver injury (e.g., active drinking in alcoholics, lack of SVR in HCV), surveillance endoscopy should be repeated at 1-year intervals (5;D).

- In compensated patients with no varices at screening endoscopy in whom the etiological factor has been removed (e.g., achievement of SVR in HCV, long-lasting abstinence in alcoholics) and who have no cofactors (e.g., obesity), surveillance endoscopy should be repeated at 3-year intervals (5;D).
- In compensated patients with small varices at screening endoscopy in whom the etiological factor has been removed (e.g., achievement of SVR in HCV, long-lasting abstinence in alcoholics) and who have no cofactors (e.g., obesity), surveillance endoscopy should be repeated at 2-year intervals (5;D).

Cost Considerations

- Whatever policy and method is adopted for screening and surveillance, cost should be taken into account in future studies (5;D).

Research Agenda

- Future studies should explore the possibility to stop surveillance after 2 controls showing no varices.
- Long-term data are needed concerning the benefits of screening and surveillance programs.

Part III

Changing Scenarios I: Impact of Etiological Therapy for Cirrhosis and of Anti-fibrotic Therapy on Portal Hypertension

(Pre)Primary Prophylaxis: Where Were We and Where Are We Heading?

10

Alexander Zipprich

Introduction

The concept of preprimary prophylaxis refers to the administration of beta-blockers to avoid the development of varices [1]. This idea was supported by experiments in animal models of portal hypertension (schistosomiasis) in which administration of beta-blockers led to less collateral circulation as determined by microsphere technique [2].

In order to test this hypothesis in the clinical setting, a large multicenter randomized controlled trial was designed [3]. This study included 213 patients with compensated cirrhosis with portal hypertension as defined by a hepatic venous pressure gradient (HVPG) over 6 mmHg without varices at baseline. Patients were randomized to placebo or timolol (a nonselective beta-blocker). The main endpoint was a composite endpoint, which included the development of varices and/or variceal bleeding. Unfortunately, no differences were observed between the two treatment groups. Many possible explanations for this negative result were suggested. One of the main explanations was that only highly compensated patients were included with a mean Child-Pugh score of 5.4 points, and almost 90 % of these patients were in Child-Pugh class A [3], so that perhaps the prophylactic treatment was given to patients who may have actually had a low risk of developing the event.

Indeed, as a consequence of this study, the last two Baveno meetings [1, 4] stated that the administration of beta-blockers in the setting of preprimary prophylaxis was not recommended. This contrasts with the results of the questions posed to the faculty members of Baveno VI, in which the concept of preprimary prophylaxis was still considered as a possibility in patients with cirrhosis in half of those who

A. Zipprich
First Department of Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle, Germany
e-mail: alexander.zipprich@medizin.uni-halle.de

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answered (Fig. 10.1); nevertheless most of these suggested that the phenomenon to prevent should be the development of decompensation, rather than the development of varices (Fig. 10.2). This is not the classical definition of preprimary prophylaxis. This change may be due to recent studies in which different risk groups among compensated patients for clinical decompensation could be identified [5–7].

Traditionally, patients with compensated cirrhosis have been divided in patients without varices (in whom the concept of preprimary prophylaxis would apply) and those patients with varices (in whom the concept of primary prophylaxis would apply) [4, 7]. These two groups have a different mortality risk as well as a different risk for decompensation [5, 6, 8]. Varices develop only in patients who achieve a threshold of clinically significant hepatic venous pressure gradient [9], which is an estimation of portal pressure. Nevertheless, although all patients with varices have clinically significant portal hypertension, not all patients without varices have an HVPG below this threshold. Indeed, there may be compensated patients without varices who already have clinically significant portal hypertension [5, 6].

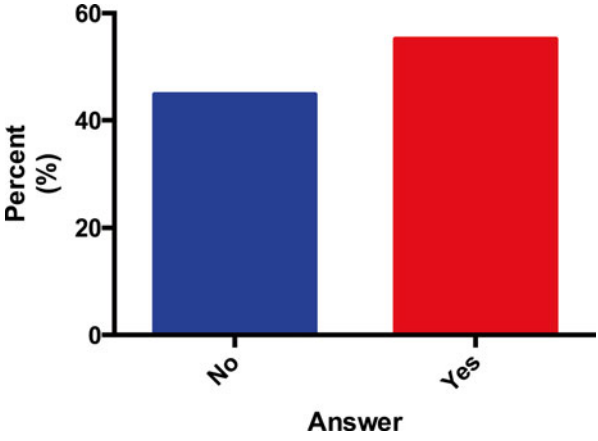

Fig. 10.1 Result of the questionnaire of the faculty of Baveno VI: do you consider preprimary prophylaxis?

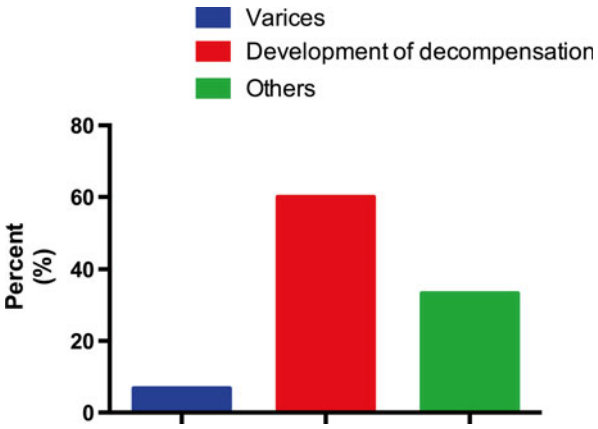

Fig. 10.2 Result of the questionnaire of the faculty of Baveno VI: what would be the relevant endpoint?

In this sense, in a secondary analysis of the abovementioned RCT (timolol study) [3], a cutoff value of 10 mmHg of hepatic venous pressure gradient was identified as an independent predictor for clinical decompensation (unadjusted HR 5.7 (95 % CI 2.7–12)) in this group of compensated cirrhosis with portal hypertension although without varices at baseline [6]. Patients with an HVPG value below this threshold had a 90 % probability of not developing decompensation with a median follow-up of 4 years. These data were confirmed in a latter study in which compensated patients with and without varices were included [10]. In this study, 98 % who developed decompensation during the follow-up had clinically significant portal hypertension at baseline. Patients with clinically significant portal hypertension have not only an increased risk for decompensation but also have an increased risk for death [5].

These results led to the theory that among compensated patients, one can identify a subgroup of patients with an increased risk of decompensation according to the presence of clinically significant portal hypertension. These patients with clinically significant portal hypertension are those who may have the most benefit from prophylactic treatment. Up to date, data supporting this strategy are lacking. Nevertheless, a decreased incidence of ascites was observed among patients who had response to acute administration of beta-blockers in the setting of primary prophylaxis. There is currently a Spanish multicenter trial ongoing aimed at evaluating the use of nonselective beta-blockers in this population group to prevent the development of decompensation.

Taking this into account, one could divide patients with compensated cirrhosis into two groups, firstly those who have clinically significant portal hypertension and who may benefit from the administration of nonselective beta-blockers and secondly those who do not have clinically significant portal hypertension, in whom the treatment should be mainly focused at managing the underlying etiology for the liver disease to avoid further progression (Fig. 10.3).

The definition of clinically significant portal hypertension requires the performance of the hepatic venous pressure gradient measurement, which is an invasive procedure [11]. However, there are promising noninvasive tools that may be useful to identify those patients with clinically significant portal hypertension among the patients with compensated cirrhosis. Among these, using liver stiffness to measure changes in chronic liver disease is the most promising one. Unfortunately, the measurement is dependent on the etiology of the liver disease, so that different cutoffs for detection of advanced fibrosis and presence of varices are identified for different etiologies [12]. However, in a recent meta-analysis, each unit increase in liver stiffness measurement was associated with a 7 % higher risk of decompensation, and this effect was stable across different etiologies of cirrhosis and therefore robust [13]. Nevertheless, although liver stiffness can detect clinically significant portal hypertension with a high sensitivity of around 92 %, it has a low specificity (around 65 %) and therefore cannot replace the measurement of HVPG [12, 13].

Other noninvasive approaches to identify the presence of clinically significant portal hypertension have combined measurements from different methods, for example, the combination of liver stiffness with spleen size and platelet count

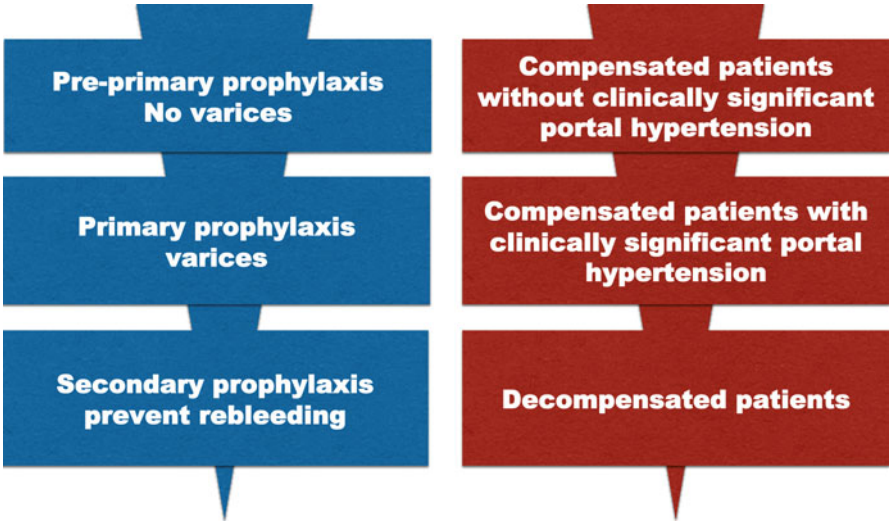

Fig. 10.3 *Left side* shows the progression of varices and variceal hemorrhage. *Right side* shows the progression of compensated patients to decompensated patients

(LSPS) [14]. This combination accurately detected clinically significant portal hypertension in compensated patients with an area under the ROC curve of 0.92. Using a cutoff from 1.72, the LSPS was able to classify correctly 84 % of the patients, while only 16 % were misclassified [14]. This cutoff was then validated in another cohort in whom almost 86 % were correctly classified.

In conclusion, the concept of preprimary prophylaxis is obsolete. Patients with compensated cirrhosis can be divided into those with and without clinically significant portal hypertension. In patients without clinically significant portal hypertension, etiological treatment seems to be the relevant step to avoid disease progression (i.e., development of clinically significant portal hypertension). On the other hand, compensated patients with clinically significant portal hypertension are at risk for decompensation and therefore may be those who can most benefit from prophylactic therapy. Upcoming studies will provide data on whether this new approach is clinically useful.

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Defining Clinical Hints to Predict Decompensation and Altering Paradigm in Patients with Cirrhosis

11

Maria Kalafateli and Emmanuel A. Tsochatzis

Introduction

Cirrhosis is the end stage of chronic liver diseases independent of etiology, characterized by accumulation of fibrotic tissue and conversion of the normal liver parenchyma into abnormal regenerative nodules [1]. Compensated cirrhosis is the first asymptomatic phase in the natural history of cirrhosis characterized by well-preserved liver function. This phase is followed by the decompensated stage characterized by the rapid development of complications due to portal hypertension and/or liver dysfunction. The complications that mark the transition to the decompensated phase are ascites, encephalopathy, portal hypertensive gastrointestinal bleeding, and non-obstructive jaundice [2]. D'Amico et al. [3] modified this two-stage classification of cirrhosis into a four-stage model taking into consideration the remarkable differences in mortality rates among the different clinical stages. The first two stages correspond to compensated cirrhosis; stage 1 is characterized by the absence of varices and ascites, whereas stage 2 by the presence of varices without bleeding or ascites. The yearly mortality rates are 1 and 3.4 %, respectively. Stage 3 is characterized by the development of ascites with or without varices and stage 4 by gastrointestinal bleeding with or without ascites. The prognosis is poor in these stages with mortality rates of 20 and 57 % per year, respectively. Arvaniti et al. [4] proposed sepsis as the fifth clinical stage with a mortality rate of 63 %.

M. Kalafateli • E.A. Tsochatzis (✉)
UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, Pond Street, London NW3 2QG, UK
e-mail: e.tsochatzis@ucl.ac.uk

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Clinical Hints to Predict Decompensation

Hepatic venous pressure gradient (HVPG) refers to the difference between wedged and free hepatic vein pressure and is considered the most important prognostic indicator in the course of cirrhosis. Portal hypertension is defined as an HVPG greater than 6 mmHg and is considered clinically significant when greater than 10 mmHg. Ripoll et al followed up 213 patients with compensated cirrhosis without varices (stage 1 cirrhosis) for a median of 51 months and showed that HVPG was an independent predictor of decompensation. The threshold HVPG value of 10 mmHg identified the patients that were at higher risk for liver decompensation with a negative predictive value of 90 % [5]. In the post-transplant setting, an HVPG >6 mmHg is associated with a higher probability of decompensation following HCV recurrence [6]. Furthermore, an HVPG value greater than 10 mmHg was associated with a sixfold higher risk for the development of hepatocellular carcinoma (HCC) [7]. The risk of variceal bleeding increases when HVPG is greater than 12 mmHg [8]. HVPG has also a predictive value on bleeding outcomes in terms of re-bleeding and survival. A baseline HVPG ≥20 mmHg in patients with variceal bleeding has been associated with longer hospital stay, increase in transfusion requirements, and worse short- and long-term survival [9], as well as with failure to control bleeding at 5 days [10]. Two meta-analyses [11, 12] concluded that a reduction of HVPG to ≤12 mmHg or by ≥20 % from baseline following pharmacological treatment is significantly associated with a three- to fourfold decrease in the risk of re-bleeding and mortality in both settings of primary and secondary prophylaxis of variceal bleeding. The beneficial effect of reducing HVPG is greater when the time interval between the repeated HVPG measurements is short.

HVPG has been also associated with other portal hypertension-related complications, such as ascites, spontaneous bacterial peritonitis, portal gastropathy, and hepatic encephalopathy [13]; however, the existing evidence is limited compared to HVPG studies in acute variceal bleeding. HVPG reduction is associated with a decreased risk of decompensation other than variceal bleeding. In a study of 132 patients with cirrhosis, those who responded to treatment with nadolol and isosorbide mononitrate (HVPG reduction to <12 mmHg or by >20 % of baseline) had a lower risk of developing ascites or encephalopathy, a lower probability of liver transplantation, and a greater improvement in Child–Pugh score compared to non-responders [14]. In a similar study of patients with baseline HVPG >12 mmHg on primary prophylaxis with propranolol, development of ascites was significantly lower in those with an HVPG reduction of at least 10 % [15]. HVPG is also a well-validated marker of postoperative decompensation in patients with cirrhosis and dictates treatment decisions in patients with HCC (resection vs. transplantation); pre-resection HVPG is the only independent predictor of decompensation within 3 months following resection [16].

Liver histology can be of additional prognostic significance to HVPG. In semi-quantitative histological scoring systems, there is no stage beyond cirrhosis despite the remarkable differences in survival of such patients. A quantitative method of measuring fibrous tissue, through digital image analysis of the proportion of

collagen in liver tissue, namely, collagen proportionate area (CPA), has been developed and can be used to subclassify cirrhosis [17]. CPA significantly correlates with both Ishak stage and HVPG values [17] and, more importantly, has been validated against liver-related clinical outcomes [18]. In a study of 69 consecutive patients with cirrhosis, CPA and MELD were the only independent predictors of future decompensation [19]. In patients with recurrent HCV cirrhosis following liver transplantation, CPA correlated with HVPG but had a wider range of values, therefore suggesting a greater sensitivity for subclassifying cirrhosis [20]. In the same patient population, CPA fibrosis progression rate was a better predictor of clinical outcomes than traditional histological stages [21]. In 533 patients with HCV infection, CPA stage gave additional information regarding clinical decompensation and liver-related death independent to Metavir stage [22]. Therefore, liver biopsy should be performed along with HVPG measurements whenever possible.

Although HVPG (and CPA) can be used to accurately subclassify patients with cirrhosis and can predict future decompensation, they are not widely available and can only be performed in tertiary centers. Therefore, research has been focused on new noninvasive methods and strategies to predict clinical decompensation without performing HVPG measurement. Transient elastography (TE) is a noninvasive method that assesses liver stiffness. The AUROCs of TE to detect clinically significantly portal hypertension (HVPG ≥10 mmHg) range between 0.76 and 0.99 with corresponding liver stiffness cutoffs from 13.6 to 34.9 kPa in both the pre- and post-transplant settings [23]. However, it seems that the correlation between liver stiffness and HVPG is great for HVPG values up to 10–12 mmHg and is reduced in more significant portal hypertension [24]. Beyond its correlation with portal hypertension, several studies have shown that TE can accurately predict clinical outcome in cirrhosis [23]. In a prospective assessment of the prognostic performance of HVPG and TE in 100 patients with chronic liver disease, the AUROCs of TE and HVPG were similar and did not show a statistically significant difference (0.837 and 0.815, respectively) [25]. A liver stiffness value >21.1 kPa had a negative predictive value of 85.4 and 100 % for predicting liver-related and portal hypertension-related complications, respectively. In a meta-analysis including 7058 patients with chronic liver diseases, baseline liver stiffness was significantly associated with the risk of liver decompensation (RR: 1.07; 95 % CI: 1.03–1.11), HCC (RR: 1.11; 95 % CI: 1.05–1.18) and mortality (RR: 1.22; 95 % CI: 1.05–1.43) or a composite of these outcomes (RR: 1.32; 95 % CI: 1.16–1.51) [26]. Fibrosis progression is a strong predictor of outcome in liver cirrhosis, and noninvasive tests can easily provide longitudinal measurements considering the difficulties that accompany the repetition of liver biopsy during follow-up. Vergniol et al. [27] studied the prognostic significance of the 3-year evolution of liver stiffness measurement (LSM), APRI, and FIB-4 in 1025 patient with CHC [28]. Baseline and delta LSM and FIB-4 were independently associated with survival, and nine patient subgroups with statistically different prognoses were identified, while LSM performed better than FIB-4. All the abovementioned data confirm the potential role of noninvasive methods in risk stratification of cirrhotic patients and in selection of these patients that need further evaluation and closer surveillance.

Altering Paradigm in Patients with Cirrhosis

The high morbidity and mortality that accompanies cirrhosis when decompensation occurs and the organ shortage for liver transplantation highlight the need for new preventative treatments. Such therapies can prevent the advent of complications related to portal hypertension and can provide a chance for regression of fibrosis and/or portal hypertension, if applied at early stages (D'Amico stages 1 and 2). Etiology-specific treatment of chronic liver diseases, such as antiviral therapy for viral hepatitis B and C, is already used in routine clinical practice and can remarkably alter the course of liver disease [29]. However, this chapter will focus on disease-specific preventative treatments, using already licensed drugs, which can improve clinical outcomes irrespective of liver disease etiology.

Obesity, insulin resistance, diabetes, and metabolic syndrome are significantly correlated with the pathogenesis of nonalcoholic fatty liver disease, but they can also aggravate the natural history of any chronic liver disease. They are associated with more severe liver fibrosis, worse overall and liver-related mortality, and increased risk for HCC [30]. In a study of 161 patients with compensated cirrhosis followed up for a median of 59 months [31], increasing BMI was an independent predictor of clinical decompensation (HR: 1.06, 95 % CI: 1.01–1.12), together with HVPG and albumin. Weight loss and specific dietary changes aiming to improve insulin sensitivity would be valuable therapeutic targets in cirrhosis, and their efficacy should be tested in randomized controlled trials. Coffee seems to play an important role in liver injury. In a prospective population-based cohort of 63,275 Chinese subjects, coffee drinking of at least 2 cups per day was independently and inversely associated with non-viral hepatitis-related cirrhosis mortality [32]. In 766 participants of the HALT-C study [33], higher coffee consumption at baseline was inversely associated to liver disease progression with a RR of 0.47 (95 % CI: 0.27–0.85) for 3 or more cups/day. These observations together with the lower risk for liver cancer development in patients consuming more than 2–3 cups/day [34] suggest that patients with chronic liver diseases should be advised to drink coffee. Alcohol abstinence is another significant lifestyle change that should be encouraged in all patients with cirrhosis irrespective of etiology, considering its well-known deleterious role on fibrosis progression, portal hypertension, HCC development, and survival [1].

Statin treatment is relatively safe in stable patients with cirrhosis [35] and should be further explored as a preventative treatment in such patients. Statin use was associated with reduced risk of fibrosis progression in 543 patients with chronic hepatitis C and Ishak fibrosis stage ≥ 3 with a hazard ratio of 0.31 [36]. In a pilot randomized controlled trial of 59 patients with cirrhosis and portal hypertension [37], simvastatin significantly decreased HVPG irrespective of the use of b-blockers and led to an improvement in effective liver perfusion and function, without occurrence of significant adverse events. Apart from its beneficial effects on liver function and portal hypertension, statin use has been associated with a reduced risk of HCC in patients with diabetes [38]. In a meta-analysis of 10 studies including 4298 cases of

HCC [39], statin use was associated with a lower likelihood of HCC development (adjusted OR: 0.63, 95 % CI: 0.52–0.76).

Metformin also merits further evaluation in patients with cirrhosis. Meta-analysis of observational studies in patients with diabetes showed that metformin use reduced the incidence of HCC by 50 % (OR = 0.5, 95 % CI: 0.34–0.73) [40]. This effect was also confirmed in a nationwide case-control study of 97,430 patients [36]. The same group demonstrated that metformin inhibits hepatoma cell proliferation and inducts cell cycle arrest at G0/G1 phase [41]. In a retrospective study of 250 patients with cirrhosis and diabetes, metformin use was independently associated with increased survival with an adjusted HR of 0.43 (95 % CI: 0.24–0.78); no patient developed lactic acidosis [42]. In subgroup analysis, the beneficial effect of metformin was confined to patients with NASH-related cirrhosis; therefore, the authors concluded that metformin might ameliorate liver fibrosis by attenuation of steatohepatitis. In a prospective study of 100 patients with HCV cirrhosis and diabetes [43], the 5-year incidence of HCC was 9.5 % and 31.2 % ($p = 0.001$) and that of liver-related death/transplantation, 5.9 % and 17.4 % ($p = 0.013$), in patients who did and didn't received metformin treatment, respectively.

The high efficacy of nonselective beta-blockers (NSBBs) in both primary and secondary prophylaxis of variceal bleeding is well established [44]. The marked effect of NSBBs in HVPG not only reduces the risk of portal hypertensive bleeding but also the risk of other complications such as ascites, encephalopathy, hepatorenal syndrome, and, subsequently, mortality [14]. However, some beneficial effects of beta-blockers are only partially justified by their role in decreasing portal pressure. In a randomized controlled trial comparing NSBBs with endoscopic variceal ligation for secondary prophylaxis, the group that received pharmaceutical treatment had a higher survival probability despite an increase in bleeding recurrence [45]. Beta-blockers thus reduce the risk for spontaneous bacterial peritonitis in patients with ascites probably by increasing intestinal motility and thus reducing intestinal permeability and bacterial translocation [30, 46]. Experimental evidence suggests that b-blockers reduce gut permeability irrespective of hemodynamic response [47]. Beta-blockers are safe and improve survival in patients with cirrhosis and ascites up to the first episode of spontaneous bacterial peritonitis [48]. When patients with refractory ascites develop SBP, then b-blockers should be stopped at least until the episode is resolved or permanently depending on the hemodynamic status of the individual patient.

Rifaximin is a nonabsorbable antibiotic that is currently used for the secondary prophylaxis of hepatic encephalopathy [49]. It has been associated with a reduction in the levels of endotoxin and other pro-inflammatory factors, as well as with a decrease in HVPG in patients with ALD cirrhosis [30]. Apart from improving liver hemodynamics, long-term use of rifaximin reduced the risk of developing variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome and improved survival probability [50]. A randomized trial is needed to confirm these observations and also determine the role of rifaximin in the primary/secondary prevention of spontaneous bacterial peritonitis.

Lastly, upcoming evidence from both animal and human studies suggests that coagulation abnormalities are implicated in the progression of liver fibrosis [29]. In a single-center randomized trial of enoxaparin on prevention of portal vein thrombosis, the enoxaparin-treated group had a significantly lower probability of portal vein thrombosis, liver decompensation, and mortality compared to the control group [51]. Currently, the use of anticoagulants treatment is reserved for patients with portal vein thrombosis on the liver transplant waiting list who are at risk of thrombus extension. However, the effect of anticoagulants on prevention of liver-related complications should be further investigated in randomized trials.

Conclusions/Future Directions

In conclusion, taking into consideration, firstly, the remarkable differences in mortality among the different clinical substages of cirrhosis and, secondly, the probability of regression of early cirrhosis, clinicians should focus on an early diagnosis of advanced liver disease before decompensation occurs. Noninvasive fibrosis tests, such as transient elastography, together with HVPG and quantitative fibrosis assessment using CPA, can be used to subclassify patients with cirrhosis and predict clinical decompensation. As previously highlighted, the management of patients with cirrhosis should change to preventing the advent of all complications while in the compensated phase [1, 29, 52]. Safe, widely available, and relatively inexpensive treatment regimens seem to have beneficial effects on reduction of portal pressure, prevention of complications, regression of fibrosis, and improvement in survival. Such drugs include b-blockers, statins, metformin, nonabsorbable antibiotics, and anticoagulants either alone or in combination. The potential effect of these drugs should be investigated in phase III randomized controlled trials. In the current era, cirrhosis should be regarded as treatable and potentially reversible with currently available therapy and not as an irreversible disease that leads inevitably to liver transplantation or death.

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Antiviral Treatments and Residual Risk of Hepatic Decompensation

12

Markus Peck-Radosavljevic

Introduction

Chronic viral hepatitis is the main cause of chronic liver disease, and as the most important cause of liver-related mortality, it is now the eighth leading cause of death worldwide, which includes death due to acute hepatitis, hepatitis-associated cirrhosis, and liver cancer (HCC) [1]. Chronic viral hepatitis affects about 500 million people globally and is responsible for 1.4 million deaths each year. Liver cirrhosis from any cause is the twelfth leading cause of death according to the "Global Burden of Disease" Study, and the deaths due to viral hepatitis and liver cancer have been steadily increasing over the time period from 1990 to 2010 [2].

Natural Course of Patients with Chronic Viral Hepatitis

Three forms of chronic viral hepatitis can be distinguished today: chronic hepatitis B (CHB), chronic hepatitis B plus hepatitis D, and chronic hepatitis C (CHC). Among those, CHB and CHC are amenable to effective treatment with a high chance of complete disease control or cure and will be the subject of this report, while efficacy of treatments against hepatitis D remains far from ideal and will not be covered here.

M. Peck-Radosavljevic, MD
Abteilung Gastroenterologie and Hepatologie, AKH and Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria
e-mail: markus@peck.at

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Chronic Hepatitis B

Acute infection with the hepatitis B virus results in chronic infection in about 5 % of adults but up to 90 % of newborns infected perinatally. About 30 % of the chronically infected Western patients will eventually progress to cirrhosis [3]. Once cirrhosis is established, decompensation has been reported to occur in 23 % of patients within 5 years and then is a frequent cause for liver transplantation or death [4]. Looking at the large REVEAL cohort from Taiwan indicates that the risk of developing cirrhosis over time is directly related to HB viral load, where patients with undetectable to <2000 IU/mL viral load have less than 6 % risk of progressing to cirrhosis over 13 years of follow-up, while patients with HBV loads >200,000 IU/mL have a 36 % chance of developing cirrhosis within the same period of time [5]. Further analysis of the same cohort later showed that even patients without disease activity as exemplified by normal transaminases and with low HBV load <2000 IU/mL but without treatment had an increase in liver-related mortality by a factor of 2.1 compared to a large age-matched control cohort without chronic HBV infection [6].

Chronic Hepatitis C

Acute hepatitis C infection results in chronic infection in an estimated 80 % of patients and then progresses to cirrhosis after 20 or more years in about 20 % of those chronically infected, depending on disease activity and cofactors [7]. Complete virological suppression with concomitant reduction in inflammation seems also to be able to have a positive impact on hard endpoints in patients with advanced fibrosis or cirrhosis in HCV infection [8], but long-term low-dose treatment was unable to show a clinical benefit in the large, prospective, randomized, placebo-controlled HALT-C trial [9]. In HALT-C, 34.1 % of patients showed a progression of disease despite continuous low-dose pegIFN treatment over 3.5 years. Hepatic decompensation during long-term low-dose pegIFN treatment in particular occurred in 4 % of cases during this trial in the treatment group and was not different from 4.1 % in the control group receiving no treatment [9].

Effect of Antiviral Therapy on Long-Term Outcome for Patients with Viral Hepatitis

Chronic Hepatitis B and Successful HBe and HBsAg Seroconversion

Antiviral treatment with the aim of achieving HBe and HBsAg seroconversion can be conducted with (peg)interferon-α (pegIFN), nucleoside, or nucleotide analogues. In HBeAg+ chronic hepatitis B, HBeAg seroconversion is the primary goal of therapy, which can be achieved in up to 32 % of patients after 48 weeks of therapy with pegIFN [10]. HBsAg seroconversion in the same study was observed in 2 % of patients after

24 weeks of follow-up. PegIFN therapy in HBeAg patients yielded good HBV suppression in 44 % of patients and HBsAg loss or seroconversion in 3.4 and 2.2 %, respectively [11]. However, in long-term follow-up studies in HBeAg patients treated with pegIFN, ultimately 12 % of patients achieved HBsAg seroclearance, and this fraction was even 28 % in patients with a HBV DNA of less than 2000 IU/mL one year after treatment. None of the noncirrhotic patients experienced decompensation. This was also a rare event in compensated cirrhotics except for the occasional patient where the HBsAg clearance was associated with a hepatitis flare [12].

Chronic Hepatitis B and Long-Term Viral Suppression with Nucleos(t)ide Analogues

Long-term treatment with nucleos(t)ide analogues is a very common practice these days in HBeAg– [12] as well as HBeAg+ [13] patients, and in studies with drugs like entecavir or tenofovir over 5 or 7 years, no case of decompensation in noncirrhotic as well as compensated cirrhotic patients has been observed. Also decompensated patients can be stabilized in many cases, which is in good agreement with the fact that about two-thirds of patients show regression of fibrosis on histology even in cirrhotic patients [12]. Even though long-term nucleos(t)ide treatment abolishes the progression of liver disease, it has less impact in the development of HCC despite virological suppression, and patients need to undergo regular surveillance for HCC development [12]. Rates of HCC development in HBeAg patients with HBV genotype D without cirrhosis are 0.6–1.4 %, while in cirrhotics the incidence ranges from 3.7 to 4 %, not different from a control population not undergoing treatment.

Chronic Hepatitis C and Treatment with (Peg)Interferon/Ribavirin and First-Generation Protease Inhibitor (PI)-Based Treatments

Interferon-based therapy for CHC was already introduced before the virus had been isolated and was carried out for many years until it was finally shown that elimination of the HC virus in patients with advanced chronic liver disease (ACLD) really results in a significant survival benefit both through reduction of HCC and liver-related mortality [14]. In another 12-year prospective study of 218 Child A patients who underwent antiviral therapy with standard combination therapy with peginterferon (pegIFN) plus ribavirin, achieving an SVR completely prevented development of esophageal varices, while they developed in 75 % of patients with treatment failure [15]. A randomized controlled trial of pegIFN plus ribavirin in decompensated cirrhotics showed that the on-treatment risk for severe infection or death was increased by 2.95-fold and 1.97-fold, respectively, compared to controls. But in 30 months of posttreatment follow-up, decompensating events occurred in 23 % of SVR patients vs. 69 % of relapsers vs. 88 % of controls [16]. Death occurred in 0 % of SVR patients but in 21 % of relapsers and in 32 % of controls with survival

curves separating as early as 6 months after the end of treatment. Furthermore, in another trial of 75 decompensated HCV-cirrhotic patients undergoing combination antiviral therapy, achieving an SVR was associated with 92 % survival compared with only 55 % 5-year survival in patients without virological cure [17]. Also, episodes of decompensation after antiviral therapy were 33 % in patients achieving SVR and significantly fewer than in patients without SVR, where further decompensation occurred in 96 % of patients. It should be noted though that SVR rates in GT1 patients with decompensation and therefore always with clinically significant portal hypertension (CSPH) are extremely low and were 16 % in this study. SVR is related to the absence of CSPH, as nicely shown in a study using HVPG measurement, where GT1 patients had an SVR of 14 vs. 40 % depending on the presence or absence of CSPH [18].

Virological cure was significantly improved by adding a first-generation protease inhibitor (PI) to the standard pegIFN-ribavirin combination therapy. Even in treatment-experienced cirrhotic patients, triple therapy with telaprevir or boceprevir was able to achieve a SVR in 19–76 % of patients [19]. But this came with severe adverse events in 50 % of patients that included hepatic decompensation, severe infections in 10 %, and death in 2 % of the study population.

Chronic Hepatitis C and Treatment with Direct-Acting Antivirals (DAAs)

Treatment of cirrhotic patients with DAA-only therapy has the potential advantage of a much better on-treatment safety due to the negligible rate of severe adverse events in the trials so far. But despite the fact that over 1000 cirrhotic patients have been included into trials with sofosbuvir-based regimens and despite the fact that Turquoise-II was a trial exclusively including 380 cirrhotic patients to be treated with a paritaprevir/r/ombitasvir/dasabuvir-based regimen [20], only scarce data are available on the treatment of more advanced Child-Pugh B or C cirrhotics with any of these regimens.

Data reported from the 108 patients from the cirrhotic groups (72–100 % with a MELD score between 10 and 20) and from the SOLAR-1 trial (sofosbuvir/ledipasvir/ribavirin, US cohort) show not only an SVR rate of around 90 % but also an improved or stable MELD score in 68 % and 17 % of CP B and 76 % and 10 % of CP C patients, respectively [21]. Already earlier, data from a placebo-controlled trial of sofosbuvir plus ribavirin in decompensated HCV cirrhotics with a median HVPG of 17 mmHg (76 % of patients with HVPG > 12 mmHg) had yielded on-treatment improvements in peripheral platelet count, albumin, and complete resolution of ascites and encephalopathy in the treatment group only [22]. Recently reported data from the SOLAR-2 trials (sofosbuvir/ledipasvir/ribavirin, EU cohort) confirm the beneficial effect of these DAA-only regimens on the short-term outcome of advanced-stage HCV cirrhotics [23]. Long-term follow-up data from these trials as well as from the large cohort studies (Hepather, Target, Trio, German cohort, etc.) will help clarify the potential long-term residual risk of

decompensation with these regimens, but this risk will likely depend more on comorbid liver conditions than the resolved viral infection. Nevertheless, rigorous testing of each of the potential combinations individually seems to be warranted. Small case series have suggested that simeprevir combination therapy has the potential to cause deterioration of liver function and decompensation in advanced-stage cirrhotics [24], and the hepatic elimination of several DAAs necessitates a cautious, data-based approach.

Overall, virological cure offers much improved outcomes to all patients that are able to achieve it and should be the prime target of any antiviral therapy. A residual risk of decompensation remains but is very low, and decompensation usually can be managed more easily after viral eradication than before. HCC surveillance in cirrhotic patients remains a priority, irrespective of whether a virological cure has been achieved or not.

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Etiological Treatments: Lifestyle Management

13

Rafael Bañares and Luis Ibáñez-Samaniego

Introduction

Cirrhosis is a markedly heterogeneous disease with a very different risk profile during its natural history, influencing the therapeutic management. In the earliest phases of the disease, the main end point should be the prevention of decompensation, while in the advanced stages, the target is survival improvement. In general, lifestyle changes tend to be overlooked in the management of cirrhosis. However, besides etiologic interventions and specific treatment of complications, there is important information suggesting that lifestyle interventions may have a role in the treatment of cirrhosis. Moreover, lifestyle changes are easy to implement, relatively inexpensive, and with little risk of side effects. Firstly, the classical alcohol abstinence should be considered in the management of cirrhosis independently of the etiology. However, lifestyle interventions may be especially relevant when considering the emerging pathogenic role of obesity and insulin resistance in chronic liver disease that may be affected by nutritional and exercise interventions. Such an

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R. Bañares, MD, PhD (✉)
Facultad de Medicina, Universidad Complutense, Madrid, Spain

Digestive Disease Department and Liver Unit, Hospital General Universitario Gregorio Marañón, IISGM CIBEREHD, Madrid, Spain
e-mail: rbanares@telefonica.net

L. Ibáñez-Samaniego, MD
Digestive Disease Department and Liver Unit, Hospital General Universitario Gregorio Marañón, IISGM CIBEREHD, Madrid, Spain

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approach would be extremely appealing because of its appropriateness and affordable costs. Thus, the aim of this chapter is to summarize the most recent advances in this field.

Alcohol Abstinence

Excessive alcohol consumption is a major public health issue that can lead to the development of liver fibrosis and cirrhosis. It is widely accepted that alcohol abstinence improves the general prognosis of patients with alcoholic cirrhosis. Several studies have shown that alcohol abstinence is associated to a short-term decrease in portal pressure, maintenance of hemodynamic improvement during follow-up, and clinical improvement [1]. In addition, a prospective study indicated that after variceal hemorrhage, abstinent alcoholic cirrhotic patients had better hemodynamic response to drugs than cirrhotic patients of viral etiology [2]. Finally, a more recent study clearly showed that alcohol abstinence and giving the maximum tolerable dose of beta-blockers were independently associated to a decrease in the risk of rebleeding and death [3]. On the other hand, a recent study has shown that liver stiffness significantly decreased after alcohol abstinence [4]. Altogether, these data clearly indicate that alcohol abstinence has a relevant impact in the natural history of cirrhosis. Nevertheless a recent meta-analysis has suggested that the beneficial impact of alcoholic abstinence on survival requires at least 1.5 years of lack of alcohol consumption, indicating that efforts should be made to maintain long-term abstinence [5].

Obesity and Human Health

Obesity is probably one of the major health problems worldwide, especially in Western countries. This is not only because of the constant increase in its prevalence, but it is also due to the severity of the consequences.

The most commonly accepted definition of obesity is based on the body mass index (BMI). Thus, those subjects having a (BMI) greater than 30 Kg/m^2 are considered obese [6]. Overall, it is estimated that 20–30 % of inhabitants of North America and Europe are obese [7]. Although genetic factors may be responsible of part of the problem, the main reason that probably explains the rising incidence of obesity is the unbalanced proportion between a high caloric ingestion and a reduced caloric consumption due to sedentary lifestyle.

Obesity is associated with a vast constellation of health problems especially including type 2 diabetes, hyperlipidemia, cardiovascular diseases including arterial hypertension, and malignancies. Nevertheless, other chronic diseases such as psychosocial, neurological, kidney, and pulmonary disturbances are also associated to obesity. Consequently, obesity is responsible of a shortening of life expectancy. Therefore, it is not surprising that health costs associated to obesity management are growing in the Western world.

The negative effect of obesity on health is related to the onset of a chronic low-grade inflammation originating in the excessive white adipose tissue that functionally behaves as an endocrine gland, producing peptides (adipokines) and metabolites. The phenotype of adipose tissue is markedly different in obese subjects, especially the visceral and perivascular tissue. Adipocyte size increases, and adipose tissue becomes hypoxic [8] promoting the previously mentioned inflammation and cellular dysfunction. Importantly, these conditions promote a modification of adipokine secretion from a protective to a damaging profile with additional macrophage infiltration and releasing of macrophage-derived cytokines [9]. These changes are associated to a well-known increase in insulin resistance but also to a pro-inflammatory, pro-fibrogenic, pro-angiogenic, and pro-oxidant consequences in different organs [8–10].

Clinical Implications of Obesity in Cirrhosis

Regarding the spectrum of liver diseases, the influence of obesity in the natural history of chronic liver disease (CLD) has been clearly recognized. Nonalcoholic fatty liver disease (NAFLD), as the liver side of metabolic syndrome, probably will become the most important challenge for hepatologists in the following decades.

Besides its implication in NAFLD, obesity is also very prevalent in patients with chronic liver disease independently of the etiology. Several studies have shown that obesity is associated to severe fibrosis in alcoholic liver disease [11, 12] as well as in nonalcoholic steatohepatitis (NASH) [13] and in chronic viral hepatitis [14]. Furthermore, obesity is an independent factor of fibrosis progression in HCV patients [15, 16]. Finally, a recent nested cohort study [17] performed in the well-known timolol trial, has shown that in patients with compensated cirrhosis and without varices, clinical decompensation of cirrhosis developed in 14 % of patients with normal weight, in 31 % of overweight patients, and in 43 % of patients with obesity. Importantly, BMI, together with albumin and the severity of portal hypertension, was an independent predictive factor of the risk of decompensation. In quantitative terms, obese patients had a threefold risk of decompensation as compared with normal weight patients, independently of the etiology of cirrhosis. Interestingly, the data showed that obesity also negatively impacts on portal hypertension. Indeed, after 1 year of treatment with timolol or placebo, only patients with normal weight or overweight showed a reduction of HVPG, whereas obese patients had a slight increase in HVPG. Moreover, insulin resistance and obesity predict the occurrence of hepatocellular carcinoma (HCC) [18].

Conversely [15], a modest weight reduction was associated to a decrease in hepatic inflammation and steatosis in patients with hepatitis C and advanced fibrosis (HALT-C cohort).

All these findings clearly indicate the existence of an interaction between obesity, portal hypertension, and the natural history of cirrhosis. From a clinical point of view, it is possible to speculate that body weight reduction may have a beneficial effect in decreasing portal pressure with a potential for decreasing the risk of decompensation. To answer this important question regarding the impact of lifestyle

interventions in the natural history of cirrhosis, a proof-of-concept study (sport-diet study) has been recently communicated [19]. The main end point of the study was to evaluate whether a reduction in body weight induced by a16-week intensive lifestyle intervention including individually tailored dietary and exercise plan is associated to a decrease in portal pressure estimated by HVPG measurements. Fifty patients with compensated cirrhosis underwent a hemodynamic and nutritional study before and after a predefined and individualized lifestyle intervention. In brief, all the patients received a personalized caloric reduction and moderate physical exercise (60 min/week).

After the intervention, a majority of patients (52 %) had a clinically relevant decrease in body weight (previously defined as a reduction greater than 5 %), entirely due to a significant decrease in fat mass. Interestingly, the lifestyle intervention was associated to a significant decrease in HVPG (13.9 ± 5.6 mmHg vs. 12.3 ± 5.2 mmHg; $p < 0.0001$; average reduction, 10.7 %), Indeed, 42 % of patients had a HVPG reduction greater than 10 %. Although a linear correlation between weight loss and HVPG decrease was not observed, a greater HVPG decrease was observed in those patients with more than 10 % of body weight decrease.

Interestingly, no safety problems were observed during lifestyle intervention. Moreover, a slight increase in indocyanine green fractional clearance was observed as well as an improvement in metabolic profile and quality of life. The main conclusion of this proof-of-concept study indicates that an intensive short-term lifestyle intervention safely decreases HVPG in patients with compensated cirrhosis and portal hypertension.

This study clearly indicates the need to evaluate in appropriately designed clinical trials the effect of weight reduction on clinical end points in patients with compensated cirrhosis.

In patients with decompensated cirrhosis, maintenance of adequate nutrition is important to avoid loss of muscle mass which can also contribute to development of hepatic encephalopathy [20].

Other Interventions

Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus should be offered as early as possible, because the antigenic response becomes weaker as cirrhosis progresses, limiting the likelihood of effective protection.

Cigarette smoking has specific deleterious effects and is associated with more severe fibrosis in patients with different etiologies of liver disease [21], including viral hepatitis, primary biliary cirrhosis, and NASH. In patients with chronic hepatitis B, the risk of HCC is higher among heavy smokers [22]. In addition, daily cannabis is associated to worsening steatosis in HCV patients [23]. Therefore, smoking cessation strategies may have additional benefits in patients with chronic liver disease, which should be evaluated in cirrhosis.

Coffee consumption has been associated with a significant reduction in risk of fibrosis in NASH [24], as well to a reduction in the risk of HCC [25].

Table 13.1 Summary of lifestyle recommendations

Lifestyle recommendations	Rationale	References
Alcohol abstinence	Decreases HVPG. Decreases liver stiffness. Improves survival	[1, 3, 4]
Weight loss	Decreases HVPG. Decreases inflammation. Decreases steatosis	[15, 19]
Tobacco smoking cessation	Tobacco increases liver fibrosis and risk of HCC	[21, 22]
Cannabis smoking cessation	Cannabis increases steatosis in CHC	[23]
Coffee consumption	Decreases fibrosis in NASH. Decreases risk of HCC	[24, 25]
Antioxidant-rich food	Decreases HVPG	[26, 27]

Abbreviations: *HVPG* hepatic venous pressure gradient, *HCC* hepatocellular carcinoma, *NASH* nonalcoholic steatohepatitis, *CHC* chronic hepatitis C

Furthermore, the use of antioxidants, dark chocolate [26], and ascorbic acid [27] is associated to improvement of intrahepatic circulation in patients with cirrhosis by improving flow-mediated hepatic vasorelaxation and decreasing HVPG.

Summary and Conclusions

Besides specific therapies aimed to controlling etiological factors and to treating cirrhosis complications, simple lifestyle interventions have a relevant impact in pathogenically relevant events (i.e., portal pressure) and should be included as potential therapeutic tools to be evaluated in the future (Table13.1).

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Liver Fibrosis: What Is Reversible and What Not? How to Assess Regression?

14

Virginia Hernández-Gea

Fibrosis Formation and Resolution

Hepatic fibrosis is the liver wound-healing response to injury and it is characterized by the accumulation of the extracellular matrix (ECM). Maintenance of the injury leads to the progressive substitution of liver parenchyma by scar tissue altering cellular homeostasis, parenchymal architecture, and liver function, known as liver cirrhosis. Fibrosis progression results when ECM production exceeds ECM degradation and has been thought to be an irreversible process for most of medical history. First reports of reversibility of fibrosis come from 1979 with the finding that the level of collagenase activity in the liver correlates with ECM degradation [1]. This scarring response is a common pathway resultant from diverse liver injuries (viral, toxic, metabolic, etc.) that results in cirrhosis, the end-stage liver disease associated with a poor outcome and high mortality. The key event in fibrosis is the activation of hepatic stellate cells (HSC) that acquire a myofibroblast phenotype that contributes to ECM synthesis. Although fibrogenic cells mainly derive from portal fibroblasts and HSC and contribute to liver fibrosis, HSC represent the major fibrogenic population in all kinds of injury [2]. Upon activation, HSC increase in number, become contractile, and remodel the ECM into one rich in fibril-forming collagens, particularly types III and I, with a deregulated matrix metalloproteinase (MMP) activity and increase in tissue inhibitors of metalloproteinases (TIPMs). Collagen I and other ECM components can further activate and sustain HSC survival, acting as a positive feedback loop by releasing additional growth factors that increase liver stiffness [3]. Stiff ECM also promotes angiogenesis that plays an active role in liver fibrogenesis, perpetuating HSC activation and collagen deposition during liver injury. A better understanding of both HSC activation, matrix degradation, and the

V. Hernández-Gea
Liver Unit, Hepatic Hemodynamic Unit, Hospital Clinic, Barcelona, Spain
e-mail: vihernandez@clinic.ub.es

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signaling pathways involved in both processes will allow identification of therapeutic points of attack for new drug development.

HSC transdifferentiation into myofibroblast consists of two major phases, *initiation* that results from paracrine stimulation from the microenvironment and *perpetuation* that comprises proliferation, contractility, ECM deposition, matrix degradation, inflammatory signaling, and retinoid loss. Every one of these steps is tightly regulated by the so-called fibrogenic pathways and may be a therapeutic target. Indeed hundreds of molecules contributing to fibrosis have been evaluated without therapeutic implications, probably due to the highly controlled experimental settings confined to one tissue, species, and model of injury. There is growing evidence supporting the identification of the core pathway [4], essential for fibrosis to develop, conserved among tissues and species. Targeting this may be sufficient to limit fibrosis progression. This strategy will allow a more efficient identification of molecules relevant to human fibrosis; however, it raises the concern of pleiotropic effects and safety of systemic administration. Targeted therapy directed not only to a core pathway but also to a fibrogenic cell population remains a very attractive approach hopefully to be developed in a near future.

What Is Reversible and How to Assess Regression?

Abrogation of the underlying disease may slow down and event revert the fibrotic process in almost all kinds of liver disease. Robust data about cirrhosis regression come from rodents' studies in which cessation of the causative agent results in fibrosis regression. In both carbon tetrachloride (CCl_4) and bile duct ligation (BDL) models of cirrhosis, discontinuation of the injury leads to spontaneous cirrhosis resolution [5]. However, a detailed examination of the scar tissue demonstrated the persistence of scar fibers in animals with advanced cirrhosis in which the remodeling is partial [6], indicating that the potential for reversibility of fibrosis declines at advanced stages. Several mechanisms are needed for an efficient fibrolysis, (a) ECM degradation, (b) myofibroblast deactivation, (c) hepatocyte regeneration, and (d) vascular and parenchymal remodeling.

At what point cirrhosis becomes irreversible is uncertain but chronic damage results in increasingly acellular and thick fibrotic septa resistant to degradation. From the biochemical point of view, collagen, the most abundant ECM scaffolding protein, undergoes extensive cross-linking and is wrapped in filaments of elastin together with a decreased expression/activity of MMPs. Moreover both collagen cross-linking and accumulation of elastic fibers, hallmarks of ancient fibrosis, then contribute to matrix stabilization and impair enzymatic degradation. Genetic manipulation has established the importance of matrix stabilization in resistance to degradation and has appointed the lysyl oxidase (LOX), an oxidase that initiates the process of covalent cross-linking of collagen, as an attractive therapeutic antifibrotic target. Reduction of LOX activity tempers tissue stiffness and prevents fibrosis in rodents and humans in different tissues [7]. Besides, ECM cross-linking influences myofibroblast behavior and undegradable ECM keeps some myofibroblast unable

to deactivate. Efficient fibrolysis depends also on other hepatic cell populations and is modulated by the ability of hepatocytes to regenerate and by the response of inflammatory cells to recurrent injury. The immune system is a crucial regulator of both progression and regression of fibrosis. Macrophages are critical regulators of wound healing and of the resolution of cirrhosis as they are a rich source of fibrolytic MMPs (MMP12 and MMP13) and recruit other immune cells implicated in regression such as neutrophils [8].

Besides matrix degradation, removal of activated HSCs has to occur for resolution to happen. Reduction in the number of activated HSC is achieved through apoptosis, senescence, and reversion to an inactivated phenotype.

All this relevant information coming from animal models may not faithfully represent what happens in human disease where data are still scarce. Cirrhosis in rodents develops within weeks and is rather different both in morphological and biochemical terms from human cirrhosis. Several clinical studies claimed cirrhosis reversal after etiological treatment; however, what most of them showed is a variable degree of fibrosis regression.

The concept that early cirrhosis might be more likely to regress than established cirrhosis has also been confirmed in humans achieving sustained virological response (SVR) after HCV treatment. Downstage of liver fibrosis has been reported in 49 % of patients achieving SVR according to noninvasive markers (FibroTest and transient elastography) [9]; however, progression to cirrhosis assessed by biopsy may also occur despite SVR in approximately 10 % of patients [10, 11], in which comorbidities and risk factors (alcohol, fatty liver disease) may contribute to progression. Cirrhosis reversibility has also been proven in biopsies of >70 % of patients with HBV cirrhosis after 5 years of viral suppression with tenofovir [12]. Full control of inflammatory activity by immunosuppressive therapy in autoimmune hepatitis has been shown to reduce biopsy fibrosis content in approximately 50 % of cases [13]. Reversibility data from other chronic liver diseases are less certain; for instance, in NASH, recent data showed some reversibility of fibrosis 1 year after bariatric surgery. All these data support the possibility of fibrosis downstaging and even, in some cases, of complete regression; however, the exact mechanism responsible for patient variability needs further investigation.

How to assess regression is nowadays a matter of debate. Liver biopsy has been considered the gold standard for many years; however, its invasiveness, sampling variability, cost, and the fact that it provides a static measure of fibrosis have questioned its prominence. So far, its replacement has not been possible, and clinical trials testing antifibrotic drugs still require liver biopsy to assess fibrosis before and after intervention. Standard pathology scoring systems are able to detect cirrhosis; however, they cannot distinguish further increases in collagen deposition. This limitation can be overcome using quantitative assessment of fibrosis by digital image analysis of the proportion of collagen in liver tissue (collagen proportionate area (CPA)) that besides accurately classifying fibrosis can also predict clinical decompensation [14]. CPA keeps its value regardless of the type of biopsy (percutaneous or transjugular); therefore, the transjugular approach with HVPG (hepatic venous pressure gradient) measurement appears to be very good option. Strong evidence

affirms HVPG as the strongest predictor of cirrhosis decompensation and survival in cirrhosis. Several serum markers of fibrosis have been developed in the last decade: they mainly evaluate indirect markers of fibrosis such as liver function (FibroTest, aspartate aminotransferase to platelet ratio index) and direct markers that represent molecules present in the fibrotic tissue (FibroSpect, the European Liver Fibrosis test) or a combination of both (HepaScore and FibroMeter). However, the diagnostic accuracy of these tests varies significantly among trials and none of them precisely mirrors intermediate stages of fibrosis. Among the noninvasive tools, transient elastography is the most validated and available method to measure liver stiffness and fibrosis content and is able to predict risk of decompensation. ARFI, supersonic shear wave, and the promising magnetic resonance elastography permit assessment of the whole liver stiffness and may acquire more prominence in the upcoming years [15].

Difficulties for Antifibrotic Drug Trials

Fibroproliferative diseases account for 45 % of all deaths in the developed world. This has a strong impact on quality of life and health costs, which makes them attractive to the drug development industry. In the case of the liver, despite the better knowledge of fibrosis progression and regression and great efforts in antifibrotic drug development in the last 20 years, no drug has been approved yet as all the promising ones failed to show efficacy in the real human scenario. The interest on the field of liver fibrosis is however still growing, and currently there are over 500 trials being conducted under the name "liver fibrosis" based on clinicaltrials.gov. This underscores the need for a better standardization of the design of antifibrotic trials and for the identification of which end points are optimal. The first issue is to define whether a given antifibrotic drug will be tested to prevent fibrosis progression, decompensation, or death as patient selection may differ for each end point. As said before, fibrosis and even cirrhosis are dynamic processes with more than one stage; therefore, the patients should be at the same stage of fibrosis and ideally stratified by etiology, genetic risk, age, gender, presence of metabolic syndrome, alcohol use, and other modifying factors. Equal stratification would permit proof-of-principle phase II trials to enrich the study population by restricting enrollment to high-risk patients.

How to detect changes in fibrosis with a meaningful clinical impact is another critical caveat as fibrosis progresses slowly over years and clinical events in patients without cirrhosis are rare. Clinical trials require enrollment of a large number of patients over a long period of time, which makes them costly and impractical. Surrogate markers able to predict mortality and morbidity risk in subjects with compensated cirrhosis may help tackle this challenge.

HVPG >10 mmHg has been suggested as a good indicator of clinical deterioration in patients with advanced fibrosis, as interventions lowering pressure below this threshold truly diminish the risk of decompensation and death. Benefit in patients with more advanced fibrotic disease may be well characterized by Child-Pugh and

MELD scores, easy to measure when compared with HVPG. However, the main problem remains in those patients in earlier stages of the disease in whom no biomarker has been proven to be accurate enough to be included in clinical trials. Finding a reproducible test that integrates data from the entire organ in a minimally invasive way and capable of predicting early changes in fibrosis progression/regression remains an urgent unmet need [16].

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Potential Antifibrotic Therapies: Approaching the Bedside: Proof-of-Concept Studies (Part 1)

15

Wim Laleman

Introduction

Progressive hepatic fibrosis in combination with nodular regeneration dominates the increased intrahepatic vascular resistance to portal flow and thus portal hypertensive syndrome (PHT), which is one of the major driving forces in the development of clinical complications associated with cirrhosis [1, 2]. Over the last decade, advances in the understanding of the pathogenesis of liver fibrogenesis and its resolution, the development of noninvasive tools to assess hepatic fibrosis, and the growing public awareness of the health impact of global hepatological killers (such as nonalcoholic fatty liver disease, hepatitis B and C, etc.) have fuelled the quest for antifibrotic strategies. In the absence of successful etiological treatment (see previous chapters), these approaches should either intend to halt progression of the underlying chronic liver disease to cirrhosis [and thus prevent clinical significant portal hypertension (CSPH) to arise] or reverse CSPH in conditions where there is no etiological treatment or CSPH persists despite these latter efforts [3–6]. The quest for antifibrotic drugs/approaches has been vindicated by the illustration of reversibility of hepatic fibrosis (and cirrhosis ?) following successful antiviral therapy for hepatitis B and C with improved clinical outcomes, reduced portal pressure, and decreased all-cause mortality as clinical trade-off [7, 8]. This chapter serves the purpose of briefly pointing out some of the most far-advanced molecules in their transition from the bench to the bedside.

W. Laleman, MD, PhD
Department of Liver and Biliopancreatic Disorders, University Hospitals Leuven, KU Leuven, Herestraat 49, Leuven 3000, Belgium
e-mail: wim.laleman@uzleuven.be

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Antifibrotic Strategies: Which Way to Go?

For in-depth review on the cellular and molecular basis of hepatic fibrosis, the reader is referred to the earlier chapter by Dr. Hernandez-Gea and other excellent recent reviews [3–6]. Of importance is that evolving clarification on the role of different parenchymal and non-parenchymal cells; humoral auto-, para-, and endocrine mediators; and intracellular signaling pathways has led to a rational mechanism-based antifibrotic approach that in essence can be confined to four strategies [3]:

1. Disease-specific therapies that control or cure the underlying tissue injury or inflammation (e.g., antiviral treatments, FXR agonism)
2. Target receptor–ligand interactions to reduce the pivotal hepatic stellate cell activation (angiotensin II-type 1 receptor, anticoagulants, etc.)
3. Inhibition of the most potent pro-fibrogenic pathways (such as transforming growth factor β (TGFβ), connective tissue growth factor, etc.)
4. Promote resolution of fibrosis by either increasing stellate cell apoptosis (CBR-1-antagonist, ACE-inhibitors, etc.) or by increasing degradation of extracellular matrix

In the current and next chapter, we will discuss different potential strategies. All of these approaches are of interest as a concept and (might) fuel preclinical exploration. As this is an expanding and highly competitive field, the current review surely does not cover all potential premises but aims to focus on the most advanced. Moreover, whether these molecules will uphold their promise in clinical practice remains to be confirmed, but at least they are interesting either as "first in class" or either from a translational targeted perspective.

The Farnesoid X-Receptor (FXR) Pathway

Background and Hepatic Relevance

FXR is a ligand-activated transcription factor belonging to the nuclear receptor superfamily and acts as sensor for a broad range of natural ligands with bile acids being the most potent ones, in particular chenodeoxycholic acid (CDC). Upon binding of bile acids to FXR, the receptor translocates to the nucleus where it forms a heterodimer with its binding partner retinoid X-receptor (RXR) and drives hormone response elements to up- or downregulate gene expression [9, 10]. Since FXR is at the crossroad of metabolic regulation, inflammation, and regeneration in normal liver, it is involved in key hepatic functions [11–13]. Conversely, upon dysfunction, it is considered to contribute to the development of cholestatic diseases, nonalcoholic fatty liver disease, impaired liver regeneration and fibrosis, and hepatocellular carcinoma [11–13]. FXR deficiency has been documented in experimental and

human cirrhosis and has been associated with complications of cirrhosis, such as spontaneous bacterial peritonitis [14–16].

Experimental Basis for the Antifibrotic Effects of FXR Agonism

Translational research has provided a rational basis for potential antifibrotic effects of FXR agonism [17–19]. First of all, restoration of the FXR pathway decelerates or halts fibrogenesis through attenuation of pro-inflammatory signaling pathways which are known major perpetuating factors in liver fibrogenesis. The pivotal anti-inflammatory role of FXR was documented by knockout animal experiments [12]. $FXR^{-/-}$ mice, in contrast to their wild-type counterpart, displayed massive hepatic inflammation and fibrosis through activation of NF-κβ which could be repressed either by FXR transfection or FXR ligands. Secondly, FXR might shape hepatic stellate cells since primary rat and immortalized human HSCs express FXR and its downstream signaling components [17]. Additionally in this context, stimulation with 6-ethyl chenodeoxycholic acid (6-ECDCA, obeticholic acid), a synthetic FXR ligand, arrested in vitro transdifferentiation of hepatic stellate cells to pro-fibrogenic myofibroblasts. These findings however could not be validated neither in activated human nor rodent HSCs [14, 16]. Thirdly, FXR agonism might impact directly on potent pro-fibrogenic pathways (transforming growth factor β, connective tissue growth factor, platelet-derived growth factor β-receptor, tissue inhibitor of metallopeptidase-1) [17, 19]. Fourthly, FXR agonism can prevent translocation of bacterial products which, through the action of Toll-like receptor-4, can drive hepatic fibrogenesis since HSCs also express this receptor [14, 20, 21, 22].

Proof-of-Concept Studies

The only FXR agonist that has entered clinical trials so far is obeticholic acid (OCA, INT-747), a first-in-class semisynthetic analog of the primary bile acid chenodeoxycholic acid (CDCA). The 6-a ethyl substitution of CDCA imparts a nearly 100-fold greater FXR-activating potency. It is currently being explored in clinical trials for NASH, PBC, early PSC, and portal hypertension [23–25]. The multicentre *Farnesoid X-Receptor Ligand Obeticholic Acid in NASH Treatment* (FLINT) trial evaluated the effect of 72 weeks of OCA on liver histology in 283 biopsy-proven NASH patients with all stages of fibrosis except cirrhosis (53 % diabetics) [25]. The primary end point was liver histological improvement defined as decrease in NAFLD Activity Score (NAS) of ≥2 points with no worsening in fibrosis. The trial was stopped prematurely based on interim efficacy results showing that OCA has a significant beneficial effect on liver damage due to NASH. Indeed, OCA improved the histological features of NASH, including hepatic steatosis, hepatocyte ballooning, and fibrosis (45 % vs. 21 %, OCA vs. placebo) and mainly in diabetic patients (OR in diabetic patients: 4.6, $P=0.0003$, vs. nondiabetics: OR: 2.0, $P=0.12$). In respect of fibrosis alone, defined as any numerical change in stage, a significant but

narrow-edged effect (−0.2 ± 1 vs. +0.1 ± 0.9, $P = 0.01$) was observed. It is important to point out in this context that most patients only had perisinusoidal and periportal fibrosis at baseline and a significant number of patients did not have a second biopsy due to early termination. This leaves open the question whether, like in experimental models, OCA is efficient in advanced fibrosis in humans, as this is associated with liver-related complications rather than earlier fibrosis stages. A partial answer to this question has been offered by post hoc analysis of the original data in which a high-risk population group (i.e., NAS ≥4 and Fibrosis Stage 1 [with BMI ≥30 kg/m^2, Type 2 Diabetes or ALT ≥60 U/L]; Stage 2 or Stage 3) at risk of accelerated fibrosis was reanalyzed. Using this definition, a higher increased overall improvement was observed (39 vs. 21 %, $P = 0.007$) with a comparable benefit occurring across all baseline fibrosis stages, supporting the potential for benefit also at more advanced stages of fibrosis. Confirmatory studies evaluating longer-term and safety effects are being scheduled. In a phase-2 RCT evaluating the efficacy of different doses of OCA for 3 months in patients with primary biliary cirrhosis and poor response to ursodeoxycholic acid [23], 69 % of patients had at least 20 % reduction in alkaline phosphatase (ALP), which has been shown to be a good correlate of both survival and liver histology in PBC and is used globally in clinical practice to predict the progression of the disease [26]. This effect was proven to be sustained in a 12-month open-label extension study. The *PESTO trial*, an open-label phase 2a proof-of-concept study [25], evaluated short-term OCA treatment to assess tolerance and HVPG response in patients with alcoholic cirrhosis. Twenty-five patients with portal hypertension received OCA 10 or 25 mg orally for 7–12 days. Interim analysis showed that 9 out of 16 patients undergoing hemodynamic assessment responded (mean reduction of 28 %), without deleterious impact on mean arterial pressure or liver biochemistry. Final results are awaited and based hereon larger controlled trials.

The Coagulation Cascade

Background: Coagulation and Liver Fibrosis

Cirrhosis has traditionally been considered as a hypocoagulable state with increased bleeding risk. However, this dogma has critically been revised over the last years since nowadays coagulation in cirrhosis is perceived as a complex and fragile balance between endogenous procoagulant (hypercoagulable) and anticoagulant (hypocoagulable) factors. This is corroborated on the one hand by an increased risk of venous thrombosis in cirrhosis and the fact that variceal bleeding is unrelated to deranged hemostasis on the other hand. For in-depth review on the coagulation cascade in cirrhosis, the reader is referred elsewhere [27]. Accumulating evidence indicates that the hypercoagulant, prothrombotic state in cirrhosis promotes accelerated fibrogenesis and conversely that a hypocoagulable state slows down fibrosis. More specifically, this premise follows from (1) observations that hepatic inflammation and cirrhosis are associated with the presence of microthrombi within the hepatic vasculature of which the extent and distribution correlate with progression

of hepatic fibrosis independent of the nature of the underlying liver disorder [28] and (2) evidence that procoagulant states (e.g., carriage of the Factor V Leiden mutation, protein C deficiency) are associated with accelerated progression to cirrhosis (3.28-fold risk increase) in hepatitis C [29, 30]. Turning this paradigm around, a study in 185 hemophiliac patients showed slower fibrosis progression with only 3 % (95 % CI 0.4–6 %) liver-related deaths [31].

How Can Hypercoagulability Drive Hepatic Fibrogenesis?

At present, two mechanisms are considered mutually enforcing to explain that intrahepatic thrombus formation is not just a consequence but rather an active player in the progression of the disease. First of all, there is the "parenchymal extinction" theory by Wanless et al. [28]. This hypothesis sets off from a persisting inflammatory injury causing venous thrombosis. The consequent hepatocyte ischemia and death leads to a parenchymal extinction lesion (PEL) which in turn induces tissue to collapse so that adjacent portal tracts and hepatic veins are approximated and replaced by fibrous septa. When PELs accumulate and become confluent, cirrhosis evolves. Secondly, there is direct thrombin-mediated HSC activation via protease-activated receptors (PARs). More specifically, thrombin, in addition to its hemostatic role, drives a wide range of biological activities, as a serine protease, which enables signaling to a variety of cell types, including the HSC, through G-protein-coupled PARs [32]. Activation of PARs on HSC was found to enhance collagen production and thus participate in scar formation [32]. Further support for this mechanism is the finding that liver injury, irrespective of the cause, increases PAR-1 expression and thus sensitizes HSCs to thrombin-mediated activation [32, 33]. Moreover, PAR triggers platelet degranulation and the release of platelet-derived growth factor (PDGF), a well-known HSC activator [34].

Proof-of-Concept Studies

The therapeutic consequence of the relation between hypercoagulation and increased fibrosis is that remediating hypercoagulability may reduce hepatic fibrosis. This intriguing therapeutic avenue might offer a valuable alternative for the growing cohort of patients in whom etiological therapies have proved unsuccessful or are not at hand. The trade-off, however, of an anticoagulant strategy is increased bleeding risk. At present, two randomized clinical trials, one in cirrhotic and one in non-cirrhotic patients, have explored this approach.

The landmark study of Villa et al. [35] showed that a 12-month course of enoxaparin (4000 IU/day) in 70 outpatients with cirrhosis of different etiology (range Child B7 to C10, without portal vein thrombosis at entry) delayed the occurrence of hepatic decompensation (11.7 vs. 59.4 % for control at 48 weeks, $P<0.001$) and improved survival ($P=0.02$). These beneficial effects were attributed to its anticoagulant actions but also to an improvement of intestinal microcirculation able to

augment enterocyte fitness and reduce bacterial translocation. There were no major adverse events related to anticoagulation use. Another study in this context is the WAFT-C trial, a prospective multicenter, randomized open-label controlled trial designed to investigate the impact of warfarin on fibrosis progression over 1 and 2 years post-liver transplantation for HCV [36]. An interim per protocol analysis at 1 year, soon to be presented as abstract, demonstrated a significant reduction in the proportion of patients with an increase in fibrosis score between the control group and warfarin group at year 1 (23.3 % vs. 0 %, $P=0.01$, $n=53$). No patients were withdrawn due to severe adverse events directly secondary to anticoagulation.

The Angiotensin Pathway

Background and Hepatic Relevance of Angiotensin

The role of the renin–angiotensin–aldosterone system (RAAS) in portal and systemic hemodynamics was acknowledged already 35 years ago and longtime before its role in fibrogenesis [2, 37]. Although studies with angiotensin-converting enzyme (ACE) inhibitors or AT1-receptor blockers (ARBs) lower HVPG to an extent similar to that observed in patients receiving beta-blockers in Child A patients (−17 % vs. −21 %), their use is offset by a marked decrease in mean arterial pressure, worsening of the hyperdynamic circulation, and a significant fall in glomerular filtration rate in Child B/C patients. As such, these agents are considered hazardous in the context of decompensated cirrhosis [38]. The finding that stellate cells harbor all the components for local signaling in response to AT-II, both autocrine and paracrine, and induce collagen I gene expression, relaunched the interest in the RAA system from an antifibrotic perspective for early stages of the disease [2, 39, 40].

Proof-of-Concept Studies

A course of 18 months of losartan in 14 patients with chronic HCV was shown to decrease NADPH oxidase, decreased inflammation, and fibrogenesis delivering proof of concept that targeting the RAA system is worthwhile [41]. These beneficial antifibrotic effects were confirmed in several small prospective randomized controlled trials in patients with advanced fibrosis or early cirrhosis of different etiologies [42–44] and a retrospective large sample size trial in hepatitis C patients [45] but offset by others, like in the HALT-C cohort where ACEi/ARB therapy did not retard the progression of hepatic fibrosis [46]. Similar discrepancies were found in other chronic liver diseases, such as NASH. Clearly, for ACEi or ARBs, data from a long-term prospective large-sample RCT stratified for diabetes and hypertension are needed to resolve an at present unanswered question. Given the potential of the RAA system and the limitation of current available drugs to fully explore this potential in advanced liver disease, alternatives to ACEi or ARBs could be explored by targeting downstream signaling effectors of the AT1R via Janus kinase or Rho

kinase or through coupling such drugs to a carrier (e.g., mannose-6-phosphate-modified albumin) to augment liver selectivity, which was proven to be efficacious in animal experiments both on portal hypertension and hepatic fibrosis [47–49].

The Gut–Liver Axis

Intestinal dysbiosis, defined as an imbalanced intestinal microbial community characterized by quantitative and qualitative changes in the composition of the microbiota itself, in its modified metabolic activities or in the local distribution of its members, represents another interesting focus for targeting liver fibrosis. In recent years, accumulating evidence has indicated that microbial products trigger liver inflammation by activating the innate immune system and a subsequent hepatic pro-inflammatory response, which is the common denominator in numerous liver diseases and an acknowledged driver of hepatic fibrosis. This is experimentally supported by the observation that the Toll-like receptor-4, a pattern recognition receptor that identifies conserved features of microbial products, enhances TGF-β signaling, a key pro-fibrogenic cytokine, and is predominantly expressed by HSCs [50]. At present, there are no proof-of-concept clinical studies to corroborate that modulation of gut microbiota impacts on hepatic fibrogenesis. However, increasing data are becoming available that long-term treatment with probiotics or selective intestinal decontamination might impact on liver disease severity and outcome [51, 52]. For a more extensive review on gut microbiota and pathophysiology or clinical implications, the reader is referred to chapters later on.

Conclusion

The saying "an ounce of prevention is worth a pound of cure" appeals to a paradigm shift to try to keep a bad thing from happening. Successful antiviral treatment encouraged the interest in the development of antifibrotic strategies since the clinical trade-off is improved clinical outcomes, reduced portal pressure, and decreased all-cause mortality. All attempts to do so, such as among others FXR agonism, anticoagulation, angiotensin blockage, and modulating dysbiosis, should be explored for their validity in preventing decompensation of cirrhosis.

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New Targets in Therapy: Statins, Antioxidants and Antiangiogenic Strategies

16

Jaime Bosch and Jordi Gracia-Sancho

Introduction

Portal hypertension develops in cirrhosis due to a significant increment in hepatic vascular resistance (HVR) to portal blood flow. Most of the increased HVR is due to the architectural distortion of liver vascular architecture due to structural changes [1]. However, a significant increase of hepatic vascular tone further contributes to raise the hepatic resistance. This dynamic and reversible component of HVR was firstly described by Bhathal and Grossmann in 1985 [2] and may represent up to 30–40 % of the total increased HVR in cirrhosis. Hepatic cells influencing the hepatic vascular tone involve sinusoidal and extra-sinusoidal elements and include liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs) and contractile cells (hepatic stellate cells [HSCs], myofibroblasts and vascular smooth muscle cells) [3–5]. We summarise below the major molecular pathways leading to increased HVR in cirrhosis, as antagonising these represents the rational treatment of portal hypertension.

J. Bosch, MD, PhD, FRCP (✉)
Hepatic Hemodynamic Laboratory, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain

Inselspital-Bern University, Bern, Switzerland

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

Hepatic Hemodynamic Laboratory Hospital Clinic, Barcelona, Spain
e-mail: jbosch@clinic.ub.es

J. Gracia-Sancho, PhD
Hepatic Hemodynamic Laboratory, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain

Inselspital-Bern University, Bern, Switzerland

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Pathophysiology and Rational Basis of Therapy

Microvascular Dysfunction of the Cirrhotic Liver

Vascular cell deregulation within the cirrhotic liver leads to the development of the so-called liver endothelial dysfunction, defined by a deficient flow-mediated vasodilatory response of the liver microcirculation, leading to an increased hepatic vascular tone due to an imbalance between a deficient availability of endothelial vasodilators (mainly NO) and increased activity of vasoconstrictor systems (mainly alpha-adrenergic stimulation, thromboxane A2, renin–angiotensin system) [6]. Liver endothelial dysfunction should probably be re-termed "liver microvascular dysfunction" since all sinusoidal cells participate in the abnormal vasoactive response of the cirrhotic liver. In cirrhosis, LSEC and KC acquire a predominantly vasoconstrictor phenotype which is further exacerbated in response to biomechanical, pathogenic and inflammatory stimuli [3, 7, 8]. In addition, hepatic contractile elements become hyperresponsive to vasoconstrictors and markedly increase the vascular tone [9]. Although the mechanism(s) responsible for sinusoidal cell phenotype deregulation are not completely understood, recent research indicates that paracrine interactions between dysfunctional LSEC or KC may impair HSC phenotype [10, 11] that becomes proliferative and pro-contractile.

Factors Modulating the Hepatic Microcirculation in Cirrhosis

In cirrhosis, the availability of *nitric oxide* (NO), the main endothelial vasodilator, is markedly decreased at the intrahepatic circulation, which represents a major determinant of the increased hepatic vascular tone. Low NO levels result from both decreased endothelial NO synthase (eNOS) translation efficiency [12] and enzymatic activity [13]. Reduced eNOS activity is attributed to several posttranslational disturbances, including reduced eNOS phosphorylation at its activation sites, low levels of its cofactor tetrahydrobiopterin and increased interaction with caveolin and asymmetric dimethylarginine [13–16]. In addition, elevated oxidative stress leads to a further decrease of NO due to its scavenging by radical oxygen species (ROS) to form peroxynitrite [12, 17].

On the other hand, an increased activity of different *endogenous vasoconstrictors* has been demonstrated in the cirrhotic liver, including alpha-adrenergic tone, endothelin, norepinephrine, angiotensin II, vasopressin, leukotrienes and thromboxane A_2 [6, 12, 18]. Clearly, these vasoconstrictive contractile systems contribute to the cirrhotic liver microcirculatory dysfunction. The phospholipase A_2–cyclooxygenase-1–thromboxane A_2 (PLA_2–COX1–TXA_2S) molecular axis represents the most extensively characterised [19]. These pathways are upregulated in LSEC and KC from cirrhotic livers, and their blockade significantly improves the hepatic microcirculation in cirrhosis [20].

COX1-TXA_2 and the NO systems reciprocally influence each other in the cirrhotic liver endothelium [21]. Inhibition of TXA_2 production results in increased

NO levels, and NO supplementation results in reduced TXA_2 production. Thus, both abnormalities act synergistically worsening cirrhotic liver microcirculatory dysfunction.

A major advance in the regulation of the hepatic microcirculation has been the demonstration that the *transcription factor Kruppel-like factor 2* (KLF-2) plays a key role maintaining a normal hepatic endothelial phenotype, as it regulates the transcription of several endothelial protecting genes, including eNOs, thrombomodulin and angiopoietin [22–25]. The physiological stimulus inducing KLF-2 expression is shear stress. Overexpressing KLF-2 by means of transfecting cirrhotic rats with adenovirus encoding the KLF-2 gene results in a marked amelioration of portal hypertension, which is due both to decreased fibrogenesis, increased NO availability, and reduced hepatic vascular tone [23]. Decreased fibrogenesis is mainly derived from its capacity to deactivate and promote the apoptosis of HSC, through a crosstalk between LSEC and HSC [23–25].

Finally, *angiogenesis* also contributes to the progression of cirrhosis. Angiogenesis inhibition targeting the VEGF and/or PDGF pathways showed marked positive effects on portal hypertension [26, 27]. Very recent data introduced two interesting novel concepts regarding targeting angiogenesis in cirrhosis: (1) VEGF has a dual role in cirrhosis, it promotes fibrogenesis during disease progression, but it is completely necessary for fibrosis resolution [28]. (2) Inhibition of pathological angiogenesis through the upregulation of the endogenous angiogenesis inhibitor vasohibin-1 or of pigment epithelium-derived factor (PEDF) had remarkable beneficial effects on cirrhosis and portal hypertension, totally comparable to exogenously administered antiangiogenic drugs [29, 30].

New Treatments

Statins

Statins have marked vascular beneficial effects that go beyond the decrease in cholesterol synthesis. These so-called pleiotropic effects of statins are thought to be responsible for most of their impact in decreasing cardiovascular mortality in patients with atherosclerosis. Although it was well known that statins (mostly simvastatin) enhanced NO availability by enhancing AKT-dependent eNOs phosphorylation and activity, and by stabilising eNOS mRNA, it was recently shown that most of these beneficial effects of statins were due to their ability to induce the expression of KLF2, an effect in which they are as powerful as shear stress [25, 31]. Subsequent experimental studies showed that simvastatin administration enhances NO production by the abovementioned mechanisms, ameliorates liver microvascular dysfunction, and decreases portal pressure and fibrogenesis in cirrhotic rats [32], effects that were confirmed using atorvastatin [24]. Atorvastatin-decreased portal pressure not only by NO-mediated hepatic vasorelaxation but also through RhoA/Rho-kinase-linked mechanisms [33].

Subsequently, a phase II randomised controlled trial demonstrated that simvastatin administration to patients with cirrhosis and portal hypertension was safe and allowed to moderately decrease portal pressure, both when given alone or on top of non-selective beta-blockers (NSBBs) [34]. The effect of simvastatin in portal pressure occurred without any decrease in liver blood flow, implying a decrease in HVR. Moreover, patients receiving simvastatin, but not those receiving placebo, had a marked improvement of quantitative liver function tests, suggesting an amelioration of metabolic exchange at the level of liver microcirculation, altogether very likely reflecting decreased liver fibrosis [34]. These findings provided the rationale for exploring the therapeutic benefit of simvastatin versus placebo administration in a double-blind multicentre clinical trial performed in 158 patients with cirrhosis that were randomised 5 days after admission for a variceal bleeding episode. The results of this study, reported in abstract form [35], showed that simvastatin administration did not significantly decrease the probability of rebleeding, but that markedly improved survival, which was especially evident in patients with moderately severe liver failure. The final results of this trial are due soon and would allow a better appraisal of the beneficial effect of simvastatin therapy in patients with cirrhosis.

Simvastatin has other potential beneficial effects, as it has been shown to improve liver preservation after cold ischemia and warm reperfusion injury and to prevent liver microcirculatory dysfunction due to LPS administration, which suggests a potential beneficial effect in cirrhotic patients during bacterial infections or shock [36, 37].

Antioxidants

As mentioned before, antioxidants have beneficial effects in cirrhosis by reducing liver injury and enhancing NO availability. Apart from experimental studies, such beneficial effects have been shown in patients with cirrhosis given either high doses of IV vitamin C or a small dose of dark chocolate per os [38, 39]. Both treatments, given short term as a single administration, were able to improve liver microcirculatory dysfunction, as shown by an attenuated postprandial increase in portal pressure after a test meal, despite a similar increase in liver blood flow.

A new and promising antioxidant is recombinant human manganese superoxide dismutase (rMnSOD), a formulation that incorporates a lead peptide allowing its entrance into cells. Administration of rMnSOD to cirrhotic rats improved portal pressure and oxidative stress and markedly decreased liver fibrosis, suggesting that this compound may have potential for clinical use [40].

Antiangiogenic Treatments

Antiangiogenic treatments have resulted in reduced formation of portal–systemic shunts, decreased splanchnic vasodilatation, improved portal pressure and decreased

fibrogenesis in cirrhotic rats. This was first achieved by using either monoclonal antibodies to VEGF, PDGF (or both) or administering multikinase inhibitors as sunitinib or low-dose sorafenib [26, 27]. In another study, rapamycin was shown to markedly decrease splenomegaly in rats with prehepatic portal hypertension [26].

All these strategies, however, are hampered by the potential toxicity of interfering with physiological angiogenesis in vivo. Although no signs of toxicity were observed in rats receiving low doses of sorafenib (20 times lower than those used in oncological applications) [27], this possibility prevented long-term clinical studies to assess the effects of sorafenib on portal hypertension in cirrhosis. Because of that, the recent demonstration that enhancing the expression of endogenous angiogenesis modulators (VASH, PEDF) [29, 30] allows an effective suppression of angiogenesis and fibrogenesis in cirrhosis offers a new way of treatment with a much lower risk of interfering with physiological angiogenesis. On the other hand, the beneficial effects of low-dose antiangiogenic therapy on portal hypertension can be potentiated by associating an NSBB [41].

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Consensus Statements: Session 2—Impact of Etiological and Anti-fibrotic Therapy

17

Jaime Bosch, Rafael Bañares, Virginia Hernandez-Gea, Markus Peck-Radosavljevic, Emmanouil A. Tsochatzis, Alexander Zipprich, and Wim Laleman

J. Bosch, MD, PhD, FRCP (✉)
Hepatic Hemodynamic Laboratory, University of Barcelona, Hospital Clinic-IDIBAPS, Barcelona, Spain

Inselspital-Bern University, Bern, Switzerland

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

Hepatic Hemodynamic Laboratory Hospital Clinic, Barcelona, Spain
e-mail: jbosch@clinic.ub.es

R. Bañares, MD, PhD
Digestive Disease Department and Liver Unit, Hospital General Universitario Gregorio Marañón, IISGM CIBEREHD, Madrid, Spain

Facultad de Medicina, Universidad Complutense, Madrid, Spain

V. Hernandez-Gea
Liver Unit, Hepatic Hemodynamic Unit, Hospital Clinic, Barcelona, Spain

M. Peck-Radosavljevic, MD
Abteilung Gastroenterologie and Hepatologie, AKH and Medical University of Vienna, Vienna, Austria

E.A. Tsochatzis
Institute for Liver and Digestive Health, Royal Free Hospital and University College, London, United Kingdom

A. Zipprich
First Department of Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle, Germany

W. Laleman, MD, PhD
Department of Liver and Biliopancreatic Disorders, University Hospitals Leuven, KU Leuven, Leuven, Belgium

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- Management of patients with cirrhosis should focus on preventing the advent of all complications while in the compensated phase (1b;A).
- Due to different prognosis, patients with compensated cirrhosis should be divided in those with and without clinically significant portal hypertension (CSPH) (1b;A). The goal of treatment in the first is to prevent CSPH while in the second is to prevent decompensation.
- The concept of CSPH is HVPG driven and cannot completely be substituted at present by noninvasive tools (NIT) (1b;A).
- Etiological treatment of the underlying liver disease may reduce portal hypertension and prevents complications in patients with established cirrhosis (1b;A) (unchanged).
- HVPG change is an acceptable surrogate of clinical outcome in patients with non-cholestatic cirrhosis (2b;B). An HVPG change of 10 % or more is to be considered significant (1b;A).
- Obesity worsens the natural history of compensated cirrhosis of all etiologies (1b;A). A lifestyle modification with diet and exercise decreases body weight and HVPG in cirrhosis with obesity (2b;B).
- Alcohol abstinence should be encouraged in all patients with cirrhosis irrespective of etiology (2b;B).
- The clinical use of statins is promising and should be evaluated in further phase 3 studies (1b;A).

Research Agenda

- Studies should focus on tools, either invasive (e.g., quantitative fibrosis assessment with CPA) and/or preferably noninvasive (e.g., elastography, biomarkers, or combinations or other means), to predict/select patients at risk of decompensation in liver diseases of different etiology.
- Anti-fibrotic strategies and approaches to target, among others, the coagulation system, FXR pathway, renin-angiotensin system, angiogenesis, and the gut-liver axis should be further explored for prevention of decompensation in patients with cirrhosis and CSPH.

Part IV

The Gut Microbiome and Cirrhosis

The Gut Microbiome and Cirrhosis: Basic Aspects

18

Reiner Wiest

Abbreviations

AMP	Antimicrobial peptide
BSH	Bile salt hydrolase
BT	Bacterial translocation
CFU	Colony forming units
FXR	Farnesoid X receptor
GI	Gastrointestinal
HFD	High-fat diet
HIP/PAP	Hepatocarcinoma-intestine-pancreas/pancreatic-associated protein
HT	Hydroxyl-tryptamine
NE	Norepinephrine
SIBO	Small intestinal bacterial overgrowth

Introduction

It is impossible not to notice the enormous surge in human microbiome research currently underway around the world. For the past decade, new molecular methods have started to unlock the secrets of this unseen universe, and suddenly it is dawning on us that human individuals are not the dominant life form in the symbiosis of our existence. This is based on the finding that we are only 10 % human but 90 % microbial when a comparative count of cell numbers is taken into consideration [1]. It is now clear that alterations of the gut microbiome may lead to dysregulation of immune responses both in the gut and in distal effector immune sites including the central nervous system, liver, kidney, lungs, skin, and cardiovascular system.

R. Wiest, MD
Bauchzentrum, Gastroenterology, Freiburgstrasse, Inselspital, University for Visceral Surgery and Medicine, Bern, Switzerland
e-mail: Reiner.wiest@insel.ch

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Multiple studies indicate that disturbance of our microbial ecosystems at critical points in development (in particular, early childhood) may result in long-lasting damage that is not easily reversible and may lead to later susceptibility to chronic diseases such as inflammatory bowel disease, asthma, atopy, diabetes, obesity, and even autism. The list of diseases postulated to be modulated by the microbiota increases constantly and includes not only liver diseases (fibrogenesis, complications of cirrhosis, nonalcoholic and alcoholic liver disease) [2], carcinogenesis [3], infections (*Clostridium difficile*) [4], and others such as chronic inflammatory bowel disease (ulcerative colitis and Crohn's disease) [5], irritable bowel syndrome [6], celiac disease [7], rheumatism [8], multiple sclerosis [9], autism [10], schizophrenia [7], depression [11], cardiovascular disease [12], and Alzheimer's disease [13]. In this chapter focus will first be on the human microbiome in terms of its diversity, physiological functions, and parameters modulating its composition and function. In the second part cirrhosis and its effect on these modulators and associated changes in the microbiome will be covered. Parts of this chapter have been covered before a) Handbook of gastroenterology and liver diseases; editors: Pier Alberto Testoni and Massimo Colombo; Chapter: The intestinal microbiota by Andrew MacPherson and Reiner Wiest; b) J. Hepatology 2014; vol. 60; 197–209 by R. Wiest, M. Lawsson, M. Geuking; Pathological bacterial translocation in liver cirrhosis.

Background and Definitions

There are approximately 5×10^{30} bacteria on Earth, forming a biomass which exceeds that of all plants and animals. In humans, about 400 m^2 of intestinal epithelial surface is colonized by approximately 100 trillion microbial cells which is more than tenfold the total number of cells in the human body. The bacterial metagenome of this microbiota in fact may exceed the human by 100-fold. If sheer number is any measure of significance, the microbiota of the gut undoubtedly play a critical role in gastrointestinal health and disease.

Bacteria are the main type of microbes present in the gut. Therefore, any human individual coexists with an enormous number of microorganisms and the mutually dependent "life together" of different species is called "*symbiosis* (win-win situation)". In *commensalism* a "win-zero" situation exists since one member of the relationship derives benefit while causing little or no harm to the other. In contrast, situations with negative outcome to one member include *parasitism* ("win-lose"), *amenalism* ("zero-lose"), and *competition* ("lose-lose") between microbes.

The normal state of the human intestinal microbiota is called normobiosis. In contrast, the term "*dysbiosis*" is ill defined but relates to an undesirable alteration of the microbiota resulting in an imbalance between protective and harmful bacteria. Such dysbiosis has been evidenced in most diseases that are known to be influenced by the microbiota. *In principle, a healthy microbiota is defined by high diversity and an ability to resist change under physiological stress. In contrast, microbiota associated with disease is defined by lower species diversity, fewer beneficial microbes, and/or the presence of pathobionts.*

Table 18.1 Taxonomic ranks

Formal rank	Example
Domain	Bacteria
Phylum	Proteobacteria
Class	Gamma-Proteobacteria
Order	*Legionellales*
Family	*Legionellaceae*
Genus	*Legionella*
Species	*Legionella pneumophila*
Subspecies	*Legionella pneumophila* subsp. *pneumophila*

However, before discussing healthy versus cirrhotic conditions with dysbiosis, a clear nomenclature needs to be delineated. Bacteria can be diverse in many aspects and hence differ from one another in many ways. Taxonomy classifies bacteria based on mutual similarity or relatedness into (Table 18.1) *domain, phylum, class, order, family, genus,* and *species*. Within this system, genus of bacteria resembles a collection of different species, each sharing some major property that defines the genus. Bacterial *richness* is the number of different species represented in an ecological community. Species richness is simply a count of species, and it does not take into account the abundances of the species or their relative abundance distributions. In contrast, species diversity takes into account both species richness and species evenness. In contrast, evenness reflects the relative abundance with which each species is represented in an ecosystem. An ecosystem where all the species are represented by the same number of individuals has high species evenness. An ecosystem where some species are represented by many individuals and other species are represented by very few individuals has a low species evenness.

Prebiotics are nondigestible fiber compounds that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth and/or activity of advantageous bacteria that colonize the large bowel by acting as substrate for them. In contrast, *probiotics* are defined by the World Health Organization as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host." The probiotic candidate must be a taxonomically defined microbe or combination of microbes (genus, species, and strain level). It is commonly admitted that most effects of probiotic are strain specific and cannot be extended to other probiotics of the same genus or species. Finally, *synbiotics* refer to nutritional supplements combining probiotics and prebiotics in a form of synergism.

Physiology of Microbiome

Functions of Microbiota

The intestinal microbiome can be compared with a previously unknown organ in terms of its effects. Indeed, the gastrointestinal tract is the greatest contributor to a

microbial-host interaction by virtue of housing the largest number of microbes in the body and by providing an opportunity for these organisms to influence digestion, metabolism, and host immunity. Beneficial effects of the intestinal microbiota have been well known for decades.

1. They are important to *salvage energy* from otherwise indigestible foods [14]. This delivers up to 10 % of daily energy requirements. Chances for adipositas increase with enhanced abundance of firmicutes which can metabolize complex carbohydrates into sugar and lipid molecules increasing energy delivery to the host. It has been calculated that a 20 % increase in Firmicutes and a corresponding decrease in Bacteroidetes can be associated with an increase in energy absorption equivalent to 150 kcal/day. Another example, co-colonizing germ-free mice with *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii* increase body weight and accelerate efficacy of bacterial fermentation. In the lower intestine, anaerobic fermentation of soluble fibers by microbiota produces short-chain fatty acids (SCFAs), key energy molecules that have a recent identified leading role in the intestinal gluconeogenesis, promoting beneficial effects on glucose tolerance and insulin resistance. These SCFAs such as butyrate, acetate, and propionate are important substrates for the intestinal epithelium and even modulate epithelial function. Besides being a major source of SCFAs microbial fermentation also affects energy salvage via several neuroendocrine mechanisms, e.g., release of peptide YY and glucagon-like peptide.
2. Metabolism of commensal bacteria provides the host with *vitamins* including cobalamin (vitamin B12); pyridoxal phosphate (the active form of vitamin B6), which is involved in several enzymatic interconversions in amino acid metabolism; pantothenic acid (vitamin B5); niacin (vitamin B3); biotin; tetrahydrofolate; and vitamin K [15]. Most of these are essential for human health and survival. Food-related lactic acid bacteria as well as human gut commensals such as bifidobacteria can de novo synthesize and supply vitamins. This is important since humans lack the biosynthetic capacity for most vitamins and these must thus be provided exogenously. The microbiota also affects the absorption of key minerals. Perhaps the best characterized micronutrient in terms of its interaction with both the microbiota and the immune system is iron. Early studies in gnotobiotic animals showed a link between the gut microbiota and the development of iron deficiency. Germ-free but not conventionally raised rats become anemic when fed with a low-iron diet. The germ-free rats also show increased loss of iron in their feces compared with their conventionally raised counterparts.
3. In addition to diet-derived macronutrients, the microbes residing in the gastrointestinal tract may be exposed to a variety of *xenobiotic* compounds (antibiotics, other drugs, and diet-derived bioactive compounds) [16]. Metabolites of microbial origin modulate expression and activities of a range of host enzymes, including those of major xenobiotic-metabolizing cytochrome enzymes. By this, specific microbes can activate or deactivate xenobiotics altering the effects of different therapeutic agents, for instance, the efficacy of multiple drugs, e.g., anti-colon-cancer drug irinotecan.

4. The human microbiota helps to protect the gastrointestinal tract from enteric infections by taking up space in the microbial niche *limiting access for pathogens* and thus providing colonization resistance [17]. In addition, bacteria-derived products such as peroxides and bacteriocins provide a natural defense against pathogens. Impressively, in presence of a normal microbiota, oral ingestion of 10^6 *Salmonella typhimurium* is necessary to cause gastrointestinal infection, whereas after streptomycin treatment even as little as 10 salmonella bacteria are sufficient to trigger infection. Moreover, the commensal microbial arsenal protects the host from radiation-induced diarrhea.
5. Finally, the commensal intestinal bacteria are key modulators of the *human immune system* [18]. Communication between the microbiota and the host establishes and maintains immune homeostasis, enabling protective immune responses against pathogens while preventing adverse inflammatory responses to harmless commensal microbes. For instance, germ-free mice are highly susceptible to a variety of intestinal pathogens and present with altered mucosal immune responses. This relates to reduced numbers of intestinal immune cell types such as particularly adaptive immune cells (e.g., Th1-, Th17, total CD4 T-, B-lymphocytes) and mucosal barrier cells (e.g., goblet and Paneth cells).
6. *Brain functions* [19]: The gut microbiota is involved in developmental programming of the brain and stress response systems. There is now good evidence from studies in adult animals that gut bacteria influence brain chemistry and behavior. Change in the hypothalamic-pituitary-adrenal axis response to stress is a common effect of modifying the gut microbiota. The vagus nerve plays a critical role in mediating effects of certain gut microorganisms on the brain and subsequently behavior.

Composition of Intestinal Microbiome

The intestinal microflora consists of a dynamic mixture of microbes with a different composition across the GI tract and considerable quantitative and qualitative differences among individuals. However, diversity of the microbiota is remarkably stable in each human individual in healthy conditions from day to day and even across many years. Corresponding to the most dominant bacteria within the intestine humans can be classified into different microbiota types, so-called enterotypes [20], in which specific indicator bacteria dominate: *Bacteroides*, *Prevotella*, and *Ruminococcus* – a large fraction of the dominant species appear to be specific to the subject. With regard to strains, stability is much less clear and will depend on the subject.

Since the vast majority of intestinal bacteria are not cultivable, it is only since new high-throughput technologies such as pyrosequencing of 16sRNA are available that the full microbial richness in the gut has been unraveled. Within the human population, the microbiome varies from several hundreds to up to 40,000 species [1, 21]. However only 30–40 species amount to about 98–99 % of the microbiota, and Firmicutes and Bacteroidetes are the predominant intestinal phyla across all vertebrates. The remaining intestinal bacteria, accounting for less than 20 % of the total

population, belong to the Proteobacteria, Fusobacteria, Actinobacteria, Verrucomicrobia, and Spirochetes.

Besides simple description in terms of quantity and composition of bacterial consortia, it is becoming more and more clear that bacteria-derived metabolites/products determine their role for disease processes. In fact, production of microbiota-related metabolites can change without detectable changes in the organization of the intestinal microbiota. This shift in focus from determining "*who is there*" toward understanding "*what are they doing*" is driving current studies of the human microbiota [22].

Basic differences in microbiome along the GI tract and across the GI wall: In any mammal the concentration of bacteria gradually increases along the intestinal tract. The proximal small intestine (duodenum, jejunum) is sparsely populated with bacteria; however, from the ileum on, there is a sharp increase in microbial density, from 10^5 colony-forming units (CFU)/ml in the jejunum to 10^8 in distal ileum and cecum up to 10^{12} in the colon. Small intestinal bacterial overgrowth (SIBO) is defined as more than 10^5 colony-forming units/ml jejunal aspirate and/or detection of colonic type (anaerobic) bacteria [23]. In addition to this longitudinal distribution, there is also a vertical dimension since the mucus compartment is dominated by bacterial species that differ from luminal species [24]. Bacteria that colonize this niche are very stable in composition over time and being remarkably similar from the ileum to the rectum for a given individual.

Modulators of Microbiota

Intrinsic	Extrinsic
Motility	Diet, alcohol
Gastrointestinal secretions: e.g., bile	Prebiotics, probiotics
Host genes: e.g., NOD2	Medications: e.g., antibiotics, proton pumps
Antimicrobial peptides: e.g., α-defensins	Nervous system and stress
Mucus	Environment, hygiene

Extrinsic factors such as dietary choices, hygiene, stress, alcohol consumption, exercise, and medications can change the ecology and function of the microbiota. In contrast, endogenous modulators of the microbiome include, besides others, host genotype, gastric, pancreatic, and bile secretion, intestinal motility, as well as extent and composition of antimicrobial peptides and mucus. That these endogenous and exogenous modulators can sometimes not completely be separated may be seen by the capability of the brain to modulate the microbiota: the hypothalamic-pituitary axis and the autonomic nervous system and its modulation of the enteric nervous system affect the environment of the intestinal microbiota. They can alter motility patterns in different regions of the intestine, as well as epithelial permeability, luminal secretion, mucosal immune function, and possibly intraluminal release of neurotransmitters from enteroendocrine and other cells in the gut. All this, for instance, can be affected by exogenous stress mediated by the brain.

Extrinsic Modulators

Diet

Diet: The greatest change in the composition of the infant's intestinal microbiota occurs with the introduction of solid foods. After 2–3 years of age, the microbiome is relatively stable. This stability may relate to the vast capacity of intestinal bacteria to adjust their metabolic function and alter substrate utilization depending on the source of substrate abundance. For example, the abundant intestinal bacterium *Bacteroides thetaiotaomicron* undergoes changes in gene expression that allow it to predominantly metabolize host-derived glycans when dietary sources of these molecules are unavailable [25]. These glycans come from the shedded epithelium being rich in phosphatidyl components of cell membranes. In fact, it is estimated that from the known physiological turnover of mucosal epithelium, about 100–200 g of such glycans can be available per day.

However, the established microflora and individual bacteria can change their metabolic profile at a genomic level also in dependency on the type of food being consumed. Ultimately species more suited to the energy source available will grow better and divide faster [26]. For instance, a diet high in fat in rodents has been associated with reduced diversity and increased ratio of firmicutes to bacteroidetes as well as a bloom of proteobacteria [27]. Agrarian-based diets (high in fruits, vegetables, and fiber) in contrast have been reported repeatedly to lead to higher abundance of *Prevotella*, lower amounts of *Bacteroides*, and overall greater microbial richness. These changes induced by agrarian diet are thought to associate with better health compared with Western diets (which are high in meat and fat) [28]. One potential explanation for this may relate to the greater production of SCFAs derived particularly from fibers by the intestinal microbiome. In fact, humans cannot digest on their own many fibers (e.g., plant polysaccharides) because our genomes do not encode the large repertoire of glycoside hydrolases and polysaccharide lyses needed to cleave the varied glycosidic linkages present in these glycans. Hence, bacteria – providing the missing enzymes – do this job for us by microbial fermentation of which SCFAs (i.e., acetate, propionate, and butyrate) are the end product. These SCFAs not only act as energy source but have been proposed to increase mucosal immune tolerance through the activation of G protein-coupled receptors and the subsequent activation of T regulatory cells [29]. Not only distinct major differences in composition of daily food (western vs. agrarian) but also minor ingredients such as sweeteners [30] or emulsifiers [31] have prominently been reported to alter the mouse microbiota and are even more fascinating than those changes in microflora associated with glucose intolerance and even development of metabolic syndrome, respectively [30, 31]. Finally food deprivation and starvation have been associated with changes in the microbiome as well [32]. Hitherto the microbiome was shown to play an important role in the development of kwashiorkor disease, a severe form of malnutrition [33]. In this study, the fecal microbiota of Malawian twins that were discordant for kwashiorkor was transplanted into mice. When fed with a Malawian diet, weight loss and metabolic perturbations were more severe in the mice that

received microbiota from the twin that had kwashiorkor compared to those that received microbes from the unaffected twin.

Best evidence for the huge impact of diet on the microbiome however comes from a simplified in vivo model of gnotobiotic mice colonized with defined collections of sequenced representatives of the various phylotypes present in the human gut. By this approach the Gordon Laboratory investigated the perturbations of four defined ingredients in the host diet [34]. In previously germ-free animals colonized with 10 defined bacterial species, refined diets in which each ingredient represented the sole source of a given macronutrient (casein = protein, corn oil = fat, cornstarch = polysaccharide, and sucrose = simple sugar) were given. *E. coli* (besides *C. symbiosum*) were the only bacteria with more than one variable significantly associated with their abundance, namely, casein and sucrose. Increasing concentrations in casein led to increased abundance of *E. coli* (as did 6 other species) among the 10-bacteria microbiome, of which three species decreased in abundance. In fact, in *E. coli* (but not in those species with less preference and hence abundance), high expression of mRNAs involved in pathways using amino acids (such as casein) as substrates for nitrogen, as energy, and/or as carbon sources was observed. Moreover, in this model more than 60 % of the changes introduced by dietary measured could be predicted highlighting the extent to which host diet can explain the configuration of the microbiota, at least for refined diets in which all of the perturbed diet components are digestible. To which degree this will also apply to humans and human diets whose ingredients are only partially known and/or digestible is not known so far. Finally, it has also been proposed that the bacterial microbiome is heavily influenced by the household environment. This is a primary determinant of the individual's bacterial microbiome and humans are the primary vector of bacterial transmission between people living within the same household [35].

Medications

Medication: Antibiotics are among the most potent agents to alter gut flora. Within 1 week of intake of beta-lactam antibiotics in hospitalized patients, a drastic shift occurs toward the predominant active taxa which are members of the *Streptococcaceae*, *Clostridiaceae*, and *Bacteroidaceae*, which are considered as "non-autochthonous" groups of bacteria [36]. In contrast, information about the degree and timing of restoration of a normal autochthonous microbiome is lacking. Another well-studied drug with an effect on the microbiome is proton-pump inhibitors [37] (see below). Finally, most likely all drugs known to affect motility and gastric acid and bile secretion will more or less affect the microbiome but data are sparse (see below).

Stress/Nervous System

*Stress/nervous system: S*tress has multiple effects on the gut including alterations in intestinal barrier, motility, visceral perception, permeability, and secretion and the microbiome [38]. One of the key effectors in situations of increased stress is the sympathetic nervous system. The small and large intestine are densely innervated by sympathetic neurons being responsible for a large proportion of the body's

norepinephrine (NE) and high concentrations of NE-containing neurons terminate within the submucosal plexus and intestinal mucosa [20–23]. It is important to stress that sympathetic nerve fibers not only terminate in vessel walls in order to control vascular tone but also the gut-associated lymphatic tissue faces rich local adrenergic input [39]. NE modulates gut motility, submucosal blood flow, and transepithelial ion transport [40]. The extrinsic sympathetic input also affects the microbiota, the mucosal barrier, and the local biodefensive functions. When the activity of the sympathetic nervous system is high, NE may spill over into the intestinal lumen where it is taken up by bacteria. In fact, free luminal catecholamines have not only been evidenced but surprisingly enough are modulated by the microbiota [41]. For instance, germ-free mice present with lower levels of free catecholamines in the gut lumen as compared to animals with normal flora and inoculation of *E. coli* strain into germ-free animals induce a substantial amount of free luminal catecholamines [41]. These enhanced luminal catecholamines have been proposed to promote bacterial growth of gram-negative flora, e.g., *E. coli*, [42] but also to modulate bacterial chemotaxis, motility, and even adherence to epithelial cells and virulence [43]. On the other hand, the microbiota has vice versa been proposed to actually tune the enteric nervous system [44] which closely interrelates with motility (see below).

Intrinsic Modulators

Gastrointestinal Secretions

Gastrointestinal secretions, although not all addressed so far in detail as to their effect on the microbiome, are most likely all influencing the microbiome to some degree. For instance, although trypsin is known to be a potent activator of several antimicrobial peptides [45], no valid data as to the impact of pancreatic insufficiency on the intestinal antimicrobial arsenal do exist in humans. In contrast, well accepted is the fact that when the *gastric acid* barrier is reduced, the normal bacterial milieu is changed and an "oropharyngeal" flora is increasingly observed in the upper gastrointestinal tract [37]. Loss of gastric acid can be due to either drug therapy, autoimmune gastritis, *Helicobacter pylori* colonization, or surgery. As for proton-pump inhibitors in the stomach, the abundance and location of *Helicobacter pylori* and other bacteria are altered. In the small bowel, proton-pump inhibitors cause polymicrobial SIBO and have been even associated with the diagnosis of celiac disease. In the colon however, proton-pump inhibitors associate with incident but not recurrent *Clostridium difficile* infection.

Antimicrobial Peptides (AMPs)

Antimicrobial peptides (AMPs): AMPs rapidly kill or inactivate microorganisms by attacking the basic cell wall structures of bacteria and constitute one of the most evolutionarily ancient mechanisms of immune defense. Bacterial cell walls include the membrane, peptidoglycan layer, and, in gram-negative bacteria, the outer membrane. This target is ideal because it is difficult for microorganisms to modify without a consequent loss in overall fitness. This reduces the likelihood that bacteria will

develop resistance to such AMPs. They include defensins, cathelicidins, resistin-like molecules, bactericidal-permeability-inducing protein, and lectins [46]. AMPs basic functions are to help maintain homeostasis at the intestinal host-microbial interface. They regulate the composition of commensal bacterial communities in the intestinal lumen and restrict access of the intestinal microbiota to host tissues. However, the diversity in susceptibility and/or resistance to AMPs for various consortia is far from being understood. *Bacteroides thetaiotaomicron* has been shown to exhibit up to 2400-fold increased resistance to most AMPs as compared to enteropathogens or *Escherichia coli* [47] and hence may present a survival advantage over those and others in situations of increased AMP secretion such as gut inflammation. This fitness and resistance to AMPs have been demonstrated to be mediated by removal of a phosphate group in the lipid A anchor of the LPS molecule (LpxF). In fact, during *Citrobacter*-induced gut infection and associated inflammation, mutated and thus LpxF-missing *Bacteroides thetaiotaomicron* are depleted but not wild-type *Bacteroides thetaiotaomicron* [47]. This is the first example of how commensal-encoded mechanisms for persistence in the host during inflammation can complement the well-known host-encoded mechanisms for immune tolerance of the microbiota.

Lectins

Lectins are carbohydrate-binding proteins, of which one of the best evaluated and expressed throughout the small intestinal epithelium is REG3 (i.e., REG3a also known as hepatocarcinoma-intestine-pancreas/pancreatic-associated protein [HIP/PAP] or in mice Reg3y) [48]. REG3a binds to peptidoglycan on the bacterial target, and hence, its bactericidal activity is selective for gram-positive bacteria because peptidoglycan is generally accessible on the outer surfaces of gram-positive bacteria but is shielded by the outer membrane in gram-negative species. Another class of AMPs is cathelicidins. The single cathelicidin gene (CAMP in humans) encodes a precursor protein that can be cleaved at an alternate site to generate several active AMPs, including the lysozyme LL-37 and the murine peptide CRAMP (cathelin-related antimicrobial peptide). Both LL-37 and CRAMP exhibit broad spectrum antimicrobial activity against gram-positive and gram-negative bacteria as well as fungi.

Defensins

Defensins are small (2–6 kDa) cationic peptides divided into three groups, α-, ß-, and θ-defensins, of which only α- and ß-defensins have been identified in the intestinal tract. All mature defensins have broad range antimicrobial activity by disrupting the structure and function of microbial membranes being effective against gram-positive and gram-negative rods. α-Defensin genes are expressed only in a few cell types, which in humans are predominantly neutrophils and Paneth cells, strategically located at the bottom of each intestinal crypt just below the stem cell zone [49]. The secretion of AMPs by Paneth cells is directly linked to bacteria and lipopolysaccharide exposure [50]. In contrast, ß-defensins appear to be expressed constitutively by most epithelial cells in both the small and large intestine [51].

Transcriptional regulation of different subsets of AMPs occurs through distinct mechanisms. AMPs that do not depend on bacterial cues probably form a constitutive chemical barrier at the mucosal surface. Bacterial induction of other AMPs (e.g., alpha-defensins) could ensure that the inducible AMPs are produced only when needed, thus limiting the risk of unnecessarily altering intestinal microbial composition or compromising the beneficial contributions of the microbiota.

Mucus

Mucus: Mucin proteins secreted by specialized epithelial goblet cells create a layer of membrane-anchored negatively charged glycoproteins that prevents direct contact of bacteria with the microvillus membrane that results in a total of about 3 L of protein per day in humans [52]. MUC2 is the major secretory mucin and contains large amounts of O-glycan providing the high water-binding capacity [53]. Secretion of MUC2 is stimulated by a wide array of bioactive factors including microbes, products, toxins, inflammatory cytokines, hormones, neuropeptides, and reactive oxygen and nitrogen species [54]. The "firm" inner mucus layer contains four times as much mucin protein as the loose outer layer and likely traps immune exclusion molecules being transocytosed across the epithelium [55]. In addition the high density of mucin proteins in the inner mucus layer limits bacterial colonization [56]. In fact, the inner layer is generally thought to be sterile. Concentration of AMPs near the epithelial surface within the inner layer of mucus has been proposed to be at least partly responsible for the lack of any vital bacteria in this "vulnerable" and metabolically and immunologically most relevant niche. In contrast, the "loose" outer layer is the habitat for commensal bacteria that consume the mucus proteins as a carbon source [57] as well as specific binding sites for bacterial adhesins [58]. This, most likely, is the basis for the observed increased count of bacteria, particularly anaerobic bacteria in human biopsies of the small intestine as compared to luminal aspirates [59]. Thus, it is important to differentiate between bacteria that are found within the intestinal lumen and those inhabiting the mucus.

Bile

Bile: Bile acids are the main functional components of bile secretions that play a role in the emulsification of dietary lipids and also act as signaling molecules in the host, triggering host responses mediated at least in part by cellular farnesoid X receptor (FXR). FXR has gained much attention because of its crucial role in preserving intestinal epithelial integrity and protection from inflammation presumably by repression of NFkB signaling [60]. In my personal view, bile acids can be considered as "language" with which the liver and gut are communicating. In fact, the gut-liver axis works as cross-talk in both directions for which bile acids are the best example.

First, microbial imprinting on bile acid signature modifies pool size and hydrophobicity, thus contributing to bile acid enterohepatic circulation but also host metabolism. Colonic commensal bacteria perform partial dehydroxylation and removal of the glycine and taurine groups from primary bile acids forming the secondary bile acids generally referred to as bile salts. In detail, bacterial

7α-dehydroxylation, mainly by a small population of spore-forming members of Firmicutes, genus *Clostridium*, converts cholic acid into deoxycholic acid and chenodeoxycholic acid into lithocholic acid [61]. Moreover, bacterial bile salt hydrolase (BSH) enzymes in the gut cleave the amino acid side chain of glyco- or tauro-conjugated bile acids to generate unconjugated free bile acids (cholic and chenodeoxycholic acids). This bile salt hydrolase activity is a conserved microbial adaptation that is unique to the gut-associated microbiota and is distributed across the major bacterial divisions and archaeal species in the gastrointestinal tract. Bile salt hydrolase contributes to bile tolerance in gut bacteria. But, even more important, expression of cloned bile salt hydrolase enzymes in the gastrointestinal tract of gnotobiotic or conventionally raised mice significantly alters plasma bile acid signatures and regulates lipid/cholesterol metabolism, gastrointestinal homeostasis, and circadian rhythm in the liver and small intestine [62]. Fascinating per se is the observation that high-level expression of bile salt hydrolase in conventionally raised mice results in a significant reduction in host weight gain, plasma cholesterol, and liver triglycerides, demonstrating the overall impact of bile salt hydrolase activity on host physiology. An additional piece of the puzzle in this fascinating cross-talk can be appreciated by the fact that pharmacologically reducing the genus *Lactobacillus* within the microbiome and hence its bile salt hydrolase activity can ameliorate high-fat-diet-induced obesity [63]. This effect has been proposed to be mediated by the associated accumulation of intestinal tauro-b-muricholic acid which has been evidenced as natural FxR antagonist. In fact, high-fat-diet-fed intestine-specific FxR-null mice show lower diet-induced obesity [63].

Second, bile vastly impacts on the composition and function of the microbiome. For example, supplementing exogenous cholic acid in the diet leads to increases in firmicutes and dominant clostridia at expense of bacteroides and reduction in diversity [64]. These changes in fact may at least partly contribute to alterations associated with high-fat diets. In addition, exogenous cholic acid enhances the level of 7α-dehydroxylating bacteria up to 1000-fold [65], consistent with the hypothesis that increased primary bile acid secretion supports these bacteria in the gut. Mechanisms by which bile acids impact on the bacterial flora include, but are not limited to, their antimicrobial activity. Indeed, the bactericidal activity of bile acid molecules generally increases as the molecules travel from the duodenum down to the distal colon, the site where bacterial density is highest. By that, not only the composition of the microbiome but also the total number of bacteria is reduced by exogenous high-dose cholic acid [64]. This is not only mediated via direct bacteriostatic effects of bile acids luminally but also via bile acid-induced intestinal FxR stimulation and associated secretion of antimicrobial substances [66]. The question why specific strains are more resistant to bile acids and associated antimicrobial activity is not completely clear but *Enterobacteriaceae* bacteria (class Gammaproteobacteria) are known to be highly tolerant of bile acids [67]. This is consistent with the preferential detection of *E. coli* after high-dose exogenous cholic acid treatment [64]. Finally, besides these effects on bacteria per se, the bile has a trophic effect on the intestinal mucosa [68], decreases epithelial internalization of

enteric bacteria [69], exerts detergent actions with anti-adherence effects and binds, and neutralizes endotoxins [70, 71], all influencing gut homeostasis.

Host Genotype

Host genotype can influence the intestinal microbiota via the availability of attachment sites and host-derived resources; in fact, the fecal communities of cohabiting monozygotic twins before weaning differ in only 10–25 % of the detected 16S rRNA sequence variants. Moreover, in adulthood monozygotic twins share more similar microbiomes than non-twin siblings. So far no systemic delineation of how and to what degree individual host gene alterations impact on the intestinal microbiome in humans is available. However, one of the best studied examples is the genetic polymorphisms related to nucleotide-binding and leucine-rich repeat proteins, involved in intracellular recognition of microbes and their products, namely, the caspase-activating and recruitment domain-15 (CARD 15/NOD2) gene. The comparison of NOD2−/− and NOD +/+ mice utilizing principal coordinate analysis of unweighted UniFrac distances based on operational taxonomic units confirmed that mice clustered differently based on their genotype. In fact, genotype alone defined the prevalence of Rikenellaceae, Alistipes, Desulfovibrio, Bilophila, and Dehalobacterium [72]. Moreover, NOD2-genotype did also modulate the susceptibility to diet-induced changes in microbiome. In particular, only HFD-fed NOD2−/− mice displayed higher abundance of *Helicobacter* and *Peptococcaceae* and a lower prevalence of *Clostridium*. Most interestingly, by transfer of the microbiota from high-fat-diet-treated NOD2−/− to wild-type germ-free mice, it could be demonstrated that this gut dysbiosis represents an independent transmissible factor that contributes to metabolic inflammation and insulin resistance.

Host genotype may also select for the first gut colonizers and could contribute to determining disease risk as has been reported for infants with high risk of celiac disease by being HLA-DQ2 positive [73]. These infants have been shown to have higher proportions of Firmicutes (*Clostridium* species) and Proteobacteria (*Enterobacteriaceae*) and lower proportions of Actinobacteria (*Bifidobacterium* species) than those with low genetic risk (non-HLA-DQ-2/8 carriers). Finally, in addition to resource competition microbial interactions have long been recognized as important determinants of intestinal niches. Common interference mechanisms include the production of toxic metabolites and specific antimicrobial compounds, such as bacteriocines as well as phages.

Motility

Motility: Intestinal motility is regulated by an intrinsic nervous system, referred to as the enteric nervous system, in addition to regulation by the central nervous system. Although the enteral nervous system normally communicates with the central nervous system to regulate gastrointestinal motility, the enteric nervous system is capable of operating autonomously even if signals from the central nervous system are absent.

Changes in motility are known for a long time to impact on the microbiome. Particularly bacterial overgrowth in the small intestine (SIBO) has long been realized to occur frequently in conditions of increased intestinal transit time (e.g.,

scleroderma, diabetic neuropathy, or opioid medication) or altered intestinal anatomy associating with stasis (blind-loop syndrome or diverticula). SIBO has arbitrarily been defined as $>10^5$ CFU/ml or the presence of colonic bacteria in upper jejunal aspirate [74]. These bacteria produce various gases (particularly carbon dioxide, hydrogen, methane, and hydrogen sulfide as by-products of fermentation, which have both direct and indirect effects on the gut. These gases can lead to abdominal distension and bloating and may as well be causative for muscular relaxation perpetuating the reduction in motility).

Less delineated so far is the effect of the commensal flora per se on intestinal motility. However, it has been reported that the gut microbiota directly activates and regulates the development and maintenance of the enteric nervous system being at least in part mediated via TLR-2 and/or TLR4 signaling [75, 76]. Moreover, germ-free animals are known to present with slower gastric emptying and intestinal transit time along with decreased expression of neuromodulators as compared to animals with normal flora [77]. Factors that are proposed to be involved are (i) reduced colonic activation of intrinsic afferent primary neurons of the myenteric plexus and (ii) decreased steady-state activation of 5-HT receptor subtype 4-expressing cells in the colonic submucosa and muscularis externa. Most recently, spore-forming bacteria (mainly Clostridia) have been shown elegantly to be capable of accelerating intestinal transit time [78]. This effect was mediated by metabolites produced by those bacteria signaling to enterochromaffin cells promoting colonic 5-HT biosynthesis. Thus, gut microbes are actively regulating levels of 5-HT in the colon impacting on motility [78].

Overall

Overall: Many interactions among all of the stated influencing factors are still not delineated, and hence, even physiological aspects are far from being understood. For instance, controversial results from probiotic clinical trials do not only relate to various strains and composition of the treatment but also on host genetic factors (e.g., NOD2 status), environmental factors (e.g., diet), level of stress, as well as previous events with impact on the microbiome (e.g., gastrointestinal infections).

Changes in Microbiome and Modulating Factors in Cirrhosis

The Liver-Gut Axis

The liver-gut axis: The liver is positioned to filter, extract, and/or metabolize products/agents being absorbed by and/or permeated through the small and large intestine. By that it is not surprising to see that the gut-liver axis plays a key role in various liver diseases which have been reviewed elegantly beforehand [2]. Among them, most prevalent in Western countries are *alcoholic* and *nonalcoholic fatty liver disease* (NAFLD), and both can progress to steatohepatitis (ASH and NASH) and liver cirrhosis giving rise to hepatocellular carcinoma. For both entities key pathophysiological features are dysbiosis and SIBO as well as altered intestinal permeability. However,

shifts in bacterial composition vary in dependency on etiology of liver disease and mechanisms leading to changes in mucosal barrier are different between alcoholic and NAFLD. Nonetheless, in both entities, increases in portal venous levels of bacterial products/wall components (e.g., lipopolysaccharide) have been reported to contribute to liver injury. NAFLD is considered the hepatological manifestation of the metabolic syndrome in obese patients. Most interestingly, in genetically modified mice which develop massive NASH on a methionine/choline-deficient diet, this phenotype could be transferred between mice upon cohabitation, suggesting that the microbiota has itself the potential to induce inflammatory liver disease. This is exciting because it suggests that, at least in this animal model, a genetic defect consecutively modulates the intestinal microbiota and shapes their composition into a "disease-promoting phenotype." Animal studies have also clearly shown that intestinal microbiota contribute to progression of chronic liver damage driving liver fibrogenesis although human data are still awaited. Even more puzzling is the most recent finding of accelerated, enhanced fibrosis in germ-free conditions [79]. This once more underlines the key role of the microbiota for the liver and its health.

In contrast, multiple randomized clinical trials evidence the role of increased bacterial translocation (BT) in advanced liver cirrhosis for complications of portal hypertension. Factors promoting pathological BT in liver cirrhosis are SIBO, increased intestinal permeability, and deficiencies in host immunity aiming to clear translocated bacteria. The proof of concept on the role of the microbiota for *portal hypertension* however comes from a pivotal milestone paper by de Gottardi and coworkers [80]. Utilizing a portal-vein ligation model, mice colonized with intestinal microbiota presented with significantly higher portal pressure as compared to germ-free mice. The presence of bacterial flora was also associated with significantly increased portosystemic shunting and spleen weight. Although the mechanisms for this hemodynamic quite impressive effect are not completely delineated, an increased abundance of intestinal lymphatic and blood vessels was observed to be induced in portal-vein-ligated mice colonized by a standardized flora but not in germ-free mice. This strongly puts the microbiota also in the center of angiogenesis driven by bacterial components and/or products.

Mechanisms in Cirrhosis Contributing to Dysbiosis and Bacterial Overgrowth (Fig. 18.1)

Extrinsic

Diet

Diet: Data on the impact of diet in cirrhotic patients on the microbiome are lacking. However, protein malnutrition is a frequent finding in advanced cirrhosis and clearly affects outcome. Whether malnutrition and cachexia per se contribute to alterations in gut flora in cirrhosis has not been investigated but it is tempting to speculate that, by worsening intestinal barrier failure and hence supporting inflammation, it may well be driving and/or accelerating dysbiosis.

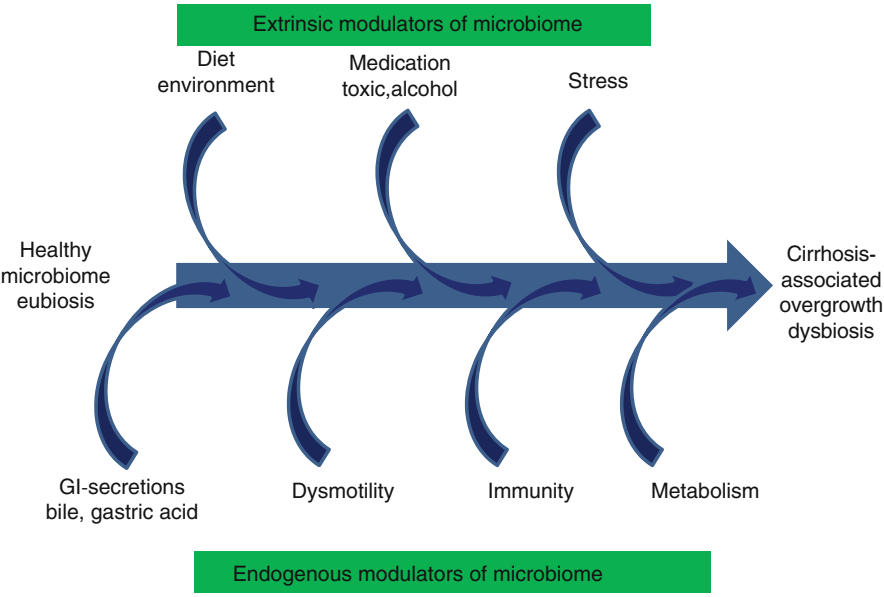

Fig. 18.1 Factors modulating microbiome and leading to dysbiosis/SIBO in cirrhosis

Alcohol, as highly prevalent causative agent in liver disease, however, has been addressed in terms of its effects on the microbiome. Data on human cirrhosis are hard to retrieve since patients with alcoholic etiology were not completely separately analyzed in mixed cohorts addressing compositional changes of the microbiome [81, 82]. Nonetheless, a significant increase of *Prevotellaceae* was described in alcohol-related but not hepatitis-B-driven cirrhosis [81]. In experimental animal conditions, ethanol feeding for 3 weeks was shown to lead to intestinal bacterial overgrowth, being accompanied by a relative abundance of Bacteroidetes (including *Prevotellaceae*) and Verrucomicrobia bacteria, while Firmicutes bacteria (including *Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Lactococcus*) were predominant in the control mice [68, 83]. A recent animal study showed that even longer alcohol ingestion for 8 weeks caused a decline in the abundance of both Bacteroidetes and Firmicutes phyla, with a proportional increase in the gram-negative Proteobacteria [84], similar to what is seen in cirrhosis (see below).

Medications

Medications: The portfolio of medications influencing the microbiome is large and includes, besides antibiotics, all drugs known to affect motility and gastric acid and bile secretion. Best investigated among those are *proton-pump inhibitors* [85]. Cirrhotics do alter their microbiota similar to healthy controls in response to a 14-day course of 40 mg/day omeprazole under constant diet conditions [86]. In more detail, relative *Streptococcaceae* abundance, normally abundant in saliva, significantly increased post omeprazole in controls (1 vs. 5 %) and cirrhosis (0 vs. 9

%). Moreover, the use of proton-pump inhibitors has been recognized to associate with potentially life-threatening infections, such as *Clostridium difficile*. Finally, the use of proton-pump inhibitors in cirrhosis has been shown to increase the risk of bacterial infections [86–88], particularly spontaneous bacterial peritonitis [86]. These detrimental effects of proton-pump inhibitors may also relate to non-microbiome-based mechanisms such as delay in gastric emptying and direct action on the immunological system (inhibition of neutrophil, cytotoxic T lymphocyte, and natural killer cell activity).

Sympathetic Nervous System

Liver cirrhosis leads to hyper activation of the sympathetic nervous system which is particularly pronounced in the splanchnic circulation, with concomitant exaggerated release of NE [89]. The impact of intestinal sympathetic hyperactivity on the gut barrier has been studied in CCl4-induced cirrhotic ascitic rats [90]. Splanchnic specific sympathectomy was able to prevent endogenous BT and ameliorated spreading of *E. coli* from the peritoneal cavity. Besides the observed improved bacterial phagocytosis after sympathectomy, additional proposed beneficial effects are accelerated intestinal transit time [91], prevention of gram-negative bacterial overgrowth [92], and improvement in gastrointestinal permeability [93, 94]. Propranolol has likewise been used and found to lower the rate of BT in experimental cirrhosis [91] as well as the incidence of infectious complications in cirrhotic patients [95]. In contrast to the sympathetic nervous system, parasympathetic input and effects on the microbiome and gut barrier have not been addressed in portal hypertension.

Intrinsic

Antimicrobial Peptides (AMPs)

Antimicrobial peptides (AMPs). Recently, compromised α-defensin antimicrobial host defense has been reported to predispose the host to pathological BT in experimental models of cirrhosis [62]. CCl4-induced ascitic cirrhotic rats with but not without BT to MLN present with a relative deficiency in Paneth cell defensins particularly in the small intestine. In contrast, level of ß-defensins is unchanged or elevated in presence of increased BT demonstrating a normal ß-defensin response in cirrhotic rats. The observed deficit in α-defensins was accompanied by a diminished in vitro antibacterial activity against various *Enterobacteriaceae*. In conjunction with this observation, mice deficient in the processing enzyme matrilysin that prevents the expression of active cryptidines enhances host colonization sensitivity to noninvasive *E. coli* species in the small intestine [63]. These changes may contribute to the observed alterations in gut flora in advanced cirrhosis. The potential mechanisms mediating the impairment in Paneth cell function in cirrhosis are so far unknown but appear not to relate to the level of portal hypertension since prehepatic portal hypertensive rats show no alterations in Paneth cell products along the GI tract [62].

Also intestinal antimicrobial lectins have been shown to be modulated in ethanol-induced chronic liver disease. The levels of messenger RNA and protein expression

of RegIIIβ and RegIIIγ were reduced after chronic alcoholic intake in mice at each segment of the small intestine with lowest levels being observed in the proximal small intestine where bacterial overgrowth was most pronounced [69]. This data was also confirmed in humans, as patients with chronic alcohol intake have downregulated RegIIIβ and RegIIIγ in the jejunum [70]. In addition, HIP/PAP expression was found to be markedly decreased in the cecum of ascitic cirrhotic rats with pathological BT as compared to animals without BT [71]. Therefore, deficiency in various AMPs (α-defensins, RegIII proteins) likely leads to decreased mucosal killing activity resulting in a shift of the bacterial composition facilitating bacterial overgrowth and increases in BT in cirrhosis.

Mucus

Mucus. Although levels of luminal bacteria are important in the development of infections in situations of bowel injury or perforation, levels of the adherent bacteria are more important in the development of BT [80]. In fact, mucosa-associated microbiome differs from stool flora in cirrhotic patients, particularly in those with hepatic encephalopathy [81]. In addition, recent elegant studies in alcoholic patients indicate increased mucus thickness in the duodenum suggesting induced changes by cirrhosis per se and/or alcohol [82]. Surprisingly, MUC-2-deficient mice exhibit lower plasma endotoxin levels and are protected from bacterial overgrowth in response to alcohol most likely due to increases in mucosal antimicrobial peptides (RegIIIα and RegIIIβ), further emphasizing the role of mucus as an active key player in host-microbial interactions and providing feedback signaling to immune responses [83].

Bile

Bile. In cirrhosis, marked alterations in bile acid homeostasis take place and have been summarized recently [96]. In brief, decreases in intestinal intraluminal concentrations of bile acids have been ascribed to decreased secretion and altered deconjugation by enteric bacteria. In fact, total fecal concentration of bile acids is decreased up to fivefold in cirrhosis [97]. De novo synthesis of primary bile acids diminishes with worsening of liver insufficiency. This has been attributed at least partly to inflammation inhibiting the classical pathway of CYP7A1-mediated production of cholic acid and chenodeoxycholic acid. In addition, secondary bile acids are vastly lacking for which the reported dysbiosis plays a key role. The reported reduction in the order *Clostridiales* with diminished (if not to say collapsed) availability of families capable of performing 7-alpha-hydroxylation (*Blautia*, *Lachnospiraceae*, *Ruminococcaceae*) in advanced cirrhosis explains an increasing lack in conversion of primary to secondary bile acids with worsening cirrhosis. Considering that the secondary bile acid deoxycholic acid is by far the most potent antimicrobial among bile acids, the observed luminal near absence of deoxycholic acid in advanced cirrhosis once more highlights the lack of antimicrobial activity as common key feature [98]. Supplementing bile acids (e.g., oral cholylsarcosine) indeed has been demonstrated to inhibit bacterial overgrowth preventing bacterial translocation and endotoxemia in cirrhotic rats [99]. This may well be mediated by its action on intestinal FxR as a more detailed look on the role of bile acids and stimulation of intestinal FxR reveals

[66]. Indeed intestinal FxR limits bacterial overgrowth and BT in bile-duct-ligated animals. A specific FxR agonist (GW4064) repressed bacterial overgrowth, attenuated mucosal injury, and reduced bacterial invasion into mesenteric lymph nodes in wild type but not in mice genetically deficient in FxR [96]. This clearly demonstrates the key role of intestinal FxR for intestinal barrier function and host-microbial interaction. In fact, activation of FxR by GW4064 led to the identification of several novel FxR target genes including those that promote antimicrobial defense. New fascinating data supporting this basic knowledge stem from studies on the newly available FxR agonist obeticholic acid. Obeticholic acid has recently been reported to improve intestinal antibacterial defense and permeability as well as to reduce gut bacterial translocation in CCl4-induced (unpublished, personal communication Prof. Albillos) and bile-duct-ligated cirrhotic rats [100]. Finally, in two different cirrhotic animal models (bile-duct ligation and TAA-induced cirrhosis), obeticholic acid has shown clear portal hypotensive action being mediated by lowering intrahepatic vascular resistance [100, 101]. Whether this hemodynamic effect is (at least partly) due to the stated intestinal action of FxR stimulation remains to be seen. But surely how FxR target genes and possibly others that have not been identified function to maintain intestinal homeostasis and modulate portal hypertension will be an active area of future investigations.

Genotype

Genotype: Considering the outlined role of bile and FxR signaling for the microbiome and intestinal barrier, the role of FxR genotype for the clinical endpoint spontaneous bacterial peritonitis [102] has been addressed. Patients with spontaneous bacterial peritonitis had a more than fourfold higher frequency of the rs56163822 GT genotype than patients without peritonitis. Moreover, this genotype increased the risk for spontaneous bacterial peritonitis by almost sevenfold and was confirmed as independent predictor of spontaneous bacterial peritonitis. Although the role of NOD2 for the microbiome has been outlined, data in cirrhotic conditions are lacking. Nonetheless, it has been established that mutant NOD2 represents a risk factor for spontaneous bacterial peritonitis in cirrhotic patients [103, 104]. However, it remains to be determined whether luminal and/or mucosa-associated changes in composition or function of bacteria are participating in this effect.

Motility

Motility: Decreased intestinal motility is well documented in liver cirrhosis [105, 106]. Prolongation of intestinal transit has been shown to be more severe in decompensated as compared to compensated cirrhotics and to correlate with the severity of liver disease (Child-Pugh score) [107]. In addition, presence of spontaneous bacterial peritonitis per se seems to aggravate dysmotility, since cirrhotic patients with history of spontaneous bacterial peritonitis present with more severe disturbances of small intestinal motility than those without prior peritonitis [108]. Dysmotility in cirrhosis has been proposed to be associated with impaired clearance within the small bowel, giving rise to a "colonic" flora (including *Enterobacteriaceae*, *Enterococcus* spp.). The pathogenesis of this dysmotility and delayed oro-cecal transit time in liver cirrhosis is most likely multifactorial, including autonomic

neuropathy, altered levels of neuropeptides, and effects of inflammatory mediators on bowel muscle and nerves. But likewise comorbidities such as diabetes and/or comedication can contribute. The clinical relevance of this can be appreciated by the fact that prokinetics, by accelerating oro-cecal transit time, ameliorate bacterial overgrowth, an effect which can help to prevent spontaneous bacterial peritonitis [109] and even may lead to improvement in liver function [106].

Quantitative Changes in Microbiota in Cirrhosis

Using the gold standard of culture of jejunal aspirate, the prevalence of SIBO in cirrhotic patients ranges from 48 to 73 % [110–114]. SIBO has been shown to be particularly frequent in patients with more severe liver disease [115, 116] and in those with a prior history of SBP and/or hepatic encephalopathy [117, 118]. In advanced liver cirrhosis, SIBO has been linked to the development of BT, SBP, and endotoxemia [114, 119]. In fact, in cirrhosis SIBO is one of the main factors that promote BT and the occurrence of BT to mesenteric lymph nodes (MLN) in experimental models routinely associates with SIBO [91, 119]. A direct relationship between the density and composition of bacteria populating a segment of the intestine and numbers of viable bacteria of this strain present in MLN has been demonstrated in mouse models [119, 120]. Importantly, in the absence of SIBO in experimental cirrhosis, BT occurs rarely (0–11 %) and at rates comparable to normal rats. However, since BT does not occur in up to half the cirrhotic animals with SIBO, it appears that SIBO is necessary but not required for BT to occur and indicates that other factors, most likely a decrease in local immunity, play the most important role in inducing BT. For instance, in experimental ethanol-induced liver injury, increases in BT do occur prior to changes in intestinal flora [68]. SIBO in cirrhosis has traditionally been attributed, at least partly, to a decrease in small-bowel motility and a prolongation in intestinal transit time [105, 108, 110]. This is also observed in the clinical setting, where small intestinal motility is especially reduced in cirrhotic patients that also have SIBO [121] and is readily restored upon the eradication of SIBO. In addition, treatment with proton-pump inhibitors has been also associated with SIBO [122] and higher rates of SBP and other serious infections [88, 123]. However, hypo- and achlorhydria have been observed in cirrhotics even without acid-suppressive medication resulting in higher pH in the small intestine and thereby promoting SIBO [124]. Finally, to which degree the stated reduction in secretory barrier components (AMPs, bile, and IgA) contributes to SIBO in human cirrhosis has to be delineated in further investigations.

Qualitative Changes in Microbiota in Cirrhosis

In experimental animal models, different etiologies share only few similarities in microbial composition of the microbiome [125]. In fact, cholestatic (bile-duct ligation), toxic (CCl4), obese (ob/ob), and alcohol-induced cirrhotic mice do not

share any common operational taxonomic unit. Thus, there are no unique and common bacterial species dominating the microbiome associated with four different liver diseases in mice. Whether this applies also to human cirrhosis is currently unclear. However, it is thought that dietary factors including alcohol or a Western diet with a high fat content appear to be stronger determinants in changes of the microbiome [26] than liver disease itself. Nonetheless, several independent investigations reveal as a common feature of cirrhosis an increase of potentially pathogenic bacteria (mainly Proteobacteria, e.g., *Enterobacteriaceae*), accompanied by reduced proportions of more beneficial bacteria (e.g., *Lactobacillus*/*Lachnospiraceae*) [126–128]. In fact, for the latter a significant negative correlation with severity of liver disease was described [126, 129]. The majority of the patient-enriched, species are of buccal origin, suggesting an invasion of the gut from the mouth in liver cirrhosis [82]. Almost 50 % of the enteral consortia being detectable in cirrhotics belong to the oropharyngeal inhabitants as compared to their near absence in healthy individuals. This once more underlines the concept of deficient intestinal antimicrobial capacity in cirrhosis. By using culture-independent techniques such as pyrosequencing analyses of fecal contents, reductions in microbial diversity and distinct dysbiosis could be demonstrated both in animal models and human cirrhosis [81, 125]. The microbiota of cirrhotics has been associated with the depletion of beneficial, mainly autochthonous, bacteria, such as *Lachnospiraceae* (particularly clostridia) [81, 130], Bacteroidetes (mainly *Bacteroidaceae*) [81], but also *Blautia* and *Ruminococcaceae*. In contrast, an enrichment in Proteobacteria (mainly class of *Gammaproteobacteria* and, among those, the particularly potentially pathogenic family of *Enterobacteriaceae*) [81, 130], *Fusobacterium* spp., *Veillonellaceae*, and *Streptococcaceae* has been demonstrated in cirrhotics [81, 127, 131].

Interestingly, particularly the depletion of clostridiae resulted in a pronounced pro-inflammatory profile [130] and correlated negatively with Child-Pugh score [81]. Moreover, the particular relevance of alterations in the mucosa-associated microbiome has been evidenced by distinct differences between cirrhotic patients with and without hepatic encephalopathy, being associated with increased levels of inflammation [132]. Finally, similar dysbiosis is observed in inflammatory bowel disease [reviewed by Danese [133]]. In conjunction with recent findings that mucosal inflammation per se modifies microbial composition inducing the expansion of microorganisms with genotoxic capabilities (such as *E. coli*) [134], it remains to be seen whether inflammation is the cause or consequence of changes in microbial composition in those situations.

Concept of Bacterial Translocation and Liver Cirrhosis

This has been reviewed recently [135] but is summarized here in brief because it establishes the link between (so far mostly observational) investigations on changes in quantity and quality of the microbiome and clinical aspects of liver cirrhosis. Anaerobic bacteria translocate only in conditions associated with intestinal

mechanical injury (e.g., athymic, lethally irradiated, or severely burned rodents). On the contrary, aerobic gram-negative bacteria translocate easily and even across a histologically intact intestinal epithelium [136, 137]. Moreover, anaerobes outnumber aerobes by 100:1 and limit the colonization and overgrowth of other potentially invasive microbes, thereby confining potentially pathogenic bacteria. In fact, selective elimination of anaerobic bacteria facilitates SIBO and translocation of facultative bacteria [138]. Bacteria that translocate most readily are facultative intracellular pathogens (e.g., Salmonella, Listeria) that are able to survive outside white blood cells but are also able to resist phagocytic killing. In contrast, commensal bacteria are easily killed after phagocytosis, surviving only when host defenses are impaired. Gram-negative bacteria (GNB) (specifically *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and other *Enterobacteriaceae*), enterococci, and other streptococci have been found to be the most adept at translocating to MLN [136]. Interestingly, these species and particularly *E. coli* are those that most frequently cause SBP and spontaneous bacterial infections in cirrhotic patients [139, 140]. As described for other disease patterns which are accompanied by BT, for example, intestinal obstruction, burn injury, or starvation, the translocation of almost exclusively coliform bacteria underlines the pronounced preference of these gram-negative strains to translocate [141, 142]. Certain *E. coli* strains (e.g., biochemical phenotype C1–C4 or C25) have been reported to translocate more efficiently than others across the intestinal mucosa when this is exposed to metabolic and inflammatory stress [143, 144]. However, so far no specific bacterial virulence factor involved in translocation has been identified, and, in cirrhosis, *E. coli* isolates from SBP cases are genetically diverse [139]. In respect to the clinical consequences of BT and SBP, in particular, encapsulated *E. coli* strains, which are more resistant to phagocytosis and complement deposition, which leads to increased survival within the bloodstream and lymphatic system, have been reported to associate with a higher incidence of SBP-related complications [145]. However, virulence factors of isolates causing SBP vary with the severity of liver disease and the use of fluorchinolones [146]. Finally, host factors are more important than bacterial factors (phylogenetic group or virulence factors) in predicting SBP- and thus most likely BT-associated mortality.

Outlook

The intestinal microbiome as the "symbiotic/commensal world" within us is just about to be unraveled. However, considering the multiple parameters influencing the microbiome in its composition and function, which supposedly are all impacting on each other and in addition are mostly not constant but dynamic, it becomes clear how complex its physiology is. This makes it foreseeable that the pathophysiology may be even more heterogeneous and difficult to assess. However, the search is more than worthwhile particularly in hepatology and liver cirrhosis, not because of my "gut feeling" but due to the fact that truly the liver-gut axis represents the Gordian knot that needs to be untied.

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The Gut Microbiome and Cirrhosis: Clinical Aspects

19

Jasmohan S. Bajaj

Background

Microbiota analysis has been revolutionized by the advent of culture-independent techniques [1]. This has led to a significantly greater understanding of the gut microbiota and their relationship with the host and other bacteria. However, this field is rapidly evolving and remains extremely relevant to the disease progression in patients with cirrhosis.

Microbiome Analysis Details

Traditional methods for microbiota analysis are *culture based*, which are useful currently for clinically diagnosing the occurrence of infections and were our only methods to analyze the presence/absence of bacteria before the current era. Cultures are also important in helping understand the biological nature of the microbes (metabolism, growth characteristics) and can also be performed in a high-throughput method. Currently cultures are used to diagnose clinically relevant infections and guide antibiotic therapy but have largely fallen out of favor with the whole-genome analysis.

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J.S. Bajaj, MD, MS, FACG, AGAF
Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, 1201 Broad Rock Boulevard, Richmond, VA 23249, USA
e-mail: jsbajaj@vcu.edu; jasmohan@gmail.com

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Culture Independent Methods

16s rRNA Sequencing

The analysis of the highly conserved prokaryotic 16S ribosomal RNA gene which is sequenced and compared to publicly available registries to form operational taxonomic units (OTUs) is the most often used technique [2, 3]. These sequences use a universal primer and the presence of these sequences is used as surrogate markers for the actual bacteria.

Shotgun Metagenomics

Unlike the 16s rRNA, which studies the presence of the bacteria, shotgun metagenomics analyzes the DNA obtained from an entire sample or ecosystem using fragmented DNA sequences that are then aligned to construct the entire genome [4]. When combined with protein and mRNA assessments, it can study the functional output of an entire genome. This has to be matched with established databases (KEGG, COG) to evaluate the functional pathways that are expressed or suppressed in systems.

Functional Analyses

Studies of the mRNAs (meta-transcriptome), proteins (meta-proteome), and metabolites (metabolome) ultimately correlated with the presence the microbiota can indicate the functional aspects of the bacteria in producing ultimate host-bacterial responses.

An overview of important terms used in microbiota studies is listed in Table 19.1.

Table 19.1 Important terms used to describe microbiota

Term	Definitions
Taxon (plural taxa)	Organism groups that are classified together at the same taxonomic level (e.g., *Proteobacteria* at phylum level)
Operational taxonomic units (OTU)	Sequences that are clustered together because of similarity that can then be assigned taxonomic groups
Abundance	
Absolute	Absolute count of organism of OTUs in a sample
Relative	Relative proportion of one group compared to the rest
Richness	Number of organisms that are unique in that particular sample
Diversity	Estimate combining abundance and richness within (alpha) or between (beta) samples to define microbial variability
Cluster	Group of similar data points on PCO or similar sequences
Microbiome	Study of organisms and their genome
Metagenome	Cumulative sum of all genomes present in an environment/ecosystem
Metaproteome	Quantification of all proteins in an ecosystem environment/ecosystem
Meta-transcriptome	Sequencing the mRNA content in an environment/ecosystem
Metabolome	Analysis of all metabolites present in an environment/ecosystem

Importance of Gut Microbiota in Cirrhosis

The change in gut microbiota is an inherent aspect of cirrhosis progression with several responsible metabolic and functional aspects. These alterations in microbiota are relevant in the development and propagation of gut-based infections such as spontaneous bacterial peritonitis (SBP), which are responsible for a large proportion of cirrhosis-associated mortality. Another important complication in which microbiota are critically important is hepatic encephalopathy (HE) that spans the spectrum from minimal to overt HE.

Ultimately the progression of cirrhosis from compensated to decompensated stage is dependent on the generation of a systemic pro-inflammatory milieu [5]. This pro-inflammatory profile can be influenced greatly by the presence of potential pathobiont microbes that impact the local and systemic immune responses [6]. Therefore most treatments in cirrhosis are geared toward influencing this dysbiosis in a beneficial manner [7].

When evaluating gut microbiota studies in cirrhosis, it is critical to pose questions in order to interpret the results accurately (Table 19.2).

Bacterial Translocation

The occurrence of bacterial translocation has been alluded to as a critical event that can impact the occurrence and progression of liver injury in several preclinical and clinical studies of cirrhosis [8, 9]. While it is traditionally defined as the presence of viable bacteria in the normally sterile mesenteric lymph nodes (MLN), that is difficult to prove in humans. It is assumed that either the lymphatic drainage or the portal vein transport of bacteria results in systemic infection after MLN colonization. Therefore the presence of bacteria normally found in the gut lumen (*E. coli*) or a higher polymorphonuclear count of the ascites is clinically used as marker of bacterial translocation in the clinical management of patients with cirrhosis. In both human and animal studies, culture positivity of MLN is directly related to severity of the liver disease [8]. This could be due to altered intestinal barrier,

Table 19.2 Microbiota and cirrhosis: important questions

Relationship of the bacterial composition with severity of liver disease
Tissue of origin of the altered microbial composition
Change in functionality along with change in composition
Impact of coexistent medications on microbial composition and functionality
Impact of treatment on microbial composition and functionality
Association of microbiota with outcomes in patients with cirrhosis
Role of changed bacteria as markers of disease or independently pathogenic organisms

impaired local immunity, and the widely prevalent dysbiosis. The role of specific types of microbiota is important because even though the majority of the mucosal and fecal microbiota belong to the phyla Bacteroides and Firmicutes, it is largely the family *Enterobacteriaceae* that is overrepresented in the bacterial translocation and indeed in SBP.

Microbiota Composition Changes in Human Cirrhosis Studies

Several studies have been performed documenting dysbiosis in various tissues in cirrhotic patients. A listing of the most prominent studies is in Table 19.3. The alteration in gut microbiota in cirrhosis, especially in HE, has also been studied through other means, such as the demonstration of small bacterial overgrowth [22].

Studies have consistently shown that there is a decrease in the relative abundance of commensal or autochthonous bacterial taxa in patients with cirrhosis. The commensals consist of families such as Clostridiales incertae sedis XIV, *Ruminococcaceae*, and *Lachnospiraceae* and their relative abundance reduces with advancing liver disease severity [23]. These are important bacteria because they can retard the overgrowth of pathogenic bacteria and generate beneficial short-chain fatty acids [23]. In addition to the decrease in commensals, there is also a relative increase in the relative abundance of potentially pathogenic families such as *Enterobacteriaceae*, whose members are responsible for the majority of SBP in cirrhotic patients. A simplistic approach to study the balance between commensal and pathogenic taxa has been termed as the "cirrhosis dysbiosis ratio" in the stool with a higher value being healthier while a lower value indicating a milieu more permissive of dysbiosis and bacterial translocation. This has been associated with organ failure and death in cirrhotic inpatients as well as prediction of ACLF,[15]. Similar findings were noted in a recent Chinese study of ACLF patients in which ACLF patients had higher dysbiosis compared to healthy controls, which was also predictive of mortality, especially the presence of *Pasteurellaceae* [20]. These findings clearly determine that the severity of cirrhosis is a major determinant of the gut microbiota and has to be accounted for when interpreting these studies.

The tissue of study is of interest because it is likely that the stool microbiota is different from that noted in the other tissues that are more closely linked with mucosal or tissue immune responses and metabolite transformations. This was brought into focus by the relatively modest differences in stool microbiota relative abundances between cirrhotic patients with and without HE despite significant phenotypic differences [11]. We found, however, that these changes were significantly more pronounced in the colonic mucosal microbiota in which HE patients had a clearly worse dysbiosis compared to patients without HE [12]. This was in turn linked with systemic inflammation and metabolic by-products suggesting a pro-inflammatory phenotype in HE associated with colonic mucosal dysbiosis.

Other tissues that have been studied in human cirrhosis studies are ascites, liver, and saliva. The dysbiosis seen in stool and colonic mucosa is also extended on to the ascites and liver in patients with cirrhosis. As expected there was a disproportionate

Table 19.3 Human studies evaluating culture-independent cirrhotic microbiota composition

Study	Population groups	Tissue(s) tested	Findings	Relationship with potential clinical endpoints/outcomes
Chen et al. (2011) [10]	Cirrhosis/control	Stool	Higher *Streptococcaceae*, *Veillonellaceae*, and *Enterobacteriaceae* and lower *Lachnospiraceae* in cirrhotic group	*Streptococcaceae* positively and *Lachnospiraceae* negatively linked with Child-Pugh score
Bajaj et al. (2012) [11]	Overt HE/no-overt HE/control	Stool	Higher *Enterobacteriaceae*, *Alcaligeneceae*, and *Fusobacteriaceae* and lower *Ruminococcaceae* and *Lachnospiraceae* in cirrhosis	Higher *Veillonellaceae* in HE compared to no HE cirrhotics, *Alcaligeneceae*, and *Porphyromonadaceae* were correlated with cognition
Bajaj et al. (2012) [12]	Overt HE/no overt HE/control	Sigmoid mucosa and stool	Higher *Dorea*, *Subdoligranulum*, *Incertae Sedis XIV*, *Blautia*, *Roseburia*, and *Faecalibacterium* and lower *Enterococcus*, *Burkholderia*, and *Proteus* in cirrhosis	*Enterococcus*, *Megasphaera*, and *Burkholderia* linked to poor cognition and higher inflammation while the opposite was seen for *Enterococcus*, *Megasphaera*, and *Burkholderia. Alcaligeneceae* and *Porphyromonadaceae* were associated with poor cognition
Zhang et al. (2013) [13]	Minimal HE/no-minimal HE/control	Stool	Higher *Streptococceae* and *Veillonellaceae* in cirrhotics, *Streptococcus salivarius* higher in MHE	Correlation of cognitive function and ammonia with *Veillonella parvula* and *Streptococcus salivarius*
Lu et al. (2011) [14]	Hepatitis B from pre-cirrhotic to decompensated cirrhotic patients	Stool	Lower lactic acid bacteria, Bifidobacteria and Clostridiales, XIV in advancing HBV with increase in *Enterobacteriaceae* in cirrhotic patients	Higher fecal secretory IgA and TNF-α were seen in HBV cirrhotic patients with worsening gene virulence abundance

(continued)

Table 19.3 (continued)

Study	Population groups	Tissue(s) tested	Findings	Relationship with potential clinical endpoints/outcomes
Bajaj et al. (2014) [15]	Cross-sectional and longitudinal study of cirrhotics in outpatient, inpatient, and ACLF stages	Stool	Cirrhosis dysbiosis ratio worsens with advancing cirrhosis remains stable in unchanged disease and is associated with 30-day mortality, organ failure, and ACLF in infected patients	Dysbiosis is associated with 30-day mortality, organ failure, and ACLF in infected patients
Qin et al. (2014) [16]	Cirrhosis/controls/diabetes patients	Stool	Dysbiosis with bacteria normally found in oral microbiota was found in cirrhotics which was different from diabetes	Association with GABA, ammonia, and manganese metabolism in cirrhosis-associated microbiota
Rogers et al. (2013) [17]	Cirrhotics with ascites	Ascites	Viable bacteria were found in a large proportion of uninfected cirrhotics and were mostly Proteobacteria	Bacteria were correlated with ascitic fluid PMN and Child-Pugh score
Tuomisto et al. (2014) [18]	Cirrhosis/controls on autopsy	Stool, ascites, and the liver	Cirrhotic fluids/organs had significantly higher bacteria compared to controls	*Enterobacteriaceae* were the most common bacteria in the liver in cirrhotics
Grat M et al. (2015) [19]	Cirrhosis patients listed for transplant	Stool	Dysbiosis, by *Bifidobacterium*/*Enterococcus* ratio was related to MELD score	

Chen et al. (2015) [20]	ACLF cirrhosis vs. healthy controls	Stool	ACLF patients had lower *Bacteroidaceae*, *Ruminococcaceae*, and *Lanchnospiraceae*, but higher abundance of *Pasteurellaceae*, *Streptococcaceae*, and *Enterecoccaceae*. *Lachnospiraceae* was decreased in ACLF HE patients	Relative abundance of *Pasteurellaceae* and MELD score were independent factors predicting mortality rate
Bajaj et al. (2015) [21]	Overt HE/no overt HE/controls	Saliva and stool	Increased dysbiosis in both biofluids with *Streptococcaceae* being predominant in saliva and *Bacteroidaceae* in stool	Stool microbiota were more correlated with systemic inflammation than salivary microbiota Salivary dysbiosis could predict 90-day liver-related hospitalizations

HE hepatic encephalopathy, *ACLF* acute-on-chronic liver failure, *MHE* minimal hepatic encephalopathy, *PMN* polymorphonuclear cells, *HBV* hepatitis B virus

Table 19.4 Important functions of the gut microbiota

Metabolism of dietary components
Immune system modulation
Cholesterol metabolism
Enterohepatic bile acid cycling
Intestinal motility
Vitamin synthesis

increase in the relative abundance of *Enterobacteriaceae* in ascites in cirrhotic patients, given the likelihood of this family to cause SBP [17, 18]. Tuomisto et al. extended these findings on to the liver in which the rate of sterility or being free of bacterial DNA was significantly higher in healthy controls and pre-cirrhotic alcoholics compared to alcoholic cirrhotic patients. Therefore the impact of cirrhosis on the gut-liver axis is based on dysbiosis leading to an environment permissive for bacterial translocation.

Since cirrhotic patients have a systemic pro-inflammatory milieu, it is reasonable to assume that dysbiosis locations unrelated to the gut-liver axis would also be impacted. The evidence of this potential global-mucosal immune change was found in the oral microbiota of patients with cirrhosis [21]. Cirrhotic patients' microbiota showed dysbiosis with increased relative abundance of potentially pathogenic microbiota and reduction in autochthonous bacterial abundance in the saliva. The changes were also reflected in the functionality that pointed toward endotoxin production from the salivary microbiota in cirrhotic patients. Interestingly, the *salivary dysbiosis ratio*, created by dividing the autochthonous bacterial to the *Streptococcaceae* relative abundance, was predictive of 90-day hospitalizations in these outpatients.

Microbiota Function

Microbial function, measured using bacterial products, gene activation, and metabolite interactions, is a critical component of microbiota change. There are several important aspects of bacterial function that can be interrogated to analyze the change in function along with change in the composition of the microbiome. A listing of the important functions is in Table 19.4.

A prominent function that is relatively easy to study is the modification of bile acids by gut microbiota. This is an intricate process that starts with deconjugation followed by 7-alpha dehydroxylation. While most bacterial species can potentially deconjugate glyco- and tauro-conjugated bile acids, the 7-alpha dehydroxylation is limited to few families that convert primary bile acids (cholic and chenodeoxycholic acids) into secondary bile acids (deoxycholic and lithocholic acids) [24]. While this can be used to test the function of microbiota, it is also useful in delineating the impact of microbiota and probiotics via their modulation of these important

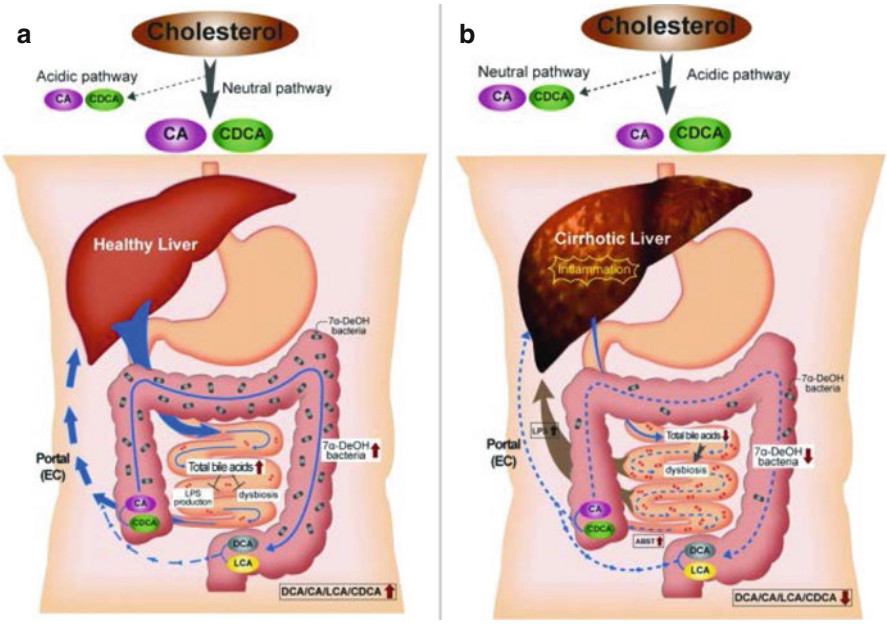

Fig. 19.1 A model for the relationship between bile acids, the microbiome, and cirrhosis (Reproduced with permission from Ridlon et al. [24]). (**a**) shows healthy controls in which the neutral bile acid synthetic pathway converts cholesterol into primary bile acids (cholic acid and chenodeoxycholic acid). These enter in the intestine in sufficient quantities to prevent overgrowth and dysbiosis and subsequent release of endotoxin (LPS). The select group of bile acid 7α-dehydroxylating bacteria is able to function with a resultant high ratio of fecal secondary to primary bile acids. (**b**) shows the situation in cirrhosis where inflammation suppresses the rate-limiting step of neutral pathway bile acid synthesis the CYP7A1. This results in the acidic pathway taking over the bile acid synthesis, and due to the inherent cholestasis, fewer quantities of bile are able to reach the gut. This milieu is permissive of dysbiosis with increase in LPS-producing organisms such as *Enterobacteriaceae* and a reduction in the 7α-dehydroxylating bacteria. Ultimately this decreases the ratio of secondary/primary bile acids in cirrhotic patients

signaling molecules. A model for enterohepatic cycling with the newer understanding of the microbiota is shown in Fig. 19.1 [24].

Other metabolites that have been studied are the mammalian-microbial co-metabolites such as hippurate and tri/dimethylamines (TMAO) that require an intact liver and functioning microbiota to appear in sufficient quantities on metabolomic analysis [25–28]. Changes in these molecules have been found in patients who withdraw from lactulose, patients with minimal hepatic encephalopathy, and after treatment with omeprazole in patients with cirrhosis.

As mentioned above, a critical bacterial product that is limited to gram-negative bacteria is endotoxin or lipopolysaccharide A (LPS) [28]. With advancing cirrhosis, there is increased endotoxemia (reflecting increased gram-negative bacteria) [27].

This engenders the systemic pro-inflammatory milieu and appropriately responds to gut microbiota manipulation with rifaximin, probiotic, and lactulose therapy.

Shotgun metagenomics of the stool in cirrhosis show activation of different pathways in stool of patients with cirrhosis related to GABA (gamma-aminobutyric acid), ammonia, and manganese metabolism [16]. In addition, metabolomics of the stool also shows changes in functional profile of the metabolome in patients with cirrhosis [29].

As is mentioned in the section below, it is now apparent that several accepted therapies that influence the microbiota may change the function rather than the composition. Therefore functionality of microbiota is critical while evaluating effects of disease processes or treatments.

Effect of Therapy

There are several treatments with proven efficacy that improve the morbidity and mortality in patients with cirrhosis using microbiota; the concepts regarding their mode of action are changing with newer studies [30–32]. Specific therapies evaluated in patients are lactulose, rifaximin, probiotics, proton-pump inhibitors, and antibiotics.

The treatment impact on cirrhosis depends on the medication, the site of action, as well as the stage of cirrhosis. Rifaximin has been studied in animal models of non-cirrhotic diseases with improvement in bacterial composition and function. However in human cirrhosis studies, it was found that the stool and colonic mucosa of patients on rifaximin, which is usually, prescribed in patients with a higher cirrhosis severity, were reflective of the underlying liver disease rather than rifaximin [11, 12]. This was further underlined in a prospective trial on MHE patients where rifaximin improved endotoxemia, brain function, and cognition [33]. Despite these phenotypic changes, there was only a modest change in the stool composition. However, patients after rifaximin were noted to have a significant increase in serum fatty acid metabolites and a change in correlation networks between bacteria and metabolites that changed from a pro-inflammatory to anti-inflammatory state. Rifaximin also reduced the primary to secondary bile acids in the same trial, again underlining its ability to change bacterial function [27]. Therefore, it is likely that the action of rifaximin in MHE is likely due to change in the microbial ecosystem functionality rather than composition.

Similarly studies using lactulose as the HE treatment have not yielded much change with respect to the bacterial composition either in a cross-sectional or a

prospective manner. Lactulose withdrawal led to a change in cognition and brain function but no significant change in composition [15, 26]. This was accompanied by a decrease in TMAO in patients who developed recurrence, indicating a differential impact on functionality. The mode of action of lactulose, whether it is the laxative, prebiotic, or stool-acidifying nature, is not borne out by the published studies in constipation or HE in humans.

Probiotics and synbiotics have a long history of use in HE with recent trials showing efficacy in the prevention, treatment, and recurrence of HE [34]. Trials have used various formulations, including VSL#3, Lactobacillus GG (LGG), and others. A recent trial showed that LGG use in MHE patients significantly reduced endotoxemia and improved dysbiosis over placebo [35]. Interestingly, the changes associated with LGG were not associated with increase in fecal *Lactobacillus* levels, but improvement in other autochthonous taxa, indicating that these organisms promote "good bacteria" as probiotics. Preclinical studies with probiotics have not consistently shown reduced bacterial translocation; however in non-cirrhotic animals, a consistent increase in hepatic bile acid synthesis and increased fecal bile acid excretion due to a reduced activation of the FGF-15/FXR axis have been demonstrated [36, 37]. Further studies are needed with other probiotic formulations to determine differences in modes of action in human studies.

Another widely used group of medications are proton pump inhibitors (PPI), which are used very commonly in cirrhosis and most often without a valid indication [38]. In recent studies of patients with and without cirrhosis, 14-day omeprazole therapy dramatically shifts stool microbial composition and function [25]. Specifically, there was a dramatic increase in oral-origin *Streptococcaceae* in the stool in both healthy controls and cirrhotic patients after PPI therapy. The use of antibiotics, all of which have individual and dramatic impacts on microbial composition and function, can serve as a fertile breeding ground for other multiresistant organisms [39, 40]. An overview of current studies that have evaluated microbial function and structure after human cirrhosis studies is in Table 19.5.

Conclusions

Our current understanding of microbiota composition and functional changes in cirrhosis as determinants of disease severity and complications is shown in Fig. 19.2 [42]. Further studies are needed to delineate the impact of therapies on bacterial composition and function, and a nuanced approach to interpretation of cirrhosis microbiota studies is needed.

Table 19.5 Human studies evaluating impact of treatments on microbiota composition and function

Study	Population groups	Medication/trial design	Tissue(s) tested	Findings	Relationship with medication
Bajaj et al. (2012) [11]	Overt HE/no-overt HE/control	Rifaximin/cross-sectional	Stool	Worse dysbiosis in patients on rifaximin compared to those without rifaximin therapy	Bacterial composition with rifaximin therapy reflects underlying changes in liver disease severity
Bajaj et al. (2012) [12]	Overt HE/no overt HE/control	Rifaximin/cross-sectional	Sigmoid mucosa and stool	Worse dysbiosis in patients on rifaximin compared to those without rifaximin therapy	Bacterial composition with rifaximin therapy reflects underlying changes in liver disease severity
Bajaj et al. (2014) [15]	Pre/post 1st episode of overt HE	Lactulose/cross-sectional	Stool	In patients who develop their first overt HE episode, there is increase in dysbiosis despite lactulose therapy	Bacterial composition with 1st HE episode reflects underlying changes in liver disease severity rather than lactulose's action
Bajaj et al. (2012) [26]	Lactulose withdrawal	Lactulose/longitudinal	Stool	*Faecalibacterium* spp. decreased with altered metabolites (TMAO) in those who recurred	Lactulose withdrawal worsens cognition, brain MRS, and changes bacterial function to result in recurrence
Agarwal et al. (2014) [41] (abstract)	Lactulose in outpatients without prior HE	Lactulose/longitudinal	Stool	6-week lactulose treatment did not show any change in bacterial populations	No change in bacterial composition in outpatients with cirrhosis when treated with lactulose

Bajaj et al. (2013) [33], Kakiyama et al. (2013) [27]	Rifaximin in MHE patients	Rifaximin/longitudinal	Stool	A modestly decreased *Veillonellaceae*, higher *Eubacteriaceae* with reduced fecal secondary bile acids	Rifaximin improved cognition and endotoxemia by changing bacterial function
Bajaj et al. (2014) [35]	Lactobacillus GG in MHE patients	LGG/longitudinal	Stool	Increased autochthonous taxa and decreased dysbiosis in the LGG group	LGG was associated with improved endotoxemia due to change in bacterial composition and function
Bajaj et al. (2014) [25]	Omeprazole in cirrhosis and controls	Omeprazole/longitudinal	Stool	Significant increase in salivary-origin *Streptococcaceae* in controls and controls	A 2-week 40 mg omeprazole course changes stool bacterial composition and functionality

HE hepatic encephalopathy, *ACLF* acute-on-chronic liver failure, *MHE* minimal hepatic encephalopathy

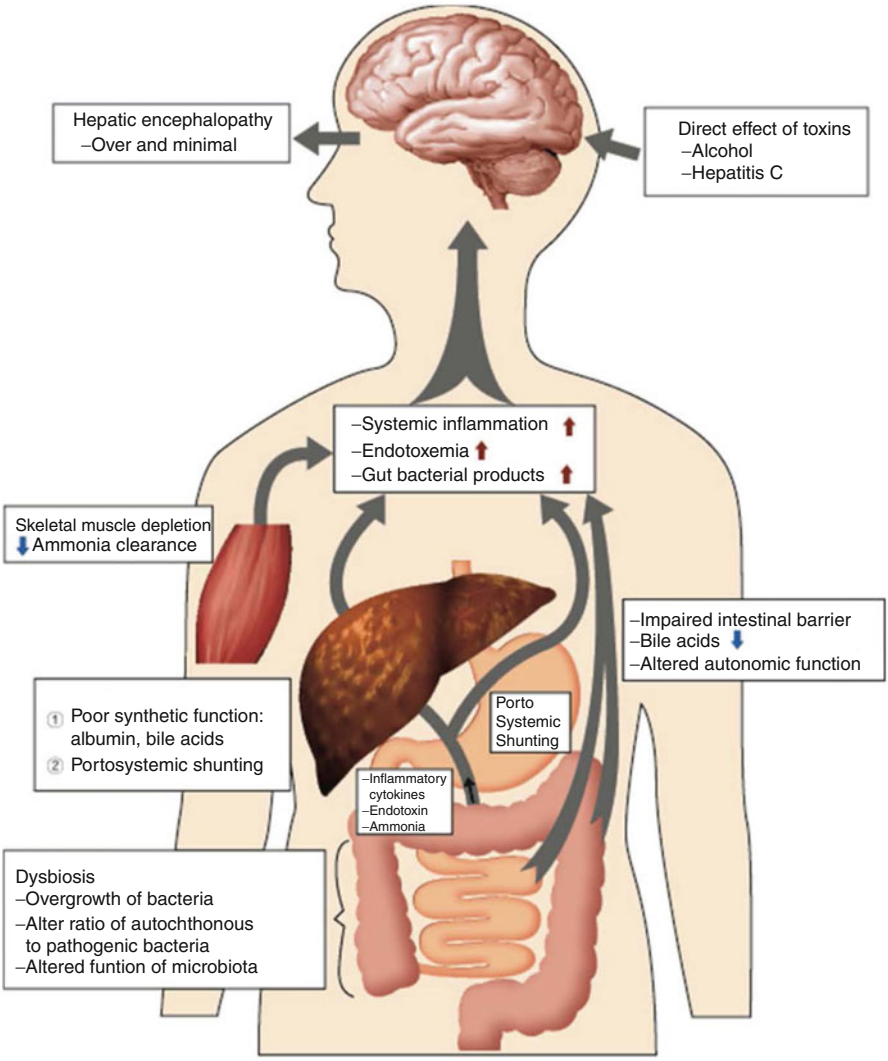

Fig. 19.2 A schematic for the development of dysbiosis and complications such as hepatic encephalopathy in patients with cirrhosis (Reproduced with permission from Bajaj [42])

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Part V

Changing Scenarios II: What to Do After Successful Cure of the Etiologic Factor

Result of the Questionnaire

20

Carlo Merkel and Aleksander Krag

General Aspects

There are a clear majority of experts (two-thirds) that agree that surveillance in patients with compensated cirrhosis should be extended to further aspects, apart from varices and HCC. In addition, it is apparent that a number of experts show a propensity to treat initial signs of decompensation, despite current guidelines do not support such active approach (Fig. 20.1). More specifically, nearly half of the experts would also treat with diuretics patients with ascites only seen at ultrasound, while EASL guidelines [1] only suggest surveillance without treatment. In addition, most experts are willing to treat patients with minimal hepatic encephalopathy (asymptomatic and only detectable by psychometric tests) with disaccharides (60 %) or with rifaximin (20 %). At variance, current EASL-AASLD guidelines only suggest treatment after the occurrence of overt hepatic encephalopathy [2].

There is a fair agreement (78 %) that it is reasonable to investigate the possible role of other treatments in the primary prevention of decompensation, beyond the treatment of the etiological factors. Statins and anticoagulants are the two classes of drugs that are most commonly cited as worthy of investigation.

Two questions concerned the possibility that patients with compensated disease without varices, in which etiological factors had been successfully cured, may deserve a less tight follow-up. Only 30 % considered that the schedule of surveillance endoscopies to detect variceal formation should not be modified; the others suggest to delay follow-up endoscopies at 3–5 years, instead of 2–3 years, as defined

C. Merkel (✉)
Department of Medicine, University of Padua, Padua, Italy
e-mail: carlo.merkel@unipd.it

A. Krag
Department of Gastroenterology and Hepatology, University of Southern Denmark and Odense University Hospital, Odense, Denmark

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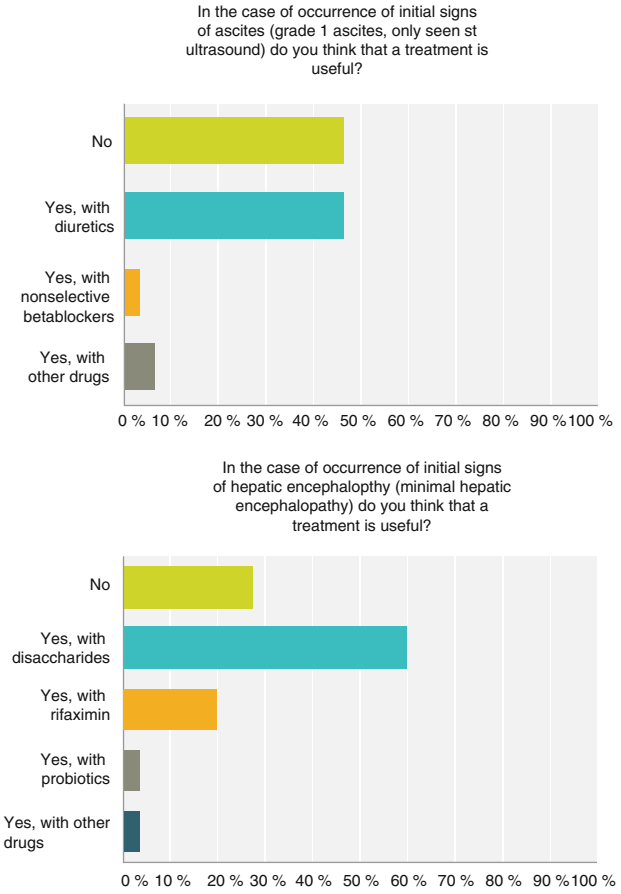

Fig. 20.1 Answers to the questions related to the propensity to treat initial signs of hepatic decompensation

for the general population of patients with cirrhosis without varices [3]. A relevant number of experts (29 %) suggest that this decision should preliminarily imply the measurement of HVPG, in order to stratify the risk. There is a general feeling that this topic requires specific studies aimed at defining the best surveillance schedule.

Malnutrition

There is general agreement (87 %) that nutritional status should be assessed in compensated cirrhosis. The reasons that underlie the importance of this statement are mainly the fact that malnutrition is a correctable factor (68 %) and a predictor of survival (48 %). A minority of responders (32 %) consider malnutrition as a predictor of decompensation. Nutritional status is generally assessed by anthropometry (71 %) or biochemical parameters (46 %). Few experts use more sophisticated systems, like bio-impedance analysis or imaging techniques.

Primary Prophylaxis of Variceal Bleeding

Nonselective beta-blockers (NSBB) are considered the best approach in primary prophylaxis by 63 % of responders or the best and equivalent to endoscopic band ligation (EBL) by 31 % of responders. Overall, NSBB are considered best approach by 94 % of responders. In the current clinical practice for primary prophylaxis, NSBB are rated as the first option by 84 % of experts and first and equal to EBL by 16 % (Fig. 20.2). Compared to the answers of the questionnaire of 2010, the use of NSBB as a first option in clinical practice is further increased.

There is consensus in the indication of treatment for patients with large- or medium-size varices regardless of Child-Pugh score or presence of red signs (98 %) and for patients with Child-Pugh class C with small varices without red signs or with small varices and red signs regardless of Child-Pugh class (84 %). No consensus exists about the treatment of patients with Child-Pugh B patients with small varices without red signs, since the opinion is divided in half. However, there is a tendency to increase the indication in this group of patients, since in the 2010 survey only 30 % of experts suggested treatment. In patients with gastric varices, there is consensus that the first-line treatment in primary prophylaxis of gastric varices is NSBB (88 %).

Rather surprisingly, two-thirds of the experts report that there is a need for new clinical trials in pre-primary prophylaxis, i.e. treatment of patients without varices. As expected, all responders are aware of the difficulties related to the costs and the length of follow-up. The suggestions about the possible treatments and inclusion criteria are different. Among the suggested drugs, statins (6), NSBB including carvedilol (3), and anticoagulants (1) are quoted. Some experts suggest including only patients without varices but with clinically significant portal hypertension, in order to decrease the length of follow-up (23 %).

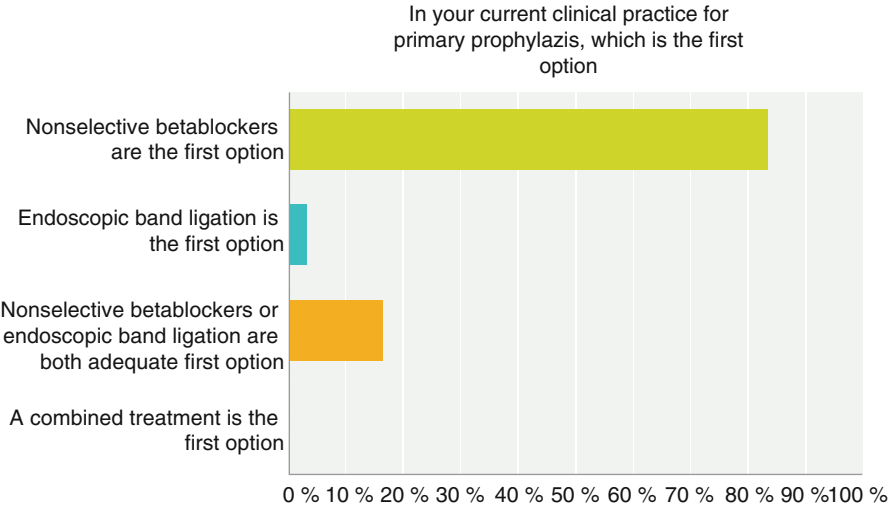

Fig. 20.2 Answers to a question related to the choice of treatment in primary prophylaxis

Use of Nonselective Beta-Blockers

Propranolol remains the most frequently used among the NSBBs. However, there is an increase in the use of carvedilol, which is now prescribed by nearly 50 % of the experts (Fig. 20.3). Five years ago, only 11 % of the experts used carvedilol. In primary prevention, there is consensus that associations between drugs should not be prescribed (94 %). Most of the drugs used in the medical treatment of portal hypertension are available in the country of the experts, except long-acting propranolol and nadolol, which are available in two-thirds of the cases. However, in very few instances available drugs have a registered indication for the treatment of portal hypertension (from 3 to 22 %).

A series of questions in the present questionnaire assessed the evaluation of possible side effects and contraindications in the use of NSBBs. In comparison with the answers of the 2010 questionnaire, there is a greater attention to the hypotensive effects of NSBBs. Indeed, 90 % of the experts would reduce or stop the drugs if systolic blood pressure is consistently lower than 85 mmHg (while in 2010 they were only 61 %) (Fig. 20.4). The attention to the decrease in heart rate has not changed very much in the past 5 years (Fig. 20.5), as 56 % would reduce NSBB if HR is lower than 50/min and 97 % if it is lower than 45. Interestingly enough, the presence of symptoms possibly related to hypotension (asthenia, dizziness) is a

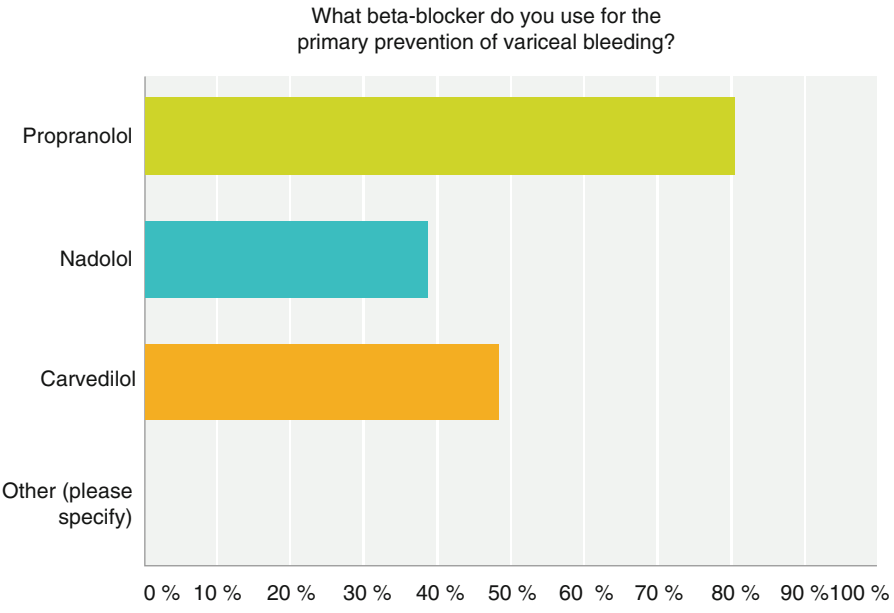

Fig. 20.3 Answers to a question related to the choice of nonselective beta-blocker in primary prophylaxis

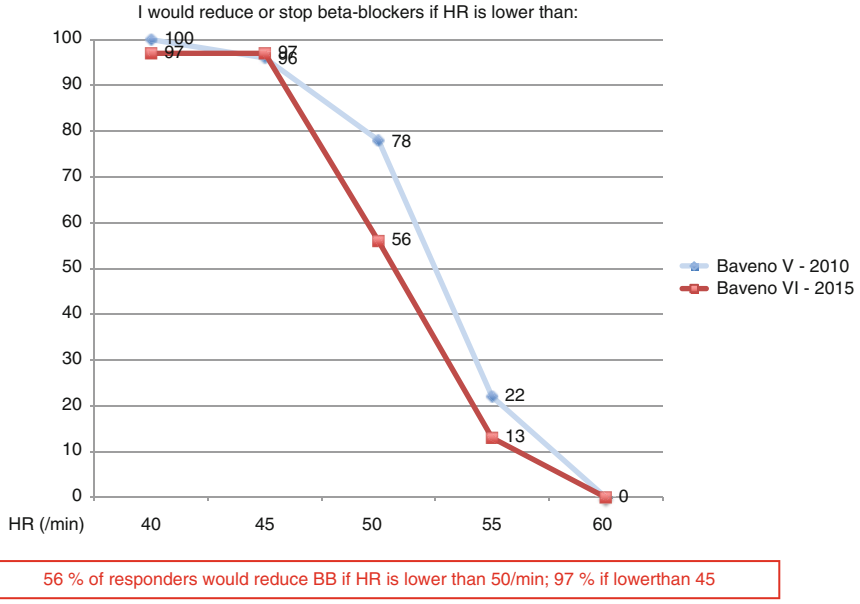

Fig. 20.5 Five-year variations in the propensity to decrease or stop beta-blockers in relation to heart rate (*HR*) during treatment

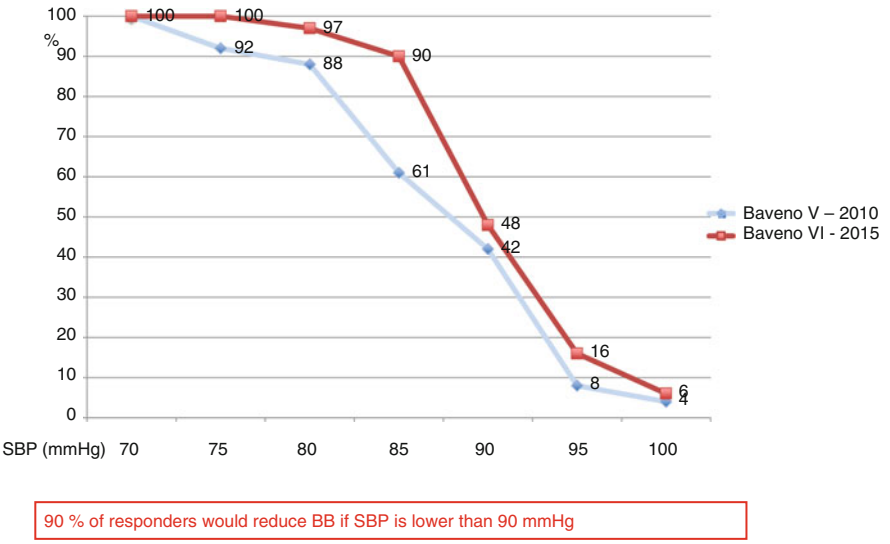

Fig. 20.4 Five-year variations in the propensity to decrease or stop beta-blockers in relation to systolic blood pressure (*SBP*) during treatment

reason to reduce the treatment for most experts, but a minority (16 %) are not prone to modify treatment, probably considering that these symptoms (if not very severe) are not sufficient to warrant a treatment change.

In relation to the evaluation of cardiac problems as possible side effects requiring reduction or withdrawal of NSBB treatment, there is consensus that clinical signs of heart failure and ongoing treatment for heart failure are reasons for withdrawal. The observation that the occurrence of 1st degree AV block is also a reason to withdraw NSBB for 73 % of the responders is surprising (to a certain extent), since it is at variance with the current concept that only advanced AV block requires withdrawal of the drug [4].

There is agreement that aggravation of liver dysfunction (Child-Pugh class C, 78 %; overt hepatic encephalopathy, 88 %; occurrence of HCC, 100 %; listing for OLT, 100 %) is not a reason for decreasing or withdrawing NSBBs.

The presence of renal dysfunction requires a more detailed report. The propensity to reduction or withdrawal of NSBBs increases with the increase in severity of renal dysfunction (53 % when there is development of renal impairment with increase creatinine, 65 % when type-2 HRS occurs, 91 % when type-1 HRS occurs). However, only 37.5 % would reduce or withdraw NSBB when refractory ascites develops. The issue of the connections between refractory ascites and NSBB has been the subject of a series of studies [5–9] and a series of comments, editorials, and clinical suggestions [10–15] that are discussed in detail elsewhere. Nevertheless, it is apparent that only a minority of responders agree with the words of caution on the use of NSBBs in this clinical setting. Similarly, in other clinical conditions in which it was suggested to reduce or withdraw NSBBs (spontaneous bacterial peritonitis, presence of hypotension with mean arterial pressure below 82 mmHg) [16], only 41 % of responders appear to follow these suggestions. Furthermore, there is agreement (from 94 to 100 %) on the re-institution of treatment (if withdrawn) when these clinical problems disappear. In advanced stage disease with circulatory dysfunction and fragile kidneys, the use of NSBB may not be safe, and these drugs should be used with caution, and may be readily discontinued in case of signs of intolerance or circulatory deterioration. In the primary prevention of bleeding EBL is equally effective and can safely substitute NSBB in these cases [17].

Most experts agree that the amount of NSBB to be prescribed should be the highest tolerated dose (83 %), and some add the request that heart rate should be lower than 55/min. If the target heart rate is not reached because of side effects, there is no agreement about how to handle the issue: 38 % would withdraw NSBB and use EBL, 34 % would reduce to the last tolerated dose and keep this dose, and 28 % would reduce the dose and attempt a slower increase of the dose in the future.

In the 2010 questionnaire, the majority of responders (65 %) considered that there was no reason to prescribe further endoscopies in patients assuming NSBB prophylaxis. In the present survey, this number is decreased to 46 %, and the majority consider that possible or observed aggravation of the disease may be a reason to perform a follow-up endoscopy. This observation highlights an increased interest in evaluating the course of the disease during follow-up.

HVPG in Primary Prophylaxis

There is agreement that, in the context of RCTs, HVPG measurement should be performed (90 %), and half of the experts regularly perform HVPG measurement in patients undergoing primary prophylaxis. These percentages are increased in comparison with the answers to the same questions in 2010, implying a wider use of HVPG in recent years.

The reduction in HVPG considered clinically relevant in primary prophylaxis was variable; 72 % consider relevant a decrease to less than 12 mmHg, and 65 % a decrease by 20 % of the baseline value; 28 % reduce this percentage to 10 %. A small number of experts (12 %) regard HVPG as not relevant in the context of primary prophylaxis.

When the target HVPG is not reached, 57 % of the experts would switch to carvedilol, if propranolol was the first choice, or would continue treatment (19 %). A minority would add EBL (22 %) or substitute EBL to NSBB (15 %).

Endoscopic Band Ligation

EBL is done during the same session of the diagnosis or during a subsequent session expressly programmed in order to perform the procedure. The two schedules are preferred by the same number of experts and probably reflect the local preference in the management. Subsequent sessions are programmed at 2- (41 %) or 4-week (53 %) intervals. Very few experts delay the second session at 8 weeks (6 %). The main reason to postpone a programmed session is the presence of post-banding ulcers, reported by 39 % of the experts.

There is a fair agreement that a course of EBL is complete when varices appear to be too small to be amenable to further treatment (84 %), although an attempt to suck the varix in the ligation chamber is performed by 45 % of the responders. A minority of responders consider eradication achieved only when no residual varix is visible in the esophagus. PPIs are always prescribed between EBL sessions by 86 % of responders and sucralfate by 47 %. Many of those who do not prescribe these drugs routinely are prone to use them in selected cases.

A minority of experts (25 %) believe that eradication is always feasible. The remaining consider that it cannot be obtained when side effects prevent further treatments (46 %) or after a variable number of session. This number ranges from 4 to 10 sessions. There is no agreement about the timing of follow-up endoscopies after eradication. The first session is scheduled at 1 month (6 %), 3 months (23 %), 6 months (58 %), and 1 year (10 %), according to the different responders. There is complete agreement (100 %) that recurrent varices should be treated as soon as they are suitable for further ligation.

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Introduction: Prevention of Decompensation Versus Prevention of First Bleeding

21

Aleksander Krag and Carlo Merkel

Introduction: Historical Perspective

The history of the treatment of portal hypertension is characterized by a progressive interest in treating earlier and earlier phases of this condition. Fifty years ago treatment of portal hypertension only included acute treatment of variceal bleeding or surgical prevention of recurrent bleeding. The seminal paper by Didier Lebrec [1] opened the era of medical treatment of portal hypertension, and initially all efforts were dedicated to the prevention of rebleeding in patients who survived an acute bleeding episode. Later prevention was progressively expanded to earlier and earlier phases. Indeed, few words were dedicated to the prevention of first bleeding in the Baveno 1 meeting (1990) [2], and in the Baveno II meeting (1995), prevention of bleeding was considered "A look into the future of pharmacological treatment of portal hypertension," according to the title of the lecture by Didier Lebrec and Richard Moreau [3].

At the Baveno III meeting (2000), primary prophylaxis was the subject of a chapter by itself, and we started to evaluate the subject of an earlier phase of portal hypertension called preprimary prophylaxis. In this meeting a section was dedicated to "Can (and should) we prevent the formation and growth of varices?"[4] The problem was considered important and was mainly related to the problem of treating patients with small varices, since only few data were available on potential treatments of these subjects, previously considered as not requiring treatment. In this

A. Krag (✉)
Department of Gastroenterology and Hepatology, University of Southern Denmark and Odense University Hospital,
Sdr. Boulevard 29 Entrance 126, 2nd floor, Odense 5000, Denmark
e-mail: akrag@health.sdu.dk; aleksanderkrag@hotmail.com

C. Merkel
Department of Medicine, University of Padua, Padua, Italy

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section, for the first time, the possible occurrence of regression of varices was considered, in particular as related to a possible improvement in liver status. At that time, the association of abstinence from alcohol in alcoholic cirrhosis with possible regression of varices was considered the paradigm of an etiological treatment of liver disease with beneficial consequences on liver disease and portal hypertension at the same time.

The preprimary prophylaxis was also the subject of a session of the Baveno IV meeting in 2005, but at this time, it was defined that the term preprimary prophylaxis should only include the prevention of the formation of varices [5]. Based on the results of the only trial that specifically addressed the usefulness of treatment with NSBB patients with cirrhosis without varices and with HVPG in the range 5–9 mmHg in order to prevent the formation of varices [6], it was stated that there was no indication to treat patients to prevent the formation of varices. The lack of effect of NSBB in these subjects was interpreted as the expression of the fact that in this phase the mechanisms provoking portal hypertension (formation of collaterals, hyperdynamic circulation) was not halted by NSBB.

At the 2010 meeting (Baveno V), the statements related to preprimary prophylaxis were updated [7], and among the recommendations, there was for the first time a statement that suggested that treatment of the underlying liver disease may have a beneficial influence on portal hypertension and reduce the risk of clinical complications. The impact of treating the underlying disease in the development of portal hypertensive-related complications, including varices, was also considered an area requiring further study.

In the present session we report available evidence about the possible treatment of patients in an evolving scenario which considers cirrhotic patients as treated successfully (or not successfully) in relation to their etiological factors. In this scenario there will be an overlap between prevention of the formation of varices (a traditional approach) and prevention of the progression of disease or even regression (a novel approach). In this approach varices appear as a part of the disease process, which has portal hypertension as a marker of disease stage and at the same time a pathophysiological mechanism involved in its progression.

Changing Scenario: Natural History of Chronic Liver Diseases from Compensated to Decompensated Stage in the Era of Direct-Acting Antivirals

The rate of progression in fibrogenic liver diseases depends on a number of factors and varies individually. Previously, fibrosis was considered an inactive tissue without regenerative potential for the organ affected. Within the last decade, this concept has changed, and fibrosis is no longer considered static or irreversible but the result of a continuous remodeling process and thereby susceptible to interventions. Presently, no treatments that specifically target the mechanism of fibrosis are available for clinical use. However, therapies that address or eliminate the cause of tissue damage (e.g., tenofovir in chronic hepatitis B virus infection) have the potential to lead to

regression of fibrosis and even cirrhosis [8]. Thus, the risk of progression may be halted or even reversed with cure of the etiological factor, and consequently the prognosis may be altered. A similar pattern may occur in hepatitis C upon sustained virological response (SVR), though this has not been documented yet. However, one would expect that control of viral replication would prevent, slow down, or delay further accumulation of fibrosis and thus risk of decompensation and risk of HCC [9]. If this holds true, the indications and interval between surveillance for varices and HCC may change. In addition the populations of patients with liver diseases and portal hypertension are also changing. With the arrival of highly efficacious and well-tolerated treatments for HCV along with an increasing burden of obesity and alcohol overuse, the need and focus may change within the foreseeable future. Obesity is a global health challenge with prevalence of up to 30 % of the population at risk of nonalcoholic fatty liver disease (NAFLD), among whom approximately 4 % will develop or have nonalcoholic steatohepatitis (NASH) and a few will develop progressive fibrosis. NAFLD is considered the hepatic manifestation of the metabolic syndrome and has become a leading cause of liver disease worldwide. Currently NASH is the second leading cause of liver transplantation in the USA, and the numbers have tripled within the last decade [10]. Similarly, alcohol abuse is a leading risk factor for morbidity and death worldwide among the young, working population (15–49 years). Chronic alcoholic liver disease is a major cause of alcohol-related mortality, accounting for 570,000 annual deaths worldwide. In 2010, alcoholic liver fibrosis and subsequent cirrhosis led to nearly 500,000 deaths and cost 14.5 million disability-adjusted life years (DALYs) worldwide [11]. Compared to other common chronic diseases, mortality from alcoholic liver disease is on the rise [12]. Yet, there is a striking mismatch between burden of alcoholic liver disease and prioritization due to the socially stigmatized status of the disease [13].

Hidden Burden of Disease

To have an effective primary prevention, we need early diagnosis of fibrosis and cirrhosis. However, due to the lack of widely available tools for early diagnosis of liver fibrosis, the latter is mostly discovered at an advanced stage after reaching cirrhosis, with 5-year mortality up to 88 % in late cirrhosis compared to 1.5 % in the earliest stage of cirrhosis [14]. In a study with more than 1300 patients, 76 % of patients had their initial diagnosis of alcoholic cirrhosis during hospitalization with a decompensating event [15]. This underlines the huge hidden burden of disease but also the unmet need of early diagnosis and associated potential of applying primary prevention in a larger portion of patients. Viral hepatitis identifies a relevant population at risk and screening for viral hepatitis is cheap. In alcohol and NASH-induced liver fibrosis and cirrhosis, this is more difficult, as the population at risk is large and noninvasive markers with high diagnostic accuracy in early stages are not available or not integrated in clinical practice. In patients who discontinue alcohol overuse, lose weight, or control the metabolic syndrome, there is likely a recovery potential similar to that observed in viral hepatitis.

Risk Stratification

The risk and speed of progression from compensated to decompensated stage define the prognosis. Therefore, early detection and preventative strategies may affect outcomes. In the advanced stages of the disease, with portal hypertension and decompensation, prognostic tools like the MELD and the Child-Pugh scores are useful, but in the early stages of the disease, measures to predict risk of decompensation, morbidity, and mortality are less developed and not widely adopted in general care. In these stages, standard liver function tests can be normal even among patients with significant fibrosis and early cirrhosis. Imaging tools are powerful [16], but the static nature of imaging limits its prognostic power in early stages because it does not reflect tissue activity (inflammation, remodeling of extracellular matrix, and fibrogenesis). However, direct markers of the pathological processes are not yet ready for clinical use [16]. HVPG measurements have repeatedly and consistently been reported as a very strong tool to assess, prognosticate, and measure the efficacy of specific interventions [17]. Thus, HVPG measurements enable diagnosis (HVPG >6 mmHg) of portal hypertension and its severity, with a level of >10 mmHg being associated with varices formation and high risk of decompensation including ascites and HCC. Higher levels of >12 mmHg imply the risk of bleeding, and similarly a reduction of >20 % or below 12 mmHg suggests effective pharmacological interventions. Thus, HVPG measurements are unique as both a diagnostic and prognostic tool and a measure of efficacy of pharmacological interventions. Limitations include limited availability and expertise outside referral centers, time, cost, and patient acceptability.

Changing Scenario: Cirrhosis and Portal Hypertension as a Systemic Disease, Need for Collaborative Care

A large proportion of patients emerge in the health-care systems with a decompensating event. A number of treatments have been developed to handle acute events and been successful to improve outcomes [18]. However, patients who develop decompensation and complications of cirrhosis have a poor prognosis which is associated to hospital admissions and frequent readmissions [19]. In addition, quality of life and working ability are negatively affected and thus associated with a significant economic burden. Thus, there is an urgent need to strengthen efforts to prevent decompensation and prevention of first variceal bleeding, and other key events are an essential part of care. The complex symptomatology and multiplicity of involved organs in chronic liver diseases underline their systemic nature. This calls for care coordination or “collaborative care” [20]. Most studies and guidelines focus on one event, i.e., varices, ascites, or hepatic encephalopathy, which increases the risk of fragmented and poorly coordinated care [21]. The overall goals are to improve clinical care by adaption and adherence to best clinical standards to prevent complications and decompensation. Currently, screening for esophageal varices and HCC are generally accepted standard of care, although the direct evidence from

randomized trials supporting the benefit of screening is weak. In clinical practice patients often fail to receive the evidence and guideline-based treatments [21]. In one study with 774 patients, only 24.3 % had an upper endoscopy during the first year after cirrhosis was diagnosed, and only 60 % of those with varices received appropriate primary prophylaxis with beta-blockers or band ligation [22]. Similarly nonadherence to HCC screening is high. Thus, less than 20 % of patients with cirrhosis undergo surveillance for HCC, with the lowest adherence in nonspecialized centers [23]. Overall there is a mismatch between recommended standards and clinical practice in this field, which likely has an impact on outcomes and resource utilization. Thus, integrated care with adoption of all documented treatments together improves outcomes [20]. A recent study among outpatients with ascites documented how care coordination versus standard care improved 12-month mortality (45.7 % vs. 23.1 %, $p<0.025$) and rate of 30-day readmission (42.4 % vs. 15.4 %, $p<0.01$). In addition, the global cost attributable to the management per patient-month of life was lower [20]. General care in early-stage disease, to prevent decompensation, should probably go beyond surveillance of varices and HCC and include comorbidities, nutrition, physical training, hepatic encephalopathy, minimal hepatic encephalopathy, early ascites, and general symptoms like fatigue. However, evidence-based treatments at this stage of disease are limited. In addition at least 40 % of patients with cirrhosis have comorbidities such as diabetes, cancer, osteoporosis, pulmonary, and cardiac diseases that increase morbidity and mortality [24, 25]. Successful treatment of comorbid diseases in the first year after diagnosis may substantially reduce the mortality rate, and thus, the presence of comorbidities is an important issue in clinical hepatology that deserves more attention [24].

Detection of Esophageal Varices and Primary Prevention of Bleeding: New Insights into NSBB

Endoscopy is still the preferred standard to screen for the presence of varices. A number of other noninvasive methods have been investigated including spleen and liver stiffness [26, 27]. In the prevention first variceal bleeding NSBB and EVL are both valid first choices [28]. In approximately one third of the patients, there are contraindications or intolerance to NSBB and EVL can be applied. In patients who tolerate NSBB, these are the best choice, especially if long-term treatment is expected, as there may be a survival benefit of NSBB above EVL in the long run. On the other hand, EVL may offer better protection against bleeding in the short term [28]. NSBB including carvedilol have been and still are the cornerstone in primary prevention of bleeding from esophageal varices. Their clinical efficacy is covered in other chapters. However, our understanding of the pharmacodynamics and safety of NSBB has been changing in recent years. In particular NSBB seem to have an impact in patients with portal hypertension in a clinically significant way which goes beyond the hemodynamic effects. Gut bacterial translocation is believed to be a key driver in the pathogenesis, progression, and cause of decompensating events [29]. NSBB have been shown to reduce bacterial translocation [30]. This

may translate into reduced risk of infections in general and spontaneous bacterial peritonitis in particular [31, 32]. Thus, both direct and indirect evidences suggest that NSBB reduce the risk of bacterial translocation. In addition NSBB may reduce risk of HCC [32]. The mechanism of action is incompletely understood but may include a weak antiangiogenic effects [33]. These non-hemodynamic effects may have a clinically significant impact, but more data are needed before NSBB can be recommended beyond the prevention of bleeding in patients with esophageal varices.

For decades, NSBB have been a cornerstone in clinical hepatology due to their very well-documented effects in terms of preventing variceal bleeding and improving survival. However, a serious concern about the safety of NSBB in advanced-stage disease has been raised in recent years [34, 35]. Thus, NSBB may only be beneficial during a certain window during disease progression, and at certain tipping points in advanced-stage disease, NSBB should be discontinued [36]. The available data are observational and prone to confounding factors that can be difficult to eliminate completely. Consequently the controversy if and when to stop NSBB in advanced-stage disease is ongoing, and there is currently no consensus on when to stop NSBB and, if they are stopped, when and if to reinstitute. In the most fragile patients with advanced-stage disease with refractory ascites, low blood pressure, acute kidney injury, or SBP, NSBB should be used with extreme caution and discontinued readily if the situation deteriorates. In patients without previous bleeding, EVL can substitute NSBB without the safety concern [28].

Emerging Interventions in the Primary Prevention of Decompensation

Prevention implies surveillance with early detection at subclinical or asymptomatic levels. Screening tests should be validated, cheap, and safe, and adherence is essential for the overall success. Treatment should be available for early stages, and early treatment should offer better outcomes than late treatment. The population at risk of decompensation is clear, but screening tools and relevant interventions are limited, and the demonstration of benefit if early detection is achieved is currently also limited; however, a number of interventions are emerging.

Cognitive dysfunction is an important event in cirrhosis that affects quality of life and the socioeconomic status [37]. Cognitive dysfunction is associated with minimal hepatic encephalopathy, which is a risk factor for overt hepatic encephalopathy [38]. Thus, minimal hepatic encephalopathy would be an important target for early detection. However, therapies to improve cognition and prevent progression to overt stages need better validation. Currently, a number of interventions including prebiotics, probiotics, antibiotics, and nutritional supplements are tested. However, current guidelines advise against routine treatment of minimal hepatic encephalopathy due to lack of evidence [39]. Consequently the drive to assess patients is limited.

The gut-liver axis in terms of translocation of bacteria and bacterial products from the gut is considered a key driver in the development and progression of liver disease [29]. This is true in particular in the more advanced stages with ascites and portal hypertension due to slower transit times, bacterial overgrowth, and increased permeability in the gut. However, in earlier stages this may also be important, in particular in alcoholics as alcohol itself induces a leaky gut. Rifaximin is a nonabsorbable antibiotic with a main effect in the small bowel, the most important area of bacterial translocation. Rifaximin is well established as a treatment that reduces the risk of recurrent episodes of hepatic encephalopathy and hospitalizations in patients with previous episodes of hepatic encephalopathy [40, 41]. In addition this treatment is associated with improved quality of life [42]. In advanced-stage disease, sarcopenia and malnutrition are very frequent and important prognostic indicators [43]. Recent evidence suggests that nutritional therapy may have beneficial effects on clinical outcomes in cirrhosis and alcoholic hepatitis [44]. The mechanisms of sarcopenia are incompletely understood, but muscle mass improves after liver transplantation and also after TIPS treatment, which suggests a relation to portal hypertension. In compensated disease, the nutritional status is also associated with prognosis [45]. Physical training can improve exercise capacity, muscle mass, and quality of life [46], and this effect may translate into an impact on portal pressure and risk of complications. Overall the concept of assessing nutritional status and muscle mass is intriguing, because interventions to modify these risk factors are at hand. However, more clinical trial data are needed to document the clinical efficacy and insight on when and how to intervene. Other pharmacological treatments with promising results include statins and low-molecular-weight heparin. Both of these may improve survival and prevent risk of decompensation and deterioration in liver function [47–49]. Obeticholic acid, a bile acid derivative which seems promising in patients with NASH and primary biliary cirrhosis, is described in detail elsewhere in this book.

Preventing Reinstitution of the Etiological Factor

The flip side of the coin in liver diseases after cure of the etiological factor is the risk of reinstitution of the same or another factor. In hepatitis C there is a risk of reinfection, and a number of patients have concomitant alcohol overuse, thus the risk of progressive disease and decompensation is not necessarily over after successful treatment with antivirals. Reactivation of hepatitis B is an important and rising clinical problem due to increasing use of immunosuppressive drugs including biologics and novel anticancer drugs. All patients undergoing chemotherapy, immunosuppressive therapy, hematopoietic stem cell transplantation, or solid-organ transplantation should be screened for active or prior hepatitis B viral infection [50]. Abstinence remains the most important therapeutic intervention in alcoholic liver disease, and in NASH lifestyle interventions with weight loss are key to success, but the success rate of lifestyle interventions is low and the rate of relapse high and better options to achieve these goals are warranted.

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Role of Comorbidities in the General Management of Compensated Cirrhosis, Including Malnutrition

22

Marika Rudler and Vincenzo La Mura

Introduction

Comorbidities are defined as diseases that are neither a cause nor a consequence of cirrhosis but that can increase mortality or induce clinical decompensation in patients with cirrhosis. Comorbidities have to be distinguished from the manifestations of cirrhosis decompensation such as variceal bleeding, ascites, or hepatic encephalopathy that are complications of liver diseases [1]. At the time of diagnosis, up to 40% of patients with cirrhosis suffer from at least one other disease [2, 3] that can influence the management of portal hypertension and can play a role in the natural history of cirrhosis. Malnutrition is frequently observed in patients with chronic liver disease, in particular in cirrhosis, and has important prognostic implications [4].

This chapter is intended to provide an overview of the most frequent practical situations in which comorbidities that expose to an additional risk of decompensation can influence the clinical decision making. The epidemiological and prognostic aspects linked to comorbidities and malnutrition will be also discussed.

M. Rudler
Department of Hepatogastroenterology, La Pitié-Salpêtrière Hospital, 47-80 boulevard de l'Hôpital, Assistance Publique-Hôpitaux de Paris, Pierre et Marie Curie University, Paris 75013, France

V. La Mura (✉)
Internal Medicine, IRCCS-San Donato, San Donato Milanese (MI),
Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
e-mail: vin.lamura@gmail.com

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Comorbidities

Comorbidities could be classified in two categories: comorbidities that influence the management of portal hypertension and comorbidities that can influence the severity of portal hypertension (Table 22.1). As patients with compensated cirrhosis may require primary prophylaxis with beta-blockers, classical comorbidities that contraindicate the use of beta-blockers have an impact in the management of portal hypertension. Among the comorbidities that can influence the severity of portal hypertension, obesity, diabetes, and malnutrition have been the best studied.

Obesity

Obesity is defined as a body mass index (BMI) ≥30 kg/m^2. Obesity is a growing epidemic worldwide. Thirty-five percent of adults >20 years old are obese in the USA, and predictions foresee 1.1 billion of obese people worldwide in 2030 [5].

Obesity has a deleterious effect on the natural history of compensated cirrhosis of all etiologies, independently of portal pressure and liver function. One study was carried out in a population of patients included in a RCT evaluating the effect of beta-blockers in patients with compensated cirrhosis of all etiologies [6]. The aim of the study was to evaluate the impact of BMI on hepatic clinical decompensation. Body weight was available at baseline in the cohort of patients, height was retrieved in clinical records, and BMI was retrospectively calculated in 161 patients. Thirty percent of them were obese. After a median follow-up of 59 months, 30% of patients developed decompensation (43% in obese patients *vs.* 15% in those with normal BMI). BMI was an independent predictor of clinical decompensation. The actuarial probability of developing decompensation was higher in the abnormal BMI group.

One of the main issues is to evaluate if obesity treatment may prevent clinical decompensation. A preliminary study [7] aimed at evaluating the impact of lifestyle intervention, including a 16-week program of diet and physical exercise in patients with compensated cirrhosis (all causes) and portal hypertension. In this prospective study including 50 non-decompensated patients, lifestyle intervention (normoproteic hypocaloric diet supervised by nutritionists + 60 min/week of supervised physical activity) significantly decreased body weight, as well as HVPG. None of the

Table 22.1 Influence of comorbidities on the management and severity of portal hypertension

Comorbidities that influence the management of portal hypertension	Comorbidities that can influence the severity of portal hypertension[a]
Obstructive pulmonary disease	Diabetes
Peripheral arterial disease	Obesity
Cardiac conduction disease	Malnutrition
Bradycardia	
Arterial hypotension	

[a]Includes only clinical conditions explored in specifically addressed studies

patients included developed decompensation during the study after a mean follow-up of 6 months. The implementation of measures aimed at reducing obesity in patients with cirrhosis should be a priority. However, long-term results have to be confirmed in obese patients, and the percentage of weight loss or the BMI target which has to be reached in order to avoid long-term decompensation needs to be defined.

Diabetes

Diabetes is frequently associated with cirrhosis, especially in chronic hepatitis C (CHC) [8]. In a recent retrospective monocentric study, among a cohort of 348 patients with CHC-related cirrhosis, diabetes was present in 40% of cases at inclusion. The impact of diabetes on the development of decompensation in compensated patients remains an unsolved question. In the previously cited paper, most patients were hospitalized for complication of cirrhosis at inclusion. However, diabetes at baseline was independently associated with the development of ascites and encephalopathy. This study does not allow drawing any conclusion on the impact of diabetes in compensated patients. A more recent population-based cohort study conducted in Taiwan [9] aimed to assess the impact of new-onset diabetes on the risk of cirrhosis and its decompensation in adults with CHC. The analysis showed a significantly higher cumulative incidence of decompensated cirrhosis in the group of patients with new-onset diabetes, as well as in the group receiving diabetes treatment. However, the study did not provide any information on the control of diabetes and its influence on complications. The same results were described in a cohort of patients with chronic hepatitis B cirrhosis [10].

Whether these results could be extended to other causes of cirrhosis is an unsolved question. Longitudinal studies are therefore warranted in patients with all etiologies of cirrhosis. Impact of treatment and particularly control of diabetes should be studied. Diabetes has to be screened in compensated cirrhosis.

Comorbidities That Need Surgery: Prognostic Factors

Patients with cirrhosis are often candidates to elective or emergency extrahepatic surgery for the management of several comorbidities; among them, gallstones and hernia are the most frequent indications [11]. The surgical risks include perioperative and postoperative mortality and worsening of liver function and decompensation. The majority of studies published on this topic are retrospective and heterogeneous, and as a consequence, evidence-based conclusions are rarely drawn [12, 13]. The series of patients included in these studies include a high percentage of Child-Pugh class A cirrhosis whatever the surgical intervention. In general, the surgical risk correlates with the severity of cirrhosis. Indeed the mortality rate for patients undergoing surgery ranges from 10% for Child-Pugh class A patients to 76–82% for Child-Pugh class C cirrhosis [14]. The nature of the surgical procedure,

in particular, major *vs.* minor intervention and emergency *vs.* elective surgery, the presence of other comorbidities, and, probably, the expertise level of the surgical team are other important risk factors [15].

A frequent challenge for physicians in daily clinical practice is the definition of the surgical risk in each patient. The American Society for Anestesiologists (ASA) developed a score widely used for this purpose [16]. It includes parameters associated to the physical status of a patient, the impact of the index disease, comorbidities, and complications on mortality. Teh et al. [15] at the Mayo Clinic showed that the most important predictors of postoperative mortality were age, the MELD score, and the burden of comorbidities assessed by the ASA physical status classification. By combining these variables, the authors proposed a new model to calculate mortality risk at specific time points after surgery. This model has been recently validated in an independent cohort of patients even though a potential overestimation of the risk has been claimed against the model [17]. Recently a large observational study published by Csikesz et al. [11] has demonstrated that both compensated and decompensated cirrhosis are associated with a significantly increased mortality rate in comparison with patients without liver disease. Interestingly the presence of clinical manifestations of portal hypertension is associated with the highest surgical risk suggesting that portal hypertension plays a determinant role for the morbidity and mortality of extrahepatic surgery in cirrhosis. In line with this hypothesis, preliminary results by Reverter et al. [18] have demonstrated that the hepatic venous pressure gradient (HVPG) measured prior to surgery is an independent predictor of perioperative and long-term mortality together with ASA class and type of surgery, but definitive results are eagerly awaited. Moreover, it would be interesting to test the ability of invasive (e.g., HVPG) or noninvasive (e.g., liver and/or spleen stiffness) measurements of portal pressure to predict the surgical risk in patients with compensated cirrhosis.

The benefit/risk ratio of extrahepatic surgery in patients with cirrhosis is an important challenge in daily practice. The invasive and noninvasive measure of portal pressure may offer an additional contribution to define the prognosis of patients in need of a surgical intervention.

The Epidemiological Importance of Comorbidities: Scoring Systems Explored in Cirrhosis

The clinical relevance of comorbidities is that they can increase the mortality of patients with cirrhosis [1, 18] and, potentially, can influence the quality of life and the outcome of cirrhotic patients in several clinical situations such as variceal bleeding, sepsis, and surgery. Notwithstanding, only few studies of natural history of cirrhosis and management of portal hypertension have taken into account this issue in the analysis [19]. This is in part consequence of the hyperspecialization that dominates both medical research and practice, but it is also consequence of the difficulties to develop an accurate system that reliably summarizes such a heterogeneous variability. To overcome this limitation, several scoring systems have been proposed

to express patients' total burden of comorbidity as a single number instead of a list of diagnosis [20]. This approach makes the communication of individual risk to the patient easier in daily clinical practice and also offers important epidemiological advantages by streamlining the process of stratification and adjustment for potential confounding factors in causal and predictive models [1]. It is intuitive that these important advantages are counterbalanced by the preclusion of a specific evaluation of the effect of an individual disease.

Charlson's score is a system developed in general medicine and frequently used for this purpose [21]. It expresses a number from one to six that corresponds to the specific weight of 19 different diseases on mortality rate at 1 year. The sum of a patient's score is a measure of the total burden of comorbidities. Although some limitations of this score can be pointed out [20], it has been used in observational studies including cirrhotic patients demonstrating a 95%-CI of c-statistic: 0.680–0.687 for inhospital mortality [22] and a strong association with liver and non-liver-related mortality after discharge [23, 24]. A recent publication by Cerini et al. successfully used the Charlson's score to adjust the mortality related with upper gastrointestinal bleeding in patients with cirrhosis under anticoagulation for portal vein thrombosis [25]. Other similar analyses in several clinical contexts of cirrhosis are strongly recommended.

Jepsen et al. have recently proposed a cirrhosis-specific comorbidity score system that in comparison with the most widely validated Charlson's score showed the advantage of being easier and showed slightly better accuracy for prognosis [23]. However, as the authors themselves state, the comparison between these two scoring systems needs further studies to decide which one is preferable for clinical and/or epidemiological studies in patients with cirrhosis.

Nutritional Status

Malnutrition is a feature of late and decompensated stages of cirrhosis. The pathogenesis is multifactorial: reduced nutrient intake because of anorexia, altered protein biosynthesis, increased in protein loss, and impaired intestinal absorption.

The reported frequency of malnutrition is highly variable (50–90%), as definition is different among studies published on the topic. Overweight and obesity are more and more frequent in Western countries [5]. Thus, patients with cirrhosis may present with simultaneous gain of adipose tissue and loss of skeletal muscle. Moreover, liver disease may influence the evaluation. Therefore, malnutrition in cirrhosis should probably be defined as a depletion of skeletal muscle [26].

Diagnostic Tools (Table 22.2)

Nutrition assessment is difficult in cirrhosis because of fluid retention and/or overweight. Moreover, as the nutritional status may vary with the severity of disease, no method is suitable to be used as a gold standard for the assessment of nutritional status.

Table 22.2 Diagnostic tools for the diagnosis of malnutrition in cirrhosis

Method	Interest/advantage	Limits
Clinical assessment SGA[a] Handgrip strength Prognostic nutritional index	Bedside	Bias of interpretation Subjective
Laboratory tests Albumin Prealbumin Creatinine	Objectivity Reproducibility	Confounding factors with liver failure Overestimate malnutrition
CT scan[b] MRI	Objectivity	Lack of validation in compensated patients

[a]Subjective global assessment
[b]Computed tomography scan

Diagnostic tools include physical examination, anthropometric measurements, biochemical data, and quantification of skeletal muscle mass with CT scan or MRI (Table 22.2).

Subjective global assessment (SGA) is a clinical evaluation that can be used at the bedside [27]. It involves weight change, dietary intake, gastrointestinal symptoms, functional capacity, subcutaneous fat, muscle wasting, edema, and ascites (both related to malnutrition). Patients are classified as nourished/moderately malnourished/severely malnourished (SGA grade A/B/C). SGA is a nonobjective method with low sensitivity in cirrhosis because of many confounding factors. It tends to underestimate malnutrition. Practitioners largely use anthropometric measurements; however, measures such as the body mass index are not useful in patients with cirrhosis.

Handgrip strength (HS) is a functional method to assess nutritional status. This method has been compared to SGA in a cross-sectional study [28] that included 50 patients with cirrhosis. HS was found to be superior to SGA to predict liver-related complications.

Biological data include albumin, prealbumin, and creatinine. Impaired hepatic synthesis in cirrhosis leads to overall overestimation of malnutrition using biological data [29]. Biological data do not help in evaluating the nutritional status.

Body composition and also the decrease in adipose/muscle tissue can be evaluated with different methods: total-body electrical conductivity, bioelectrical impedance, dual energy X-ray absorptiometry, air displacement plethysmography, and magnetic resonance spectroscopy. All these methods suffer from poor availability and reproducibility.

Computed tomography scan (CT scan) and MRI are considered as gold standards for the quantification of skeletal muscle mass [30]. In a recent study conducted in patients with an indication for liver transplantation [31], CT scan was used at the 3rd lumbar vertebra in order to analyze muscle quantification. 112 consecutive patients with cirrhosis were evaluated, and 40% of them had sarcopenia using the previously described cutoff. In this study, the authors reported the analysis of two patients with cirrhosis and identical body mass index, with or without

sarcopenia. This underlines the inability of usual methods to evaluate nutritional status in cirrhosis. MRI has been mainly evaluated in decompensated patients.

A validated, accurate, simple, and reproducible tool for nutritional assessment is needed.

Prognostic Influence of Malnutrition on Compensated Cirrhosis

Malnutrition influences quality of life in cirrhosis [32]. In a study conducted in patients with all sort of diseases, malnutrition negatively influenced the validated Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36). However, in this study, it was difficult to distinguish the effect of liver disease from malnutrition on quality of life.

Several studies were conducted in patients with decompensated cirrhosis [31, 33, 34], and all of them concluded that malnutrition was an independent factor predictive of poor outcome, i.e., decompensation and mortality. However, recent data are lacking in compensated cirrhosis. One paper published in 1994 [35] described a cohort of 55 patients (31 Child-Pugh A) with esophageal varices and found that a poor nutritional status was associated with a higher risk of bleeding and death. Nevertheless, subgroup analysis in Child-Pugh A patients was lacking, and nutritional status was subjectively assessed. More recently, a prospective Mexican study [36] suggested that survival was lower in malnourished patients when compared to well-nourished patients, in a subgroup of compensated patients. Unfortunately, cause of death was not reported.

Larger prospective studies should focus on the impact of malnutrition on mortality and the development of ascites, HE, and variceal bleeding in patients with compensated cirrhosis. Strong data are lacking in order to clearly demonstrate that malnutrition itself – and not confounding factors – is deleterious in compensated patients.

Potential Therapeutic Strategies

There is evidence to consider malnutrition as a correctable factor. The aims of therapeutic strategies should be (1) improvement of survival, (2) prevention of complications, and (3) improvement of quality of life.

Increased protein intake is efficient and safe in compensated cirrhosis [37]. However, long-term data on muscle mass are lacking.

Physical exercise is an important factor for muscle metabolism. The effect on sarcopenia of this therapeutic option has not been studied in compensated cirrhosis. However, physical exercise may increase portal pressure and patients should be closely monitored.

TIPS has shown to be efficient in improving body composition in patients with clinical indications for TIPS [38]. Whether TIPS could reverse sarcopenia in compensated patients remains an unsolved question, with issues regarding balancing risks and benefits.

More recently, a preliminary experimental prospective study including six well-compensated patients suggested that leucine-enriched branched chain amino acid supplementation could reverse muscle autophagy, one of the mechanism of sarcopenia [39]. Prospective larger and long-term clinical studies are warranted.

Conclusions

Comorbidities are frequently present in patients with compensated cirrhosis. Among them, obesity impacts on portal pressure and the risk of decompensation. Lifestyle changes and pharmacologic strategies aimed at managing obesity and, potentially, other features of the metabolic syndrome are a promising approach to reduce the risk of long-term decompensation in patients with cirrhosis.

The definition of the benefit/risk ratio of extrahepatic surgery in patients with cirrhosis is an important challenge in daily practice. At present, the Mayo Clinic score is the most validated to predict perioperative and postoperative mortality. The invasive and noninvasive measure of portal pressure may contribute to define the prognosis of patients in need of a surgical intervention, but definitive results are awaited.

Malnutrition can have an impact on mortality and the development of ascites, HE, and variceal bleeding in patients with compensated cirrhosis, but further studies are needed to draw definitive conclusions on this topic.

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Primary Prophylaxis of First Variceal Bleeding

23

Manuela Merli and Roberto J. Groszmann

Treating the Primary Liver Diseases

In the last Baveno consensus meeting, "*the impact of treating the underlying chronic liver disease in the development of varices and other portal hypertensive-related complications*" was considered a relevant area requiring further studies [1]. In this regard an increasing number of studies are becoming available, following the improvement of antiviral therapies for chronic hepatitis. Older studies, dealing with other reversible causes of liver disease, should also be reconsidered.

The majority of severe complications of cirrhosis are associated to the development of portal hypertension. Initially portal hypertension closely correlates with a progressive fibrogenic process in the liver, with fibrillar extracellular matrix deposition overwhelming its degradation and remodeling. At a later stage the hyperdynamic splanchnic circulation plays an important role in aggravating the portal hypertensive syndrome [2].

The distinction of a fibrogenic process which is in progress but still reversible, from a more advanced irreversible stage, is a matter of debate [3].

Nowadays, treatments have become available to cure the etiologic factor of a number of liver diseases. These treatments have been shown to achieve not only stabilization of liver fibrosis but, in some cases, also regression of liver cirrhosis.

M. Merli (✉)
Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Viale dell'Universita' 37, Rome 00185, Italy
e-mail: manuela.merli@uniroma1.it

R.J. Groszmann
Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA
e-mail: Roberto.groszmann@yale.edu

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Therefore, an important clinical issue is to analyze the potential influence of the treatment of the primary liver disease on portal hypertension in patients with cirrhosis and its repercussion in the treatment of portal hypertension and its complications.

Cirrhosis of Nonviral Origin

The regression of liver fibrosis in liver disease has been reported anecdotally in old observations.

The histological improvement of hepatic fibrosis after surgical biliary decompression was first reported in a small group of 11 patients with hepatic fibrosis due to chronic obstruction of the common bile duct [4]. Similar reports have appeared dealing with fibrosis of different etiologies. Eighty-seven patients with corticosteroid-treated autoimmune hepatitis showed no progression (23 patients) or improvement (46 patients) of the histological fibrosis score after treatment, and in 4 of these patients, a regression of cirrhosis could be documented [5]. Improvement of liver fibrosis has also been described in 36 patients with genetic hemochromatosis submitted to venesection therapy [6]. The regression of fibrosis was more frequently seen in patients with a less advanced METAVIR stage, introducing the idea that stages could be identified in which regression of fibrosis could not be achieved.

More interestingly some studies have evaluated the effect of treatment on the regression of portal hypertension. In a small series of 20 patients, spontaneous regression of esophageal varices was reported in six alcohol-abstinent patients, nine posthepatitis B cirrhosis with spontaneous seroconversion, and five hemochromatosis treated with phlebotomy [7]. In another study, 30 patients with alcoholic cirrhosis and portal hypertension were followed prospectively for 5 years by means of endoscopy and HVPG [8]. All patients had esophageal varices at enrollment ranging from grade 1 to 3, and none had a history of portal hypertensive bleeding. Twenty-one out of 30 patients remained alcohol abstinent, and in this group the HVPG decreased significantly in 16 out of 21 patients. In abstainers esophageal varices were absent or grade 1 at the first follow-up, and the probability of remaining free of bleeding was significantly reduced vs. non-abstainers ($p < 0.05$). These data confirm that endoscopic and hemodynamic parameters can improve following sustained alcohol abstinence at least in previously non-bleeding portal hypertensive alcoholic cirrhotic patients. A case report [9] evidenced the disappearance of esophageal varices and hypersplenism in a woman treated for primary biliary cirrhosis (PBC), and the authors discontinued propranolol treatment without any harmful effect. In a larger series of 132 patients with PBC, a direct effect of chronic ursodeoxycholic acid treatment was shown on the progression of portal hypertension during a 6-year period. The stabilization or improvement of the porto-hepatic gradient and the normalization of AST levels at 2 years were associated with a better patient survival free of liver transplantation [10]. In this study the authors suggest, for the first time, that patient "responders" to treatment of the underlying disease may be identified by measuring the changes in portal pressure.

Cirrhosis of Viral Origin

It is important also to explore what has been reported with regard to portal hypertension when patients with chronic liver disease of viral origin are treated with antiviral therapy.

The main target of the antiviral therapy is to terminate virus replication; however, this may also cause other positive biological effects such as regression of inflammation and fibrosis. These changes may influence portal hypertension.

Hepatitis B Virus Cirrhosis

Interferon treatment may induce sustained virological response in about 30 % of HBV patients; however, as it is known, this treatment has several limitations due to its poor tolerability in cirrhotic patients. In the last few years, five different antiviral agents have been approved for HBV treatment in patients with HBV cirrhosis. These are three nucleosides (lamivudine, telbivudine, and entecavir) and two nucleotides (adefovir and tenofovir). Being free of relevant adverse events, when employed according to guidelines, these agents have been largely utilized in patients with chronic hepatitis B or HBV cirrhosis and have been shown to delay the progression of fibrosis and even to possibly reverse fibrosis and cirrhosis. In patients achieving long-term suppression of HBV replication, with nucleoside or nucleotide analogs, the regression of cirrhosis has been reported to be about 60 %. This is in patients undergoing a protocol liver biopsy after 3–6 years of treatment [11–14].

Interestingly only few studies have focused their attention on the consequences of HBV therapy on portal hypertension. As a matter of fact, some authors felt that while histological changes may be limited by sampling variability and problems in the definition of histopathological features, the measurement of changes in portal pressure could represent a useful parameter to assess the real effectiveness of antiviral treatment in patients with cirrhosis [15].

In a small series of 19 cirrhotic patients with HBeAg-negative chronic HBV infection and HVPG $\geq$10 mmHg, the effect of 12 months of lamivudine monotherapy was evaluated by means of HVPG measurement at baseline and at 12 months [16]. Overall 60 % of the patients showed a decrease of HVPG of $\geq$20 % from baseline or at values <12 mmHg, and this improvement was especially associated with the achievement of complete and persistent virological suppression with lamivudine. Another more recent study has focused on a group of 117 HBV cirrhotic patients with advanced esophageal varices [17]. The majority of these patients were under propranolol treatment (95 out of 117), and 63, with a history of previous bleeding, underwent endoscopic eradication. Seventy-nine of the patients included in the study were treated with different nucleosides analogs and 38 served as controls. By the end of the study, the authors reported a significant decrease of the bleeding rate in the group receiving antiviral therapy vs. controls ($p<0.001$). However, four patients with virological breakthrough following lamivudine treatment (3 lamivudine alone and 1 lamivudine and adefovir) all bled concomitantly to

high HBV DNA levels. The small sample size and heterogeneity of antiviral treatment were a relevant limitation of the study. As a matter of fact, well-designed studies about the newer antiviral agents, with a high genetic barrier, which avoid the virological breakthrough are still lacking.

Hepatiis C Virus Cirrhosis

The antiviral treatment for HCV with PEG-IFN plus ribavirin has been utilized in the last decade in patients with compensated cirrhosis providing that the hematological parameters were within the recommended limits for hemoglobin, neutrophil count, platelets, and creatinine. In a prospective, monocentric, uncontrolled study including 20 HCV cirrhotic patients (fibrosis stage 3 or 4) with HVPG >5 mmHg, hemodynamic measurement were repeated at the end of antiviral treatment either if the treatment was stopped or completed [18]. The authors observed a significant drop in HVPG although this effect was mainly due to patients who achieved a virological end of treatment response. Furthermore, a long-term follow-up was lacking. A similar study enrolled 47 HCV cirrhotic patients with portal hypertension who received antiviral treatment and were followed for 6 months after treatment was discontinued. HVPG measurements were performed in 33 patients at baseline and at the end of follow-up, showing a significant decrease in HVPG in patients with a sustained virological response vs. nonresponders [19].

The effect of HCV eradication on esophageal varices was examined by two Italian studies. One study evaluated, in a 12-year prospective follow-up, 218 HCV-compensated cirrhotic patients without esophageal varices [20]. One hundred eighteen of these patients received antiviral treatment with IFN monotherapy; they were younger and had a lower MELD score compared with the untreated group. This in itself represents a bias. During the follow-up, none of the patients who achieved a sustained virological response (34 patients) developed esophageal varices, while varices appeared in 30 % of the untreated patients and in 39 % of those who were nonresponder to treatment. Following their findings the authors suggest that the endoscopic surveillance could be tailored according to the results of antiviral treatment. In contrast a similar study, in which 127 HCV cirrhotic patients with absent or small varices were treated with combined interferon, ribavirin therapy, with a higher number of sustained virological responses (62 patients), added a word of caution with regard to endoscopic surveillance [21]. In fact these authors reported that during a median follow-up of 68 months, two patients developed esophageal varices and one patient developed enlarged small varices in spite of achieving HCV eradication.

It is worth reminding that all the abovementioned studies refer to results obtained with interferon monotherapy or interferon plus ribavirin regimens for the treatment of HCV infections which justify the small percentage of cirrhotic patients (20–25 % or 40–50 %, respectively, for mono- or combined therapy) who achieved a sustained virological response.

We have recently entered the new era of the direct antiviral agent (DAA). This means two relevant changes in the near future: first, a much higher response rate is expected following antiviral treatment, and second, the lack of many of the previous

collateral effects and the overall treatment safety are going to enlarge the number of patients with advanced cirrhosis and portal hypertension who will be ready to receive new treatments. Our knowledge with regard to the effect of HCV eradication in advanced liver disease and portal hypertension is still limited, and whether we could expect a return to a well-functioning liver is still a matter of debate [22]. It is likely that there will be cirrhotic patients who will not reverse even after viral eradication, especially those patients with advanced disease [23]. We will have to follow these patients carefully to evaluate the liver diseases and the repercussion on the portal hypertensive syndrome.

Portal hypertension is caused initially by collagen deposition, but neoangiogenesis, architectural vascular disturbance, and microthrombosis in the liver vascular system may progressively contribute as pathogenetic factors. At present we do not know the degree of portal hypertension which can be reversed. It is more likely that we will prevent the development of esophageal varices in patients with mild portal hypertension, but we do not know the fate of severe portal hypertension after viral eradication.

Specific attention seems to be needed for patients with viral breakthrough or viral relapse who may experience a more rapid increase in HVPG [18].

With respect to early portal hypertension, treating the primary liver diseases is the equivalent of what we used to call "pre-primary prophylaxis of variceal bleeding" with the advantage of being more effective and specific [1].

Open Questions to Answer

Open questions to answer, which need well-designed studies, are the following:

- Should we continue the same endoscopic surveillance schedules in cirrhotic patients after the successful cure of the primary liver disease?
- Should we continue treating with NSBB for primary prophylaxis patients with esophageal varices after the cure of the primary liver disease?
- Should we repeat HVPG and/or endoscopy in cirrhotic patients, at risk of developing or having varices (HVPG $\geq$10 mmHg) after the cure of the primary liver disease? In fact, it is known that patients with HVPG of less than 10 mmHg do not bleed nor do they develop varices [24].
- Should we utilize less invasive techniques such as real-time shear wave elastography, which can be easily repeated during time, to assess "changes" in portal hypertension after the cure of the primary liver disease [25]? Could histological changes (regression of inflammation) in this setting represent a confounding factor?
- Should we investigate for accurate noninvasive biomarkers for portal hypertension?

How Can We Effectively Use Nonselective Beta-Blockers for Primary Prophylaxis of Variceal Bleeding?

Beneficial effects of non-selective beta blockers (NSBB) for the prevention of the first variceal bleeding due to portal hypertension, have been clearly shown in old studies. More recently attention has been focused on other possible effect of NSBB

on portal hypertension.The timololtrial [24] included 213 patients, without esophageal varices, randomized to timolol or placebo to investigate: (a) the effects of timolol in the prevention of the development of esophageal varices and variceal hemorrhage and (b) the predictive value that sequential measurements of HVPG could have in the development of primary (development of varices/variceal hemorrhage), secondary (ascites/portal systemic encephalopathy), and terminating events (transplant or death). Only patients with cirrhosis and portal hypertension (i.e., HVPG >6 mmHg) were included. Hepatitis C virus (HCV)-related cirrhosis accounted for 53 %, alcohol for 20 %, and alcohol plus HCV for 15 % of the study patients, respectively. Yearly endoscopies and HVPG measurements were performed and the median follow-up was 4.2 years. One hundred eight patients received timolol. The incidence of variceal formation ($n=84$) and of variceal hemorrhage ($n=6$), ascites ($n=46$), encephalopathy ($n=17$), and terminating events ($n=22$) did not differ between drug and placebo. Moreover, no significant differences in HVPG were observed between the groups. An HVPG $\geq$10 mmHg at baseline and at year 1 after inclusion was highly predictive of the development of primary, secondary, and terminating events ($p<0.0001$). The systemic hemodynamic profile in patients with HVPG $\leq$10 mmHg is more likely to be normal than hyperdynamic. Therefore, it is possible that at early stages of disease, the reduction in portal blood flow induced by NSBB, even though quantitatively similar to that produced in advanced portal hypertension, results in minimal or no effect on portal pressure. This occurs because under these close to normal conditions the relation between portal blood flow and portal collateral resistance is flat and reductions in portal blood flow induced minor to insignificant changes in pressure [26]. In fact, no effect from NSBB on the HVPG was observed in the group of patients with HVPG <10 mmHg. However, a significant drop on HVPG was observed in the group of patients with pressures $\geq$10 mmHg [27].The absence or presence of "clinically significant portal hypertension," manometrically defined, was, by itself, an important prognostic indicator in patients with cirrhosis [28].

Anextensive debate has been recently generated about the possible harmful effect of beta-blockers in cirrhotic patients with increasing severity of liver disease and hemodynamic instability [29]. A short discussion of this issue is required in a chapter dealing with primary prophylaxis of variceal bleeding. Nowadays, NSBB, if not contraindicated, are in fact an essential therapeutic cornerstone of portal hypertension therapy.

NSBB are probably among the most widely used drugs in cirrhotic patients. It certainly needs to be recognized that randomized trials with NSBB, initially, excluded most severely ill patients such as those with tense or refractory ascites. Low blood pressure is more frequent in these patients and could represent a contraindication to BB, especially at a full dose. However, due to their beneficial results for prophylaxis of variceal bleeding, the use of NSBB has been progressively extended to all cirrhotic patients even to those with a more decompensated disease and with possible contraindications.

NSBB are recognized to decrease portal pressure, and we know that in patients who are "hemodynamic responder," we can prevent first variceal bleeding and at the

same time additional beneficial effects have been suggested to occur and to involve also those patients who do not reach a complete hemodynamic response. NSBB have been reported to reduce the incidence of ascites, refractory ascites, and hepatorenal syndrome [30]; decrease the rate of spontaneous bacterial peritonitis [31]; improve intestinal permeability; decrease bacterial translocation [32]; and decrease the rate of infections [33]: all these effects may contribute to improve patients' survival.

The concern about a possible harmful effect of NSBB came from the observation that survival might be decreased by beta-blockers in patients with refractory ascites [34]. Although retrospective, not based on a randomized study, and weakened by many confounding factors, this observation moved some authors into a working hypothesis which has been presented as the "window hypothesis" for the use of beta-blockers in cirrhotic patients [35]. According to this hypothesis, the indication for NSBB therapy needs to be modulated in cirrhotic patients due to the modification of the hemodynamic conditions, portal hypertension, and sympathetic nervous system activity. Accordingly, NSBB might not be useful in early cirrhosis without varices as the splanchnic blood flow is not increased. On the contrary, NSBB might be even deleterious in end-stage cirrhosis mainly due to a negative impact on the cardiac compensatory reserve. Some more studies have appeared in the literature adding data in favor or against this hypothesis. One large retrospective study reported that up to the development of SBP, BB were associated to improved survival, while after development of SBP, BB treatment could increase the risk for hepatorenal syndrome and reduce the transplant free survival in cirrhotic patients [36]. Another study evaluated retrospectively 61 patients with refractory ascites in whom the survival analysis between patients treated with BB or not receiving these drugs failed to show any significant difference in survival [37]. Similar results were also reported in 114 consecutive patients with refractory ascites, 36 of whom received propranolol with a total daily dose between 40 and 80 mg and had a similar survival as the non-treated group [38]. Finally, a recent study showed that in a large prospectively collected database of patients in the waiting list for liver transplantation, all with ascites, treatment with beta-blockers was associated with better survival [39].

The aforementioned studies are all retrospective and biased by numerous confounding factors. Results are controversial, and caution is needed before a generalized clinical application of these indications is recommended.

Open Questions to Answer

- Do we need to discontinue NSBB in cirrhotic patients with refractory ascites?
- How should we withdraw this therapy? Partially? Completely? Rapidly? Slowly?
- Should we simply take more care to the presence of contraindications such as hypotension and asthenia being more sensitive to the appearance of these symptoms?
- If cardiac reserve is so relevant for the decision of beta-blocker therapy, how should we assess this condition? In fact cirrhotic cardiomyopathy is not strictly correlated with the severity of liver disease.

While this debate could represent a great opportunity for increasing our knowledge on the best use of our therapeutic armamentarium for portal hypertension, it is important to underline that conclusions should not be drawn before real evidences have given enough support to definite recommendations.

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Endoscopic Band Ligation in Primary Prophylaxis

24

Àngels Escorsell and Julio D. Vorobioff

Introduction

Endoscopic band ligation (EBL) has an important role in the therapeutic strategy for both acute esophageal variceal bleeding (emergency EBL) and prevention of variceal rebleeding (therapeutic EBL). Whenever technically feasible, EBL has become the first endoscopic therapy of choice for either primary hemostasis during the acute bleeding episode and for variceal eradication during long-term therapy [1–5].

The place for EBL in primary prophylaxis (prevention of first variceal bleeding in patients at risk) has been strongly debated during the last two decades [6–11]. The most recent consensus definition, reached during the Baveno V meeting, agreed that either nonselective beta-blockers (NSBB) or EBL may be recommended to prevent the first variceal bleeding in patients with medium or large varices, the final decision based on several specific considerations [12].

The Scenario

Along the natural history of liver cirrhosis, patients may progress across different stages. Accordingly, they may be considered as compensated or decompensated [13, 14]. Within the compensated status, we may observe cirrhotic patients without (stage 1) or with already developed, but not previously bleeding, esophageal varices (stage 2). Patients are considered decompensated once any of the following events occurs: variceal bleeding (stage 3), a first non-bleeding decompensating event, such

À. Escorsell
ICU Liver Unit, Hospital Clinic, Barcelona, Spain

J.D. Vorobioff (✉)
Associate Professor of Medicine, University of Rosario Medical School, Rosario, Argentina
e-mail: vorodiez@fibertel.com.ar

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as ascites, portosystemic encephalopathy (PSE) or jaundice (stage 4), and any second decompensating event (stage 5) [15].

Transition into successive stages depends on patient's and/or disease's characteristics. Nevertheless, the previously held concept that cirrhosis had a unidirectional, irreversible, and almost inexorable course, with no-return points along its evolution, has been strongly challenged. In fact, several etiological and/or best available treatments have provided tools for modifying the natural history of the disease. As a consequence, concepts such as stopping the evolution and/or curing chronic liver disease have emerged as new and realistic end points [16–23]. Thus, hepatologists are called to assume a more active and optimistic role in the therapy of chronic liver diseases.

Successful treatment of the etiologic factor may be reached at any of the previously mentioned stages. Nevertheless, although the disease may be "cured," the prognosis may significantly differ among groups. Whereas patients on stages 1 and 2 require therapy to prevent their first decompensation, patients on stages 3, 4, and 5 need, at the same time, therapy to both solve the actual decompensation and prevent a new one. Hypothetically, a significant prognostic change of cirrhosis at different stages would be observed, in case of a synergistic effect of both successful cure of the etiologic factor and available therapies for preventing first or new decompensating events.

The following lines of this chapter will be exclusively devoted to the prevention of first variceal hemorrhage by means of EBL.

The Place for Prophylactic Endoscopic Band Ligation (EBL)

Compensated, cirrhotic patients at stage 1 (without esophageal varices) comprise two different risk populations: those with and those without clinically significant portal hypertension (CSPH) [i.e., a hepatic venous pressure gradient (HVPG) >10 mmHg] [24]. Patients with CSPH are at a higher risk of variceal development than those without CSPH [15, 25, 26]. Therefore, the first question should be the natural history of portal hypertension (estimated by the HVPG) after the successful cure of the etiologic factor. In fact, previous studies in alcoholic cirrhosis showed that alcohol abstainers had significantly greater decreases in HVPG than non-abstainers [27]. Thus, it is probable that the disappearance of the causative agent of the liver disease may be associated with a significant decrease in the risk of CSPH and variceal bleeding. *From a practical point of view*, unless HVPG measurements are routinely performed at the corresponding medical center, the time period between screening endoscopies for variceal development may be similar for all cirrhotic patients [28] although in already cured, compensated stage 1 patients, this time frame should be reconsidered. Compensated, stage 2 cirrhotic patients (with esophageal varices and no previous bleeding) are a relevant target population for prophylactic EBL. At the last Baveno V meeting, it was agreed that "either NSBB or EBL is recommended for the prevention of first variceal bleeding of medium or large varices" and that "choice of treatment should be based on local resources or expertise, patient preference or characteristics, side-effects and contraindications" [12]. It is important to consider that this recommendation was

specifically related to prevention of first bleeding, without considering other effects, if any, of prophylactic EBL on survival or prevention of other portal hypertension-related events.

Background

EBL is an effective therapy for preventing first variceal bleeding in cirrhotic patients. Early evidence for this beneficial effect came from a meta-analysis of five randomized controlled trials (RCT) including 601 patients and comparing EBL with untreated controls, showing a significant reduction in first variceal bleeding (RR = 0.36, 95 % CI 0.26–0.50), bleeding-related mortality (RR = 0.20, 95 % CI 0.11–0.39), and all-cause mortality (RR = 0.55, 95 % CI 0.43–0.71) [29]. Needless to say, these five studies are unethical, given that a no treatment arm was already unjustifiable. However, they contributed to settle EBL as a reliable technique for variceal eradication, rapidly displacing endoscopic injection sclerotherapy (EIS) as the first choice endoscopic treatment for esophageal varices.

By the same time, NSBB (mostly propranolol and nadolol) were already established as the first recommended therapy for primary prophylaxis of variceal bleeding in cirrhotic patients with medium and large varices [30–32]. Moreover, small varices were lately included in the target spectrum of NSBB [33, 34]. However, up to 15 % of patients may not receive NSBB because of an absolute or relative contraindication. Moreover, dose reduction or discontinuation due to side effects may be necessary in another 15 % [10, 32, 35].

Therefore, EBL was initially proposed as an alternative for patients with medium/large varices and with contraindications or intolerance to NSBB [34].

Endoscopic Band Ligation Versus Nonselective Beta-Blockers in Primary Prophylaxis

Several meta-analyses comparing EBL with NSBB for the primary prophylaxis of variceal bleeding were published during the last 15 years. The first one, reported in 2001, included 283 patients from four trials, published in abstract form. Results favored EBL, showing a reduction of the overall risk of first variceal bleeding from 15.7 to 7.6 %, with an RR of 0.48 (95 % CI 0.24–0.96) but with no significant effect on bleeding-related mortality. The risk for all-cause mortality in 253 cases from three of these trials was 17 % in EBL group and 19 % in the NSBB group (RR = 0.95, 95 % CI 0.56–1.62) [29].

A second meta-analysis including 596 patients from eight trials (three published in abstract form) showed that EVL reduced the rates of both first gastrointestinal bleeding by 31 % (RR = 0.69, 95 % CI 0.49–0.96) and first variceal bleeding by 43 % (RR = 0.57, 95 % CI 0.38–0.85). No significant differences were observed in all-cause deaths and bleeding-related deaths. Severe adverse effects were less frequently observed in the EBL group; however, eight patients in this treatment arm

bled from esophageal ulcers, leading to death in two cases. Adverse effects caused by NSBB resulted in no death. This study concluded that EBL compared with NSBB significantly reduced the incidence of the first bleeding and of severe adverse events with no effect on mortality [7].

The third meta-analysis, including 13 RCT, found that EBL reduced the risk of first variceal bleeding compared with NSBB, with no significant differences in mortality. However, the authors noticed conflicting results from individual trials and the possible underestimation of EBL-associated adverse events [36].

A subsequent meta-analysis included 734 patients from nine RCT comparing EBL with NSBB. EBL was better than NSBB in both the incidence of first variceal bleeding (RR = 0.63, CI 0.43–0.92) and the development adverse effects requiring treatment withdrawal (RR = 0.24, CI 0.12–0.47). Six patients had EBL-related bleeding (fatal in two of them). Bleeding-related deaths and overall mortality did not differ between the two treatment groups. The authors concluded that EBL was superior to NSBB in preventing first variceal bleeding and suggested a role for EBL in patients on NSBB with poor drug compliance or intolerance [37].

A contemporary study, including 1167 patients from 16 trials (six in abstract form), was published in 2007. All-cause mortality was similar between the two groups, either in trials with adequate ($n = 3$) or unclear ($n = 13$) bias control (RR = 1.22, 95 % CI 0.84–1.78 and RR = 1.02, 95 % CI 0.75–1.39, respectively). When data from the three trials with adequate bias control were analyzed separately, bleeding-related mortality and variceal bleeding rate did not differ between EBL and NSBB (RR = 1.29, 95 % CI 0.61–2.72 and RR = 0.80, 95 % CI 0.50–1.28, respectively). On the contrary, trials with unclear bias control showed that variceal bleeding was significantly reduced by EBL (RR = 0.57, 95 % CI 0.38–0.85) whereas bleeding-related mortality did not differ (RR = 0.68, 95 % CI 0.31–1.53). Interestingly, trials with at least 20 months of follow-up showed no difference in upper gastrointestinal bleeding between EBL and NSBB (18 % vs. 22 %, respectively; RR = 0.78, 95 % CI 0.57–1.06), while trials with less than 20 months of follow-up favored EBL (8 % vs. 22 %, respectively; RR = 0.38, 95 % CI 0.24–0.61). In summary, trials with less than 20 months of follow-up and published in abstract form were more prone toward showing beneficial effects of EBL over NSBB than those with longer follow-up and published as full paper articles. Thus, the beneficial effect of EBL on bleeding in some trials may be influenced by selection or publication bias [9].

A more recent study comparing EBL with NSBB included 1504 patients from 19 RCT (seven published in abstract form). All-cause mortality (RR = 1.09, 95 % CI 0.92–1.30) and bleeding-related mortality (5.1 % vs. 6.3 %, respectively) did not significantly differ between the two groups. Considering all trials, EBL reduced both upper gastrointestinal bleeding (RR = 0.69, 95 % CI 0.52–0.91) and variceal bleeding (RR = 0.67, 95 % CI 0.46–0.98) compared with NSBB. But, again, the higher efficacy of EBL was related to the duration of follow-up and the publication status of the trial. In fact, the beneficial effect of EBL on the incidence of first bleeding was not confirmed in a subgroup analysis only including RCT with adequate randomization or full paper articles. The authors suggested that long-term and bias-controlled RCT are needed on this issue to provide strong results on the

efficacy and safety of EBL as compared with NSBB in the prophylaxis of first variceal bleeding [38].

The most recent meta-analysis included 1483 patients from 19 RCT (seven published in abstract form). Main outcomes were variceal bleeding rate and all-cause mortality at 6, 12, 18, and 24 months. In summary, bleeding rates were significantly lower for the EBL group overall [OR = 2.06, 95 % CI 1.55–2.73 ($p < 0.0001$)] and at 18 months [OR = 2.20, 95 % CI 1.04–4.60 ($p < 0.04$)]; however, publication bias was once more detected: only considering high-quality trials differences for bleeding rates disappeared. Bleeding-related mortality was similar between the two groups, and all-cause mortality, at any time point, did not significantly differ between EBL and NSBB. In a subgroup analysis, patients receiving "low dose" of NSBB (mean dose <75 mg/day) had significantly higher overall bleeding rate [17.7 % vs. 8.5 % ($p < 0.007$)] than those who underwent EBL. Patients receiving "high dose" of NSBB (mean dose ≥75 mg/day) showed a bleeding rate similar to that of patients receiving EBL. Although severe adverse effects were significantly more frequent in the NSBB group [OR = 2.61, 95 % CI 1.60–4.40 ($p < 0.0001$)], fatal adverse effects were significantly higher in the EBL group [OR = 0.14, 95 % CI 0.02–0.99 ($p < 0.05$)]. No patient died directly as a consequence of NSBB treatment, while four fatal adverse events were reported in the EBL group, all of them due to bleeding from EBL-induced ulcers. According to the authors, "current evidence is insufficient to recommend EBL as first-line therapy over NSBB for primary prophylaxis of variceal bleeding" and "further high quality studies are needed in order to confirm the superiority of EBL over NSBB concerning bleeding rates" [39].

In conclusion, when only high-quality trials are considered, EBL and NSBB are equally effective in preventing first variceal bleeding in patients with high risk esophageal varices. This conclusion endorses Baveno V conclusions regarding primary prophylaxis.

Future studies must improve trial quality by increasing the number of patients included and the length of the follow-up and providing an adequate control of bias. Interestingly, meta-analytic studies of NSBB vs. placebo for primary prophylaxis showed that "side effects were reported in less than 15 % of patients and were usually minor (mainly weakness), requiring withdrawal in less than half of them" and usually "no more than 5 %" [32, 40]. Surprisingly, in trials of EBL vs. NSBB, side effects induced by NSBB averaged 32.5 % [39]. Moreover, in trials of EBL vs. NSBB, a propranolol dose <75 mg/day was associated with higher bleeding rates than a dose ≥75 mg/day, and the average daily dose of propranolol exceeds 75 mg in most RCT of NSBB vs. placebo in primary prophylaxis [32].

Preventing Decompensation After Successful Cure of the Etiologic Factor

Hypothetically, the progression of chronic liver disease would stop after successful cure of the etiologic factor, with improvements of liver structural abnormalities and function and, consequently, a reduction in portal pressure (PP). Therefore, the risk

for portal hypertension-related decompensating events could decrease over time. First variceal bleeding is faced in patients at stage 2 and stages 4 and 5 with no previous bleeding. These populations are candidates for primary prophylaxis, either EBL or NSBB [15–22]. It is important to remark that EBL effects are limited to esophageal varices by achieving their eradication with no short- or long-term effect on any other possible decompensation. On the other side, long-term NSBB administration has shown to effectively prevent not only first variceal bleeding but also other decompensating events related to portal hypertension [41, 42]. In fact, the bleeding rate in NSBB hemodynamic responders (patients whose HVPG decreases ≥20 % vs. baseline or to <12 mmHg) was as low as 5 % at 3 years [41, 43]. Nevertheless, this optimal response was only achieved in ~30/40 % of the treated patients [41, 43]. Previous studies identified an acute HVPG response to IV propranolol (a decrease by 10 % or to ≤12 mmHg) as a factor associated with the achievement of this chronic optimal response to NSBB in cirrhotic patients [44, 45].

As mentioned, in stage 2 cirrhotic patients with medium/large esophageal varices, either EBL or NSBB may be recommended for the prophylaxis of first variceal bleeding [12, 35, 46, 47]. At this relatively early stage of cirrhosis and having reached successful cure of the etiological factor, which is expected to be associated with an improvement in liver function and portal hypertension, physicians must wonder how often post-EBL surveillance endoscopic studies should be performed. Thus, EBL and NSBB may become not only accessory but also temporary therapeutic strategies in primary prophylaxis.

Successful cure of the etiologic factor might also be achieved at both stage 4 and stage 5, in previous non-bleeders [48, 49]. Outcome of these patients afterward remains speculative. Meanwhile, either EBL or NSBB may be offered as primary prophylaxis. However, certain circumstances preclude NSBB administration or advise their interruption. In this way, previous studies reported a decreased survival in patients with refractory ascites [50] or developing SBP [51] while treated with NSBB. Moreover, this therapy was shown to increase the post-paracentesis circulatory dysfunction in patients with ascites [52]. Therefore, in those specific situations, patients would rather receive EBL.

Finally, some patients with advanced liver failure will already be in a transplant list. An RCT in this population, including 62 patients, showed no significant differences in variceal bleeding rate, mortality, or bleeding-related mortality among those randomized to EBL vs. those receiving NSBB [53].

Summary

Endoscopic band ligation is an effective technique for the eradication of esophageal varices and, accordingly, a rational option for primary prophylaxis of variceal bleeding. Several studies and meta-analysis comparing EBL with NSBB in this setting have been reported. Most of them favored EBL over NSBB. However, when only high-quality trials were considered, this superiority vanished, resulting in EBL and NSBB being equally effective in preventing first variceal bleeding with no

significant differences in mortality. Therefore, at this moment, either EBL or NSBB may be recommended for prophylaxis of first variceal bleeding.

Main drawbacks of commonly used NSBB (propranolol and nadolol) are the following: (1) their low hemodynamic responsiveness and (2) a relatively high incidence of contraindications/side effects requiring withdrawal. Looking at the first problem, new drugs with higher portal hypotensive effects than "classic" NSBB have been introduced. One of such drugs is carvedilol, an NSBB with intrinsic anti-α-1-adrenergic activity [54]. Carvedilol may be a reliable option for hemodynamic nonresponders to NSBB [55]. Simultaneously, it also may represent a challenging option to face EBL in this population. Two RCT comparing EBL with carvedilol in primary prophylaxis look promising in this way [56, 57]. Another exciting pharmacological strategy for improving outcomes in primary prophylaxis is the combined administration of propranolol and statins [58, 59]. Finally, looking at the second problem, NSBB side effects, although frequent, are of no or low clinical relevance.

Successful cure of the etiologic agent in chronic liver disease opens new questions and challenges in primary prophylaxis. An improvement in both liver structure and function should translate into a portal pressure reduction. If this is so, compensated cirrhotic patients at either stage 1 or 2 might benefit from a decrease in the risk of portal hypertension-related decompensations (variceal bleeding, ascites, etc). A successful cure may also occur at more advanced stages of the disease (stages 3, 4, and 5). However, it seems reasonable to anticipate that the prognosis of these patients will differ from that of compensated ones.

In the next future, and according to the results of ongoing and new study outcomes, EBL and NSBB may become partners of other drugs in the field of primary prophylaxis. Moreover, this partnership may be transitory, and beneficial outcomes may not be exclusively reflected on variceal bleeding prevention but also on other portal hypertension-related decompensating events [60].

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Consensus Statements: Changing Scenarios: Prevention of Decompensation

25

Aleksander Krag, Àngels Escorsell, Roberto Groszmann, Vincenzo La Mura, Manuela Merli, Marika Rudler, Julio D. Vorobioff, and Carlo Merkel

Cure of the Etiologic Agent

- Successful cure of the etiologic agent in chronic liver disease may improve both liver structure and function, and this could translate into a portal pressure reduction (1b;A).

A. Krag
Department of Gastroenterology and Hepatology, University of Southern Denmark and Odense University Hospital, Odense, Denmark

À. Escorsell
Intensive Care Unit, Liver Unit, Hospital Clinic, Barcelona, Spain

R. Groszmann
Digestive Diseases, Yale University School of Medicine, New Haven CT, USA

V. La Mura
Department of Internal Medicine, IRCCS-San Donato, San Donato Milanese (MI), University of Milan, Milan, Italy

M. Merli
Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy

M. Rudler
Department of Hepatogastroenterology, La Pitié-Salpetrière Hospital, Pierre et Marie Curie University, Paris, France

J.D. Vorobioff
Hepatic Hemodynamic Lab, University of Rosario Medical School, Rosario, Argentina

C. Merkel (✉)
Department of Medicine, University of Padua, Padua, Italy
e-mail: Carlo.merkel@unipd.it

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Comorbidities and Malnutrition

- Comorbidities (obesity, diabetes, cancer, osteoporosis, pulmonary, renal, and cardiovascular diseases) are frequently present in patients with compensated cirrhosis. Some of them can contribute to decompensation, while others are a consequence of liver disease (2b;B).
- Malnutrition and sarcopenia have been shown to have an impact on hepatic encephalopathy, development of ascites, incidence of infections, and survival in cirrhotic patients (1b;A). As the evidence was mainly reported in decompensated patients, further studies are needed to draw definitive conclusions on this topic also in patients with compensated cirrhosis (5;D).

Patients with No Varices or Small Varices

- There is no indication, at this time, to use beta-blockers to prevent the formation of varices (1b;A).
- Patients with small varices with red wale marks or Child C class have an increased risk of bleeding (1b;A) and should be treated with nonselective beta-blockers (NSBB) (5;D).
- Patients with small varices without signs of increased risk may be treated with NSBB to prevent bleeding (1b;A). Further studies are required to confirm their benefit.

Patients with Medium-Large Varices

- Either NSBB or endoscopic band ligation (EBL) is recommended for the prevention of the first variceal bleeding of medium or large varices (1a;A).
- The choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications, and adverse events (5;D).

Carvedilol

- Traditional NSBB (propranolol, nadolol) (1a;A) and carvedilol (1b;A) are valid first-line treatments.
- Carvedilol is more effective than traditional NSBB in reducing HVPG (1a;A) but has not been adequately compared head-to-head to traditional NSBB in clinical trials.

Patients with Gastric Varices

- Although a single study suggested that cyanoacrylate injection is more effective than beta-blockers in preventing first bleeding in patients with large gastroesophageal varices type 2 or isolated gastric varices type 1 (1b;A), further studies are

needed to evaluate the risk/benefit ratio of using cyanoacrylate in this setting before a recommendation can be made (5;D).

Role of HVPG Measurement

- The decision to treat with beta-blockers should be taken when indicated, independent of the possibility of measuring HVPG (1a, A).
- HVPG measurement provides prognostic information (1b, A).
- HVPG change is a relevant surrogate outcome (1b;A).
- The measurement of HVPG response to therapy offers additional relevant information: a decrease in HVPG of at least 10 % from baseline or to ≤12 mmHg after chronic treatment with NSBB is clinically relevant in the setting of primary prophylaxis (1b;A). Similarly, acute HVPG response to intravenous propranolol may be used to identify responders to beta-blockers; specifically a decrease in HVPG of 10 % or to ≤12 mmHg may be relevant in this setting (1b;A).
- HVPG response to NSBBs is associated with a significant reduction in risk of variceal bleeding (1a;A) and decompensation (1b;A).
- HVPG measurements should be encouraged in clinical trials investigating novel therapies, but are not essential if portal hypertension-associated endpoints are well defined (5;D).

Use of Nonselective Beta-Blockers (NSBB) in Patients with End-Stage Liver Disease

- The safety of NSBB in subgroups with end-stage disease (refractory ascites and/or SBP) has been questioned (2b;B).
- NSBB contraindications may be absent when the therapy is firstly prescribed but need to be monitored during the evolution of the disease (5;D).
- Close monitoring is necessary in patients with refractory ascites, and reduction of dose or discontinuation can be considered in those who develop low blood pressure and impairment in renal function (4;C).
- If NSBB are stopped, EBL should be performed (5;D).

Research Agenda

- More data are needed to unravel the course of disease after cure of the etiological factor.
- Successful treatment of the underlying liver disease (alcohol abstinence, antiviral therapy) may reduce HVPG, size of varices, and risk of bleeding. Novel anti-

virals are expected to expand this knowledge and reinforce data to suggest changes in surveillance intervals of varices and other complications.
- Competing risks from comorbidities should be taken into account in future studies.
- Future studies are required to describe the impact of early detection and treatment of comorbidities.
- The impact of treatments to improve nutritional status on prognosis and mortality should be evaluated.
- New prospective studies to assess the safety of NSBB in end-stage disease are warranted.

Part VI

Management of the Acute Bleeding Episode

Management of Acute Variceal Bleeding in Patients with Cirrhosis: General Management, Drug Therapy, and Endoscopic Treatment

26

Puneeta Tandon, Ian M. Gralnek, Gin-Ho Lo, Lars Aabakken, Frederik Nevens, and Juan Carlos Garcia-Pagán

Introduction

Acute variceal bleeding (AVB) is a life-threatening complication of patients with cirrhosis and is the most common cause of acute upper gastrointestinal bleeding in this patient population. Therefore, AVB should be the diagnosis of suspicion in all

P. Tandon, MD, FRCP(C), MSc (Epi)
Division of Gastroenterology, Department of Medicine,
Cirrhosis Care Clinic, Edmonton, AB, Canada
e-mail: ptandon@ualberta.ca

I.M. Gralnek, MD, MSHS, FASGE
Rappaport Faculty of Medicine, Technion-Israel Institute of Technology,
Institute of Gastroenterology and Liver Diseases, Ha'Emek Medical Center, Afula, Israel
e-mail: ian_gr@clalit.org.il

G.-H. Lo
Division of Gastroenterology, Department of Medical Research, E-DA Hospital,
School of Medicine for International Students,
I-Shou University 1, Yi-Da Road, Kaohsiung County 824, Taiwan
e-mail: ghlo@kimo.com

L. Aabakken
Department of Cancer, Surgery and Transplant Surgery, Oslo University Hospital,
Rikshospitalet, Oslo, Norway
e-mail: Lars.aabakken@medisin.uio.no

F. Nevens, MD, PhD
Division of Liver and Biliopancreatic Disorders, University Hospitals Leuven,
KU Leuven – University of Leuven, Leuven, Belgium
e-mail: frederik.nevens@uzleuven.be

J.C. Garcia-Pagán, MD, PhD (✉)
Barcelona Hepatic Hemodynamic Lab, Liver Unit, Hospital Clinic,
IDIBAPS and CIBERehd, University of Barcelona, Barcelona, Spain
e-mail: jcgarcia@clinic.ub.es

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cirrhotic patients admitted with hematemesis and/or melena. Improvements in general management and available hemostasis treatments have led to a marked reduction in AVB-related mortality [1].

In this chapter we will review treatments aimed to control the AVB episode and strategies to prevent bleeding-related complications.

General Management of Acute Variceal Bleeding

General management is aimed at correcting hypovolemia and at preventing complications associated with gastrointestinal bleeding (bacterial infections, hepatic decompensation, and renal failure).

Blood Volume Restitution and Transfusion

Blood volume replacement should be initiated with plasma expanders, aiming to maintain systolic blood pressure around 100 mmHg. Caution must be taken not to over-transfuse because this may induce rebound increases in portal pressure and subsequent rebleeding [2]. Indeed, a certain degree of hypovolemia and hypotension promotes the activation of endogenous vasoactive systems leading to splanchnic vasoconstriction and, therefore, a reduction in portal blood flow and pressure. On the other hand, prolonged hypotension may facilitate the development of bacterial infection and renal failure. A restrictive packed red blood cell transfusion strategy has been shown to improve survival in Child-Pugh A and B patients. Therefore, a blood transfusion strategy should aim at maintaining the hemoglobin at a target level of 7–9 g/dL, transfusing when the hemoglobin drops below 7 g/dL [3] except in patients with rapid ongoing bleeding or those with cardiovascular disease.

In patients with cirrhosis, the prothrombin time and INR are not reliable indicators of coagulopathy and/or the risk of further bleeding. In fact, two randomized controlled studies have evaluated the effect of recombinant factor VIIa (rFVIIa) on variceal bleeding in cirrhosis without showing significant benefit. Although a meta-analysis of these two trials using individual patient's data showed a small benefit in the subgroup of patients with active variceal bleeding at endoscopy, the use of rFVIIa was associated with a higher incidence of thrombotic events [4]. Therefore, there is no indication for the use of rFVIIa in the treatment of acute variceal bleeding, although it might be considered in exceptional cases in patients with lack of control of bleeding with standard treatment. Although there is no scientific evidence for its use in AVB, many centers use a transfusion threshold for platelets of ≤40,000 platelets/mL.

Bacterial Infections

Patients with cirrhosis are at an increased risk for bacterial infections due to a combination of innate and adaptive immune dysfunction, increased intestinal permeability,

and pathological bacterial translocation [5]. Upper gastrointestinal bleeding, poor liver function, low-protein ascites, and a prior episode(s) of spontaneous bacterial peritonitis (SBP) are the major clinical risk factors that predispose to infection.

In the setting of AVB (in the absence of antibiotic prophylaxis), approximately 20 % of patients are infected on the day of admission and up to 50 % develop an infection during their hospital stay [6]. Most infections develop within the first 5–7 days after the bleeding episode. The most commonly reported infections are bacteremia (19–56 %), SBP (19–37 %), urinary tract infections (12–34 %), and pneumonia (12–19 %) [6–9]. Bacterial infections increase AVB-related mortality [5, 6, 8] and in smaller studies have been associated with the failure to control bleeding and increased rebleeding [10, 11]. These adverse outcomes are explained in part by infection-induced increases in portal pressure [12] and changes in hemostasis, including the production of endogenous heparin-like substances and the release of cytokines which impair platelet function, increase fibrinolysis, and increase the consumption of clotting factors [13, 14].

Systematic reviews and meta-analyses [6, 8, 15] have demonstrated a clear reduction in the rates of bacterial infection, rebleeding, and mortality with antibiotic prophylaxis [6, 8, 15]. Accordingly, the Baveno V consensus guidelines recommended that antibiotic prophylaxis be instituted as early as possible on presentation of AVB and continued for 5–7 days in all patients [16, 17].

The antibiotic of choice recommended by the Baveno V consensus was oral norfloxacin (400 mg twice daily) [17]. A third-generation cephalosporin (ceftriaxone 1 g intravenously once daily) was recommended for the subgroup of patients with a recent infection with a quinolone-resistant organism, those receiving quinolone prophylaxis, or those with "advanced cirrhosis" as defined by at least 2 of the following: ascites, jaundice (bilirubin >3 mg/dL), hepatic encephalopathy, or malnutrition [16]. Data supporting the use of a third-generation cephalosporin in selected patients comes from a randomized controlled trial by Fernandez et al. [18] where patients with "advanced cirrhosis" and AVB were randomized to oral norfloxacin or intravenous ceftriaxone for 7 days with a primary endpoint of bacterial infection within 10 days. Patients randomized to norfloxacin had a higher rate of bacterial infections. Quinolone resistance was the major cause of quinolone failure in these patients.

There is a well-known association between worsening liver disease severity and increasing risk of bacterial infection [1, 9, 16]. Therefore it has been proposed that because *the risk of bacterial infection and mortality are very low in patients with Child-Pugh A cirrhosis, they may not require antibiotic prophylaxis.* This risk stratification of antibiotic therapy is especially relevant considering:

(a) Antibiotic stewardship is a matter of clinical urgency [19] and an important responsibility of all physicians. Stewardship is defined as "the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance."
(b) The well-known side effects of antibiotics (e.g., antibiotic associated diarrhea, hypersensitivity reactions, class-specific complications). Robust studies have

linked antibiotic exposure to *Clostridium difficile*-related colitis [20, 21]. A series by Bajaj et al. compared cirrhotics with *Clostridium difficile* infection to those without and found that infection increased the adjusted odds of death by 1.6 times [20, 21].

(c) Infections with multi-drug-resistant bacteria [22]. In a series by Fernandez et al. [23], infection with antibiotic-resistant organisms was associated with a threefold increase in septic shock and a twofold increase in mortality as compared to infections caused by antibiotic-sensitive organisms.

Data from a recent propensity-matched sample of 381 patients with AVB who either received or did not receive antibiotic prophylaxis supports the Child-Pugh stratified increases in bacterial infection [24]. In Child-Pugh A patients, the risk of infection (2 % vs. 1 %) and mortality (2.5 % vs. 0.4 %) were both very low, regardless of exposure or non-exposure to antibiotics. Among patients categorized as Child-Pugh class B who were given antibiotics, 6 % developed infections, compared with 14 % of patients who did not receive antibiotics ($p < 0.05$). Antibiotics did not have a significant impact on mortality in the Child-Pugh class B group, likely due to a low baseline risk (mortality rate of 5 % vs. 7 %). Administration of antibiotics in Child-Pugh class C patients did however result in significant reductions in both bacterial infections (19 % vs. 39 %) and mortality (35 % vs. 62 %). Although there is both pathophysiological and clinical rationale to support the low risk of infection in Child-Pugh A patients, prospective multicenter trials have been suggested before a formal recommendation can be made to avoid antibiotic prophylaxis in AVB patients with Child-Pugh A disease.

In patients exposed to quinolone prophylaxis, there is a rapid emergence of quinolone-resistant bacteria in the fecal flora. In addition, rates of infections resistant to quinolone-based therapy (both as a result of resistant gram-negative organisms and also growing number of infections with gram-positive organisms against which quinolones are known to be ineffective) are increasing [18, 25], with rates above 50 % at several centers across the world (European country-specific data available from the European Centers for Disease Control). This high rate of quinolone resistance is also supported by specific data obtained from patients with AVB. At two tertiary care centers in Edmonton, Canada, investigators retrospectively evaluated 347 patients with AVH who had not received antibiotic prophylaxis as part of their management. Of 51 culture-positive infections, there was a 65 % quinolone resistance rate, largely due to gram-positive infections. Although the rates of cephalosporin resistance are also increasing in patients with cirrhosis, a third-generation cephalosporin has broader gram-negative and gram-positive coverage as compared to the quinolone class of antibiotics. Even broader coverage may be needed in some patients with AVB, depending on individual risk factors. For example, the European Association for the Study of the Liver has published a position statement suggesting that patients who have had a recent (within 3–6 months) infection with an extended-spectrum ß-lactamase-producing *Enterobacteriaceae* should receive oral nitrofurantoin 50 mg/6–8 h or ertapenem 1 g/day [5]. The ideal antibiotic choice will therefore vary depending upon individual risk factors and

local antibiotic susceptibility patterns. Although further prospective studies are required in this area, we propose that *individual patient risk characteristics and local antimicrobial susceptibility patterns must be considered when determining appropriate first-line AVB antimicrobial prophylaxis at each center. Within this overlying guiding principle, we would suggest that oral quinolones are no longer appropriate as first-line therapy at most centers. Per the previous Baveno guideline, intravenous ceftriaxone given at a dose of 1 g intravenously every 24 h should be considered in patients with advanced cirrhosis, in hospital settings with a high prevalence of quinolone-resistant bacterial infections, and in patients on previous quinolone prophylaxis.*

Hepatic Encephalopathy

After bacterial infections, gastrointestinal bleeding is the second most common precipitant of episodic overt hepatic encephalopathy (HE).

HE management in AVH should be based on recent AASLD/EASL guideline recommendations [26]. The guideline's "four-pronged" approach includes (1) initiating care for altered consciousness, (2) looking for and treating altered mental status, (3) identifying and correcting precipitating factors, and (4) starting empirical HE treatment. Lactulose is used as first-line therapy for AVB precipitated episodic HE, with 25 mL given every 12 h until at least 2–3 soft bowel movements per day are produced, followed by titration of the dose to maintain 2–3 soft bowel movements per day. Careful titration is important as excessive lactulose can lead to dehydration, hypernatremia, acute kidney injury, aspiration, and even precipitation of HE. As suggested by the HE guidelines, once the symptoms of HE resolve and the precipitating event (e.g., AVB) is brought under control, continued prophylactic lactulose may not be needed [26].

Although there have been studies performed more than 15 years ago that have evaluated the role of whole gut irrigation with mannitol in preventing HE episodes [27–29], there are only two more recently published prophylaxis studies in patients receiving contemporary management. The first study by Sharma et al. randomized 70 AVB patients to lactulose vs. no lactulose with a primary outcome of the development of overt HE within 5 days (assessors determining presence of HE were blinded to randomization) [30]. Patients with overt HE at presentation, a past history of HE, lactulose within the past 6 weeks, and severe non-liver comorbidities were excluded. The majority (>80 %) were males and the mean Child-Pugh score was 9.6. HE developed in 40 % of the placebo group and 14 % of the lactulose group, 53 % of the episodes were grade 2 HE, and the median time to development was 2 days. There was no significant difference in the secondary outcomes of mortality or time in hospital. Twenty-six percent of the lactulose group had diarrhea and 11 % abdominal bloating but there was no reported electrolyte or renal dysfunction at day 5 as compared to baseline. On multivariate analysis, the three independent predictors of HE were the baseline arterial ammonia level, blood transfusion requirement during the hospital stay, and lactulose therapy.

The second study by Maharshi S et al. was reported as a letter to the editor [31]. One hundred and twenty AVB patients were randomized to lactulose vs. rifaximin with a primary outcome of overt HE within 5 days. Patients with overt HE on presentation were excluded. There was no significant difference in the percentage of patients who developed HE (17 % of the lactulose group and 15 % of the rifaximin group), duration of hospitalization stay, or mortality. Fifty-three percent of the EH episodes were grade 2 and occurred within a median of 2 days. Twenty-seven percent of the lactulose group had diarrhea and 15 % had abdominal bloating. Similar to the first study, baseline arterial ammonia and blood requirement during the hospital stay were independent predictors of developing HE. Although both groups of investigators suggested that prophylactic anti-HE therapy be incorporated as part of standard management in AVB, we would suggest that there remains insufficient data to make recommendations regarding the prevention of HE in patients with cirrhosis and upper GI bleeding. Although it is possible that future studies will provide evidence that anti-HE therapy is an important treatment for some high-risk patients, the empiric use of lactulose for all AVB patients has the potential to cause more harm than good particularly given the discrepancies in side-effect monitoring that may occur between "real-world" and trial patients and the volume-contracted state these patients are in. Therefore, before prophylactic therapy can be recommended as standard management in a contemporary cohort of patients, we need to be able to identify high-risk patients and prospectively validate available data in additional sites, including North America and Europe.

Acute Kidney Injury (AKI)

Patients with AVB are predisposed to develop AKI predominantly as a result of intravascular volume depletion, bacterial infections, and in some patients the use of nephrotoxic medications such as nonsteroidal anti-inflammatory drugs. In the study by Cardenas et al., including 161 patients [32], renal failure was diagnosed in 11 % of patients (increase in creatinine of ≥50 % to a value >1.5 mg/dL within the first 7 days following AVB) and was transient in 40 % of cases. Independent predictors of renal failure included Child-Pugh class, hypovolemic shock, the number of units of packed red blood cells transfused, and baseline platelet count. Mortality was 55 % in the renal failure patients as compared to 3 % in those without renal failure. Non-transient renal failure was associated with the highest mortality at 83 %. These data have been confirmed in a more recent cohort of 159 patients with cirrhosis [33]. Therefore, as with many other groups of patients with cirrhosis, AKI in AVB appears to be a robust predictor of mortality.

The International Ascites Club has published a consensus guideline that summarizes the principles for the prevention and treatment of AKI in cirrhosis. These recommendations can be applied to the AVB setting and include the removal of all potentially nephrotoxic drugs, plasma volume expansion, prompt recognition and early treatment of bacterial infections, and in selected patients the early initiation of vasoconstrictor therapy.

Specific Hemostatic Therapy

Vasoactive Agents

Drugs and Dosing

Vasoconstrictors are used as a first-line therapy for acute esophageal variceal hemorrhage. Vasopressin was the first pharmacological agent on the market to be used for arresting acute esophageal variceal hemorrhage and was widely used approximately two decades ago. However, a high frequency of adverse events directly related to nonselective arterial vasoconstriction such as hypertension, severe arrhythmia, abdominal cramps, and coronary artery spasm may be associated with the use of vasopressin. With the advent of newer and more selective vasoconstrictors, vasopressin has been almost completely substituted by other agents for the treatment of acute esophageal variceal hemorrhage.

Terlipressin is an analogue of vasopressin but is slowly metabolized to vasopressin and released in the circulation upon administration. Thus, terlipressin has the advantages of a longer half-life, i.e., 1.5 h and a lower frequency of adverse events. Terlipressin is generally administered intravenously as a 2 mg bolus intravenously for a loading dose and subsequently given 1–2 mg every 4 or 6 h. It has been suggested that terlipressin can be administered at a dose of 1 mg every 4 or 6 h once the acute bleeding episode has been controlled [34]. The hemostatic rate of terlipressin ranges between 19 and 80 % [35]. Chang et al. showed that the hemostatic rates were similar between patients receiving high-dose (2 mg) and low-dose (1 mg) terlipressin, i.e., 53 % vs. 48 %, respectively [36].

Somatostatin is naturally synthesized by the body and can be commercially produced for clinical use. It has the shortest half-life, i.e., 3 min, as compared with other vasoconstrictors. Thus, somatostatin should be administered by continuous intravenous infusion, usually a bolus dose of 250 μg, followed by 250 μg per hour. The reduction in portal pressure is more pronounced when somatostatin is administered at a dose of 500 μg/h than 250 μg/h [37] A controlled study from Spain showed that high-dose somatostatin (500 μg/h) was superior to low-dose somatostatin (250 μg/h) in the control of active variceal hemorrhage whereas both dosing regimens had similar hemostatic rates in patients without active hemorrhage at the time of endoscopy [38].

Octreotide is an analogue of somatostatin with a half-life of approximately 2 h. Octreotide can be administered either intravenously or subcutaneously. The recommended intravenous dose of octreotide is 25–50 μg hourly. Though the half-life of octreotide is prolonged, rapid desensitization is noted during hemodynamic studies, and lowering of portal pressure may be as short as a few minutes [39]. Although the clinical efficacy of octreotide has been doubted by some scholars, octreotide is widely adopted in the United States to control acute esophageal variceal hemorrhage and a meta-analysis has shown that octreotide compares favorably with other vasoconstrictors [40].

A recent meta-analysis showed that the use of vasoactive agents was associated with a significantly lower risk of acute mortality and transfusion requirements, improved control of bleeding, and shorter hospital stay [41]. No significant

differences in efficacy were found between the different vasoactive drugs [41]. Terlipressin may be the vasoconstrictor of choice for patients with acute variceal bleeding in association with hypotension or hepatorenal syndrome. On the other hand, somatostatin or octreotide instead of terlipressin should be the first option for patients with acute variceal bleeding in association with hypertension or with history or potential risk of coronary artery disease or peripheral vascular disease.

Vasoconstrictors should be administered as soon as possible when there is a clinical suspicion of acute esophageal variceal hemorrhage. Indeed, several studies [42–44] have unquestionably shown that early administration of vasoconstrictors such as terlipressin or somatostatin should be adopted before endoscopic evaluation. The duration of vasoconstrictor use prior to endoscopy has varied from 1 to 24 h in previous studies. It is suggested that vasoconstrictors should be administered for at least 30 min prior to endoscopy.

A meta-analysis of eight studies comparing endoscopic treatment alone with endoscopic plus vasoconstrictor treatment for acute esophageal variceal hemorrhage demonstrated that 5-day hemostasis and 5-day mortality were significantly lower in patients receiving combination therapy than in those receiving endoscopic treatment alone [45]. The methods of endoscopic treatment used were sclerotherapy in 5 studies, EVL in 1 study, and either sclerotherapy or EVL in 1 study. Five-day hemostasis was 58 % in patients receiving endoscopic treatment alone and this rose to 77 % in patients receiving combined endoscopic and vasoconstrictor therapy. Therefore, for decades, combination therapy has been the treatment of choice in the management of acute esophageal variceal hemorrhage. Since EVL has replaced sclerotherapy as the endoscopic therapy of choice for acute esophageal variceal hemorrhage [46], combination therapy with EVL and vasoconstrictors is considered the treatment of choice [47]. Regarding the choice of vasoconstrictors, one study showed that terlipressin was not inferior to octreotide as an adjuvant therapy with EVL for the control of acute esophageal variceal hemorrhage, i.e., 92.6 % vs. 95.6 % [48]. Another study also showed no difference between terlipressin, somatostatin, and octreotide as adjuvant therapy to EVL in the 5-day hemostasis rate of acute esophageal variceal hemorrhage, 86.2 %, 83.4 %, and 83.8 %, respectively [49].

The duration of vasoconstrictors in these studies varied between 3 and 5 days. A study from Pakistan found that after successful hemostasis by EVL, adjuvant therapy with terlipressin 1 mg every 6 h for 24 h was as effective as adjuvant therapy with terlipressin 1 mg every 6 h for 72 h for the outcomes of 5-day hemostasis, 30-day rebleeding, and mortality [50].

A recent study revealed that, in patients initially treated with vasoconstrictors in which initial hemostasis was achieved by EVL at the diagnostic endoscopy, the extension of treatment with either terlipressin or the proton pump inhibitor, pantoprazole, achieved similar 5-day hemostasis, 96 % and 98 %, respectively [51]. This data may suggest that there is a specific group of patients that after the initial successful control of the AVB episode with drugs until a successful EBL is performed may not need further treatment to control the bleeding episode. However, until more data on this issue is provided, the general recommendation must be to extend drug therapy for 2–5 days after EBL.

Side Effects of Vasoactive Drugs

The overall safety of all the vasoactive drugs is acceptable but many of the studies exploring the beneficial effect of these drugs for variceal bleeding are older studies and none of the trials were registration trials, audited by authorities. This explains why in several studies a detailed description of all possible drug-related side effects is not well reported. In addition, as variceal bleeding is a condition associated with severe complications, it is challenging to definitively attribute adverse events to the drug as opposed to the underlying hemodynamic instability or associated liver failure. Nevertheless, despite similar numbers [49], the profile of reported side effects is quite different when comparing those produced by terlipressin or octreotide/somatostatin. Terlipressin, in contrast to somatostatin/octreotide, has cardiovascular side effects such as ischemia of extremities, cardiac arrhythmias, hypertension, left ventricular failure, myocardial ischemia, and sudden death. For this reason, studies using terlipressin have routinely excluded patients with a history of cardiovascular diseases, thereby improving its safety profile but reducing its applicability. In order to reduce the side effects of terlipressin, two trials have explored a shorter duration of administration [50, 52]. Both studies concluded that a short course of terlipressin of 24–48 h was an effective treatment and there was a tendency to fewer side effects with shorter duration of therapy. Hyperglycemia is the most commonly reported mild adverse effect when using somatostatin/somatostatin analogues and occurred in 13 % vs. 8 % of the patients receiving placebo.

Hyponatremia

Although terlipressin-related hyponatremia was already reported in other trials [53, 54], the frequency was less than 6 % and neurological complications were not systematically reported. None of these older studies focused systematically on the presence of hyponatremia. Recent studies [49, 55–57] reported a much higher incidence of hyponatremia, many of these patients with reductions in sodium greater than 10 mEq/L. (Table 26.1.). Three of the 21 patients in the study by Solà et al. [55] had marked reduction of serum sodium and developed neurological manifestations, including osmotic demyelination syndrome in one patient. Terlipressin-induced hyponatremic seizure has been also reported [58]. The most likely explanation of terlipressin-induced hyponatremia is that this drug has strong agonistic activity on renal V2 vasopressin receptors causing free water retention. The administration of hypotonic fluid strongly favors the development of acute hyponatremia in this situation. In the study by Solà et al. [55], patients who developed hyponatremia had less advanced liver disease and higher baseline serum sodium concentration, suggesting that in these patients the V2 vasopressin receptors were not yet occupied by endogenous vasopressin. This observation was confirmed in another retrospective analysis of 151 patients with variceal bleeding receiving terlipressin: rapid severe hyponatremia developed in 19 % of the patients, and lower Child-Pugh score and higher serum Na levels were independent risk factors together with a lower body

Table 26.1 Incidence of hyponatremia in recent trials with terlipressin

	Number	Hyponatremia
Solà et al. [8]	58	21 (36 %)[a]
Seo et al. [7]	261	30 (11 %)[b]
Yim et al. [12]	151	29 (19 %)

[a]Decrease >10 mEq/L
[b]vs. 3 (1.5 %) with somatostatin and 2 (1.2 %) with octreotide

mass index [57]. These facts may explain why hyponatremia is uncommon during the administration of terlipressin for hepatorenal syndrome, a situation which occurs in more advanced liver disease. These studies point out that serum sodium levels should be monitored daily in patients receiving terlipressin for acute gastrointestinal bleeding due to portal hypertension and that in patients with low MELD and normal to near-normal baseline serum sodium concentrations, hypotonic fluids should be avoided. Whether the administration of albumin might counteract this side effect has to be further explored.

Endoscopic Therapy

Timing for Endoscopy

Upper endoscopy is the most accurate and practical method for diagnosing the source of acute gastrointestinal bleeding (UGIB). Given the risk of aspiration of blood, endotracheal intubation may be necessary for airway protection prior to upper endoscopy, especially in patients with hepatic encephalopathy who may have difficulty controlling their airway. The transfusion of fresh frozen plasma and platelets can be considered but should not delay performance of upper endoscopy.

Following hemodynamic stabilization, patients suspected of variceal bleeding should undergo "early" upper endoscopy (within 12 h of patient presentation) [16]. Very early or emergency upper endoscopy has not been shown to confer any additional benefit or alter patient outcomes compared with "early" endoscopy [59]. Data from bleeding registries show that a significant proportion of UGIB patients have a delay of greater than 24 h before undergoing upper endoscopy [60, 61]. Reasons behind such delays are likely multifactorial; however several reports from administrative databases report a "weekend effect" whereby UGIB patients presenting on weekends are less likely to undergo early endoscopy and have higher mortality, which may or may not be due to the delay in receiving endoscopy. Nevertheless, early upper endoscopy should be targeted when managing patients with suspected acute variceal bleeding. Moreover, the availability both of an on-call GI endoscopist proficient in endoscopic hemostasis and on-call support staff with technical expertise in the usage of endoscopic devices enables performance of endoscopy on a 24/7 basis and is recommended at least for non-variceal UGIB [62].

Use of Prokinetics

In patients with acute UGIB, the quality of the endoscopic examination can be adversely affected by poor visibility due to obscuring blood, clots, and fluids in the gastric lumen and duodenum. This may be, at least in part, the reason why in 3–19 % of UGIB cases, no obvious cause is identified [63]. In addition to the use of water-jet irrigation and adequate suction through the working channel of the endoscope, the patient may also need to be rolled over into various positions in an effort to move fluids/clots and thereby improve endoscopic visualization, especially of the gastric fundus.

The use of an intravenous prokinetic agent (e.g., erythromycin) should be considered during the pre-endoscopy patient management phase. Since 2010, 4 meta-analyses analyzed this issue [64–67]. Barkun et al. reported that an intravenous infusion of different prokinetic agents administered up to 2 h before endoscopy in patients with acute UGIB improved endoscopic visualization and significantly decreased the need for repeat endoscopy to determine the site and cause of bleeding without improvement in hospital length of stay, blood transfusion requirements, or need for surgery [64]. The observed treatment effect was not preserved when only analyzing metoclopramide. Two subsequent meta-analyses, solely evaluating the use of IV erythromycin, reported similar results with improvement in the visualization of the gastric mucosa and a decrease in the need for a second-look endoscopy [65, 66]. Interestingly, the effects of pre-endoscopy IV erythromycin in decreasing the units of blood transfused and reducing hospital length of stay reached statistical significance when an additional trial that only included patients with variceal bleeding was added to the meta-analysis [66]. The most recent meta-analysis that included seven randomized controlled trials ($n = 558$ subjects) and was also restricted to only evaluating erythromycin concluded that IV erythromycin given prior to upper endoscopy significantly improved gastric mucosa visualization and decreased the need for second-look endoscopy, units of blood transfused, and duration of hospital stay [67].

Thus, the use of intravenous erythromycin (suggested dosing = 250 mg infusion 30–120 min before planned upper endoscopy) may be the favored prokinetic agent based on current evidence [64–67]. It should be noted however the QT interval-prolonging effect of erythromycin should always be taken into consideration, and an electrocardiogram is advisable prior to infusion in "at-risk" patients.

Esophageal Varices: Endoscopic Treatment

Endoscopic therapy, either sclerotherapy or banding ligation, is highly efficacious achieving 85–90 % rates of initial control of bleeding. Results of RCTs in AVB have shown that banding ligation achieved higher rates of control of bleeding with a lower incidence of adverse events than sclerotherapy, allowing experts to conclude that band ligation is the recommended form of endoscopic therapy for AVB, although sclerotherapy may be used in the acute setting if ligation is technically difficult or unavailable [17]. The rationale for combining vasoactive drugs and endoscopic therapy relies on the different and complementary hemostatic mechanism: a

local effect on the varices, induced by endoscopic treatment, and the decrease in portal and variceal pressure caused by drugs. In fact, RCTs have shown that such a combination is more effective than the isolated use of any of these therapeutic options [17]. At present, the combination of vasoactive drugs and ligation is considered the first therapeutic option in acute variceal bleeding [17].

Gastric Varices

While esophageal varices (EV) remain the most prevalent cause of variceal bleeding in patients with cirrhosis, gastric varices are seen in 15–20 % of cases [68]. In various pre-hepatic conditions, the relative prevalence of GV is higher. GV are the cause of bleeding in 10–30 % of such cases. Gastric varices tend to bleed less frequently, but the clinical situation is more serious than with EV bleeding, with higher mortality, and a greater propensity to rebleed, particularly after spontaneous hemostasis. Treatment principles differ from those of EV, for acute bleeding as well as for secondary prophylaxis. This is due to the character of the varices, the features of the gastric mucosa, as well as the vascular anatomy feeding and draining GV.

GV Categories

Gastric varices differ in location and character, and this has important therapeutic and prognostic implications. They can be categorized according to location, endoscopic appearance, or underlying vascular makeup. However, for therapeutic purposes, the Sarin classification is most applicable [68]. According to this classification, gastroesophageal varices (GOV) 1 are the extension of esophageal varices across the cardia onto the lesser curve, while GOV2 extend onto the fundus. Isolated gastric varices (IGV) are vascular protrusions without direct connection to the esophageal varices. IGV1 are located in the fundus, while IGV2 are located elsewhere in the stomach, typically in the distal body and antrum. GOV1 can be treated similarly to EV, although sparse data indicate that even for this subgroup, glue injection confers a reduced rebleeding rate, similar to other gastric variceal categories [51].

GOV2 and IGV1 (also called cardio-fundal varices by some authors) constitute the most important subtype of GV, with an estimated one-year bleeding risk of 10–16 % [69], while IGV2 are rare and bear more resemblance to other "ectopic varices," e.g., in the duodenum or rectum.

Acute Bleeding: Endoscopic Therapy

It is important to remark when discussing treatment of gastric varices that in most published RCT dealing with gastric varices, only half of patients included in the trials had cardio-fundal varices (most of these patients having GOV2 and a minority

IGV1). This is a major drawback for the interpretation of the results of published studies. Intravascular injection of a thrombus-forming material is well established as the preferred endoscopic modality for treating GV bleeding. Although alternatives exist, tissue adhesives, particularly *N*-butyl-2-cyanoacrylate, remain best documented [69] alone and in head-to-head comparisons with band ligation [70–72] or sclerosing agents [73, 74]. Rates of hemostasis are comparable or better, while the risk of rebleeding appears substantially reduced with cyanoacrylate. However, a mortality difference has yet to be proven.

The use of cyanoacrylate requires certain technical skills and, in particular in the context of a severe bleed and/or an uneasy patient, may complicate the procedure. The details of the technique are beyond the scope of this text, but are well described elsewhere [2]. The procedure is not without risks, the most serious being systemic glue emboli (2–3 %) [75, 76]. Again, proper technique and dosing of the glue injection are vital.

To improve on the glue technique and reduce the risk of systemic complications, EUS-guided combined intravascular coil placement and glue injection have been suggested. This technique allows for a more accurate understanding of the vasculature treated, the effect of the therapy on variceal flow, as well as a theoretical reduction of embolization risk. Preliminary data are encouraging [77] but too limited for general recommendations. Also, the utility of the EUS endoscope in the context of acute bleeding is questionable, and the access to the most relevant fundic region is often difficult with this instrument [78]. So far, there is insufficient evidence to recommend this variant of glue therapy outside of clinical trials.

Thrombin has been suggested for varix obliteration with promising small-scale results but has not been well established in Europe. Sclerosing agents and band ligation have also been reported in small series, but appear inferior to cyanoacrylate glue, with the exception of GOV1 type varices. The higher prevalence of rebleeding seems the biggest concern.

Combination therapy of endoscopy and pharmacological therapy is considered the standard of care in acute esophageal variceal bleeding [17, 79]. However, due to the paucity of data, it is unknown if this recommendation also applies to GOV2 or IGV1 variceal bleeding. Given that drug therapy is in most cases started before diagnostic endoscopy (and therefore before the identification of the gastric variceal origin of bleeding), it seems the most rational approach to combine drug therapy plus endoscopic treatment (preferably tissue adhesives) in patients with acute GV bleeding.

Secondary Prophylaxis

Despite the initial technical and clinical success of cyanoacrylate injection therapy for GV, the rebleeding rate is high, albeit variable (7–65 %) with most of the large series reporting rates below 15 % [69]. Therefore specific treatment to prevent rebleeding should be instituted.

Further Glue Injections

Repeated injections with cyanoacrylate until complete GV obliteration, with endoscopic follow-up and additional therapy as indicated, is superior to band ligation and sclerotherapy.

Nonselective Beta-Blockers

Beta-blockers have also been proposed, after the initial session of glue, to prevent GV rebleeding. Data are scarce and only 2 RCTs comparing further glue injections vs. nonselective BB have been published with conflicting results. No significant differences between the 2 groups in the incidence of variceal rebleeding and death but more and severe complications in the glue group were observed in one study [80]. However, the number of cardio-fundal varices was very low in that study. In a more recent RCT [81], rebleeding and mortality in the glue group were significantly lower than in the beta-blocker group with a low rate of complications in the glue group (3 %).

In a recent study, after successful control with initial glue injection, the strategy to prevent rebleeding of combination nonselective BB plus further glue injections vs. only further glue injections was compared [82]. Overall rebleeding and survival were not different between groups. This study suggests that adding beta-blockers to repeated sessions of CA provides no benefit. Despite these findings, and because nonselective beta-blockers are effective in patients with concomitant esophageal varices, until larger studies with longer follow-up are available, the use of nonselective beta-blockers may be used as an adjunct to endoscopic therapy in the secondary prophylaxis of GV rebleeding.

TIPS

The role of TIPS vs. cyanoacrylate in preventing GV bleeding has been evaluated in three small studies [83–85]. In all three, most patients included had GOV1 and the stent used was uncoated. Overall, a higher rebleeding rate in the CA group vs. the TIPS group was observed without significant differences in survival. However, TIPS-treated patients showed a higher incidence of hepatic encephalopathy requiring hospitalization. More data are needed to clarify the role of TIPS in the secondary prophylaxis of GV bleeding and determine if this therapy must be universally applied or reserved as a rescue therapy after failure of more conservative approaches.

Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

BRTO has been introduced as a treatment method that aims to directly obliterate the GV. This method is based on the frequent development in gastric varices of gastrorenal shunts, which allows wire-guided transvenous access in a retrograde fashion

to the varicose gastric veins. Upstream of balloon occlusion and sclerosing agents, typically ethanolamine oleate, can then be instilled and kept in place by the balloon occlusion for 6–8 h.

A recent meta-analysis by Park et al. [86] including 1016 patients treated with BRTO from 24 studies reported a technical success rate of BRTO of 96 % and a low rate of major adverse events of 2.6 %. Worsening of EV may pose a problem, in addition to a small but real risk of pulmonary edema, renal dysfunction, and anaphylaxis. Hepatic encephalopathy, on the other hand, appears to remain stable or be improved with this method, as compared to the use of TIPS in a similar population [87]. The technical aspects of the procedure present another challenge, given the comparatively long period of an indwelling balloon catheter to ensure a sufficient exposure time of the varices to the sclerosant. Also, this method relies on an excellent understanding and visualization of the aberrant shunt anatomy of the various portosystemic shunts. Thus, at the present time, this method is not likely to replace TIPS in the European context, with the possible exception in patients with hepatic encephalopathy and given local expertise.

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A la Carte Treatment of Acute Variceal Bleeding

27

Càndid Villanueva, James O'Beirne, Christophe Bureau, and Dominique Thabut

Review of the New Published Works on Factors Predicting Failure in Patients with AVB (Now Treated with the Current Standard of Care). Review Recent RCTs of AVB

As not all patients with acute variceal bleeding have the same risk of unfavorable outcome, adapting the different available treatments to the expected risk constitutes a rational therapeutic approach. In fact, strong predictive factors of treatment failure and rebleeding have become a real need, especially after the demonstration that early placement of a TIPS can improve survival in patients with acute variceal bleeding and high risk of failure [1, 2].

To date, several prognostic indicators of mortality within the 6-week period after admission due to an episode of acute variceal bleeding have been proposed. These estimates are mainly based on statistical models inferred from cohort data with methods such as logistic regression or Cox proportional analyses. The most consistently reported risk indicators of death include elements that capture severity of liver

C. Villanueva
Gastrointestinal Bleeding Unit, Department of Gastroenterology, Hospital de Sant Pau, Barcelona, Autonomous University, Barcelona, Spain

(CIBERehd), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Barcelona, Spain

J. O'Beirne
The Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK

C. Bureau
Service d'Hépato-Gastroentérologie, CHU de Toulouse, Toulouse, France

D. Thabut (✉)
Liver ICU, Service d'Hépato-Gastroentérologie, Hôpital de la Pitié-Salpétrière, APHP, UPMC, Paris, France
e-mail: dthabut@gmail.com

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disease, such as Child–Pugh class or its components, model for end-stage liver disease (MELD) score, and measures of portal hypertension (mainly hepatic venous pressure gradient) [3]. Other factors reflect relevant characteristics of severity of bleeding such as high-risk stigmata on varices, active bleeding at endoscopy, hypotension, hypovolemic shock, degree of anemia, or red cell transfusion requirements. Renal failure, bacterial infection at admission or shortly after, and hepatocellular carcinoma (HCC) have also been identified as consistent predictors of early mortality after esophageal variceal bleeding among others [3].

Prognostic models may allow patient stratification according to risk and could be used to guide therapeutic decisions, treating high-risk patients by a more aggressive approach and sparing in addition low-risk individuals unnecessary procedures. As stated above, risk stratification has gained relevance since the demonstration that early preemptive TIPS can improve the outcome of high-risk patients. However, the majority of studies assessing prognostic factors in patients with acute variceal bleeding were done using monotherapy, mainly with sclerotherapy or with vasoactive drugs, treatments associated with failure rates of 30–40 %. The current recommended therapy of acute variceal bleeding combines vasoactive drugs from admission to the hospital with endoscopic therapy (preferably band ligation) at the time of diagnostic endoscopy plus prophylactic antibiotics. Such an association significantly improves the efficacy of each therapy alone decreasing the rate of therapeutic failure to 15–20 % [4].

It has been shown that, even in patients receiving the currently recommended combined therapy for acute variceal bleeding, early measurement of HVPG is a strong prognostic indicator [5]. The risk of 5-day failure in patients with HVPG above 20 mmHg is four times greater than in patients with HVPG <20 mmHg. It has also been shown that the predictive capacity of HVPG is improved by the use of additional variables reflecting the severity of bleeding (systolic blood pressure at admission <100 mmHg) and the demographics of the patient (nonalcoholic etiology of liver cirrhosis) [5]. However, the applicability of HVPG is limited since it is not universally available, particularly in the emergency setting. Therefore, identifying accurately the risk of failure in these patients using clinical, easily obtained variables is of obvious relevance. The previously mentioned study has also shown that, when the HVPG is not included, the Child–Pugh class becomes a strong independent predictor of failure, together with systolic blood pressure and nonalcoholic etiology [5]. It is important to remark that prognosis of 5-day failure in acute variceal bleeding can be established with only these clinical variables (which are easily obtainable at the bedside), with a similar degree of accuracy as with the model containing HVPG. Another study has suggested that a model based on Child–Pugh score, creatinine level and bacterial infection, allowed an accurate predictive assessment of 6-week mortality after acute variceal bleeding in patients treated with current first-line therapy [6].

Subjectivity, which is characteristic of some components of the Child–Pugh classification, and lack of external validation constitute problematic issues of prognostic models in acute variceal bleeding. To deal with these issues, a recent study assessed the performance of recently described prognostic models

offering continuous quantitative estimations of 6-week mortality in acute variceal bleeding treated with current first-line therapy [7]. The study showed that in patients with cirrhosis and acute variceal bleeding, a MELD-based model accurately predicts mortality with objective variables available early after admission.

As previously mentioned, risk prediction in acute variceal bleeding has gained relevance since the demonstration that an early preemptive TIPS improves the outcome [1, 8]. Two randomized trials support the potential efficacy of early TIPS in patients with variceal bleeding at high-risk of failure. In one of these trials, in which high-risk patients were identified with hemodynamic criteria (HVPG >20 mmHg shortly after admission), early treatment with TIPS improved prognosis in comparison with medical treatment [8]. However, in this study the medical treatment group did not receive current standard of care, which may have resulted in a worse outcome than that currently expected in this group. Furthermore, the use of HVPG to identify high-risk patients has the previously mentioned inconveniences, and it is not readily available particularly in the acute setting. To overcome this problem, in a subsequent trial, high-risk patients were selected by clinical criteria (Child–Pugh class C up to 13 points or Child B and active bleeding at endoscopy despite vasoactive drug treatment) [1]. In this study early TIPS significantly improved rebleeding and survival, further reinforcing the potential of this therapy to improve outcomes in patients with acute variceal bleeding at high-risk of failure. However the clinical criteria used in this study have limitations as well. The definition of active bleeding and some components of the Child–Pugh classification are hampered by some subjectivity. A recent multicenter study suggested that both Child–Pugh score and active bleeding could be evaluated in a heterogeneous way in different centers [9]. Another issue is that the prognostic value of these criteria has not been confirmed in an observational study using current first-line therapy (including emergency endoscopic variceal ligation in all patients) in which the outcome of Child B patients with active bleeding was much better, with death risk lower than 10 % [10]. This point was confirmed in a recent study where Child B patients with variceal bleeding had an excellent 6-week survival of 93 %, with absolutely no impact of active bleeding at endoscopy on short-term prognosis (D Thabut et al. Abstract 2056 AASLD 2013). Furthermore, in the observational study even Child C patients fulfilling the criteria of eligibility for therapeutic trials (Child<14, age $\leq$75 years, creatinine $\leq$3.0 mg/dL and no hepatocellular carcinoma, or portal thrombosis) had a relatively low 6-week mortality (of 12 %). This study proposed a new prognostic model (Augustin model) to identify high-risk patients based on Child–Pugh score, baseline creatinine, and hepatocellular carcinoma, which showed a good discriminative ability (AUROC of 0.852) [10].

Using the Child–Pugh score acutely to determine prognosis and the need for early TIPS may also be difficult in some centers as albumin levels are sometimes not available in the emergency setting. While albumin levels will usually be available within 24 h, it is probable although not proven that the earlier a TIPS is placed, the better the outcome. Therefore using Child–Pugh score in some centers may cause a delay in treatment allocation which may affect prognosis.

In order to improve risk prediction in acute variceal bleeding, a previously mentioned study assessed prognostic models offering continuous quantitative estimations of 6-week mortality. This study included the Augustin model and the D'Amico model which was specifically developed for variceal bleeding before current first-line therapy was widely used [10, 11]. MELD, which has shown prognostic value in different clinical situations in cirrhosis, including variceal bleeding, and Child–Pugh score were also evaluated [7]. MELD proved to be the best model in terms of discrimination (AUROC of 0.795 with 95 % CI = 0.689–0.901) and overall performance and had the additional advantage over the other models of including only objective variables. However, calibration (agreement between expected and observed mortality) was poor. Because good calibration is essential to derive decision thresholds to guide therapeutic decisions, MELD calibration to predict the 6-week mortality was updated. Once recalibrated, MELD values of >19 predicted 20 % or greater mortality (and values >25 predicted >50 % mortality), whereas MELD scores <11 predicted less than 5 % mortality. It should be noted that variables reflecting the severity of bleeding, including a systolic arterial pressure <100 mmHg within the first 3 h from admission and active bleeding at endoscopy, did not significantly add to the predictive value of the MELD-based model in this study. MELD-based predictions were validated in a cohort of patients from Canada and performed well at all risk levels and also in a cohort of patients from Spain (in which all patients were treated with band ligation), and predictions were accurate up to the 20 % risk threshold [7]. The results of this study clearly indicate that MELD offers an objective and accurate prognostic prediction in acute variceal bleeding with variables available early after admission. Also in another retrospective study performed in patients with severe variceal bleeding requiring admission to the intensive care unit due to requirement for invasive monitoring, airway protection, or organ support, MELD score performed as well as APACHE II, SOFA, and number of failed organs in predicting hospital mortality with AUROC of 0.84 (95 % CI = 0.78–0.90) [12].

An issue to consider is that these studies deal with models to predict 6-week survival. The majority of patients who die after acute variceal bleeding episode have previously uncontrolled bleeding or a rebleeding episode within the first 5 days or, in some cases, between 5 days and 6 weeks. However, some patients die because of liver dysfunction or other reasons (infections, renal failure, or other complications) with bleeding controlled from the beginning and without further bleeding. Rescue therapies to prevent death in high-risk patients without previous rebleeding may be different from therapies to prevent rebleeding. Accordingly, it is relevant to identify high-risk patients for further bleeding within 5 days or even patients at high risk of early rebleeding within the first 6 weeks. In this regard, predictive risk factors of 5-day failure were assessed in a recent study including unselected cirrhotic patients with acute variceal bleeding treated with current first-line therapy (92 % of them receiving EVL as emergency endoscopic therapy), 28 % of them with hepatocellular carcinoma, and 17 % with portal vein thrombosis. Child–Pugh class C, a white blood cell count $>10 \times 10^9$/l, and the presence of PVT were independent predictors of the 5-day failure. However, 17 out of 31 patients (55 %) with 5-day failure in this study died with controlled bleeding, thus compromising the value of the model for

the prediction of further bleeding [13]. Predictive factors of 6-week rebleeding have been assessed in another recent study in which only patients with active variceal bleeding at endoscopy were included [14]. Door-to-endoscopy time, MELD score, and portal vein thrombosis were indicators of 6-week rebleeding in this study [14]. The study has weakness such as only including patients with active bleeding (an issue influenced by subjectivity) or the possibility of confounding by indication regarding door-to-endoscopy time. It is unclear if delayed endoscopy may be associated with worse outcome or if sicker patients needed more resuscitation time before endoscopy thus selecting a subgroup at higher risk.

When considering the clinical applicability of prognostic models, some issues should still be taken into account. Prognostic factors usually assess two main outcomes, 6-week survival or therapeutic failure. 6-week survival constitutes a strong and thoroughly validated endpoint, which captures the consequences of acute variceal bleeding on different outcomes such as further bleeding, effect on liver function, infections, or renal failure. However, the treatment to prevent these outcomes may be different, i.e., interventions to prevent further bleeding may not be the same as those to prevent infection. If our aim is to stratify patients and prevent further bleeding by applying invasive therapies, such as early TIPS, to patients at high risk, we need to identify prognostic indicators of further bleeding despite first-line therapy. Because treatment failure is a strong predictor of death, some indicators of death risk will also indicate risk of further bleeding, whereas some are different [11, 15]. Furthermore, in acute variceal bleeding, the majority of deaths occur in patients with further bleeding within 5 days of acute treatment. However, also patients who have early rebleeding after the inception of elective first-line secondary prophylactic therapy, with β-blockers and endoscopic variceal ligation, are at higher risk of death. Consequently, prognostic factors to identify those with initial control of acute variceal bleeding but who are at risk of early rebleeding under secondary prophylaxis will be valuable to identify a subgroup who may potentially benefit from preventive treatments. Furthermore, to adequately identify predictors, we need a solid definition for treatment failure in acute variceal bleeding. This issue has been a difficult task in previous Baveno meetings and is still a non-resolved issue. Such a lack of a widely accepted definition accounts for inconsistencies observed among old trials assessing prognosis before the application of current first-line therapy. Furthermore, whether prognostic reassessment after the first few hours (24–48 h) may improve the predictive accuracy has not been completely evaluated.

At the present time, most prognostic variables and scores lack external validation, and the majority includes subjective or time-dependent variables and is, therefore, inconsistently evaluated. Identification of solid and unbiased predictive factors of treatment failure and rebleeding has become an urgent need, especially after the demonstration that placement of a TIPS improves survival in patients with acute variceal bleeding and high risk of failure. Defining high-risk variceal bleeding is the aim of a multicenter European study which is ongoing and will obtain prognostic information from a large number of patients (more than 1300) with acute variceal bleeding admitted to referral centers with the ultimate purpose of identifying the best prognostic factors defining high risk.

Critical Review Studies on Definition of Treatment Failure and/or Applicability of Baveno Criteria

As discussed previously, the majority of patients who die after acute variceal bleeding episode have uncontrolled bleeding or a rebleeding episode within the first 5 days or, in some cases, 6 weeks. Hence, we need to identify prognostic indicators of further bleeding despite first-line therapy. However, the definition of failure to control bleeding is unclear despite the efforts made by the community of experts to develop reliable and clinically relevant endpoints for RCTs in this setting. Key events considered important during an acute bleeding episode were "failure to control bleeding" and "failure to prevent rebleeding." Definitions were introduced first at the Baveno II conference [16] and reviewed at the Baveno III conference [17] and were based on several criteria resulting in two composite endpoints. Although not validated, these endpoints have been extensively used in clinical trials, and the clinical efficacy of several drugs has been established using these endpoints [18]. However, Baveno II/III criteria are described as nonspecific and sometimes impractical and do not adequately reflect the situation in clinical practice [19, 20]. Moreover, a study suggested that hemodynamic criteria such as pulse and blood pressure (part of the Baveno II/III criteria) are not accurate enough to identify patients with uncontrolled bleeding due to lack of specificity (Calés, unpublished data). Therefore, new definitions and criteria were proposed at the Baveno IV consensus meeting, aiming to be more specific and closer to clinical practice [4]. These new criteria were closer to clinical practice, including hematemesis, hemoglobin drop, and death, and did not take into account hemodynamic parameters, and a new index termed ABRI, based on transfusion requirement adjusted by the variation in hematocrit level, was introduced. As stipulated by the Baveno report, these criteria needed validation [4], particularly because ABRI required hematocrit measurements at two different time points that were not specified in the consensus meeting and featured an arbitrarily chosen cut-off. A first validation of Baveno IV criteria was performed, using data from a large multicenter trial [21]. This validation was retrospective. This study showed that Baveno IV criteria were more accurate than Baveno II/III criteria to assess outcome of patients with variceal bleeding. However, there was a substantial observer variability linked to timing of hematocrits for ABRI calculation. With its first definition, ABRI did not add to the performance of the other criteria. Hence, at the Baveno V conference, new criteria were proposed, so-called Baveno V criteria. Those criteria presented only slight differences from the Baveno IV criteria; the major change was that ABRI usefulness had to be investigated; hemoglobin drop should be restricted to 24 h; also, hypovolemic shock was included in this new set of criteria. It was stipulated after the Baveno V conference that Baveno IV and V criteria needed a prospective validation, with a special attention for ABRI index which had to be refined [4].

Recently, two prospective studies aiming at validating the new sets of criteria have been undertaken [22, 23]. The French prospective multicenter study aimed at assessing the diagnostic performance of the new Baveno IV criteria for 5-day success or failure to control upper digestive bleeding in cirrhotic patients and to

compare it to that of the previously widely used Baveno II/III criteria [23]. This is important, as Baveno II/III criteria were never prospectively validated, even though these criteria were used as endpoints in several RCTs confirming the efficacy of many drugs in the acute setting. Moreover, exploratory analyses were performed to assess the diagnostic performance of the Baveno V criteria, as those criteria were proposed after the start of the present study. In this study, Baveno IV criteria were investigated with and without ABRI, whereas Baveno V criteria included always ABRI. Overall, 249 patients were included. The originality of this study resides in the fact that the gold standard for failure in 5-day control of bleeding was the clinical judgment of three independent experts based on all the clinical/follow-up data. The experts were blinded to Baveno IV, V, and II/III assessments. The major findings of the study were that: (1) the Baveno IV criteria outperformed the Baveno II/III criteria; (2) the use of an index based on transfusion requirement adjusted by the variation in hematocrit level did not increase the diagnostic performance of the criteria, even if hematocrit measurements were performed according to a standardized time schedule; and (3) the performance was significantly lower for Baveno V criteria than Baveno IV criteria, but those criteria were studied including an ABRI index. In order to assess the reliability of endpoints, 6-week survival was studied. The definition of treatment failure that best predicted 6-week mortality was the gold standard (the chart review by the experts). Failure defined according to Baveno IV had predictive value, but was not as good as the gold standard in predicting 6-week mortality. Baveno II/III criteria did not predict survival at all.

In the same issue of hepatology, a Chinese study addressed the same topic [22]. Two hundred and forty-six consecutive liver cirrhosis patients with acute bleeding associated with portal hypertension were enrolled prospectively. The treatment outcome on day 5 was assessed by endoscopy, which, although subjective, was performed to address the issue of no gold standard for the definition of failure. Here, treatment failure was defined by a repeat endoscopy showing active bleeding or fresh blood in the stomach. Baveno IV criteria were investigated with ABRI, whereas the Baveno V criteria applied did not include ABRI. The study was limited to 5 days and did not provide data on the association between treatment failure and 6-week mortality. Again, the authors proved that ABRI did not improve the accuracy of the criteria. With ABRI included, Baveno IV criteria were significantly less accurate than Baveno V criteria.

Overall, the findings of the two studies do not really differ. Baveno IV and V criteria probably perform in the same way, but ABRI was included in a heterogeneous way, which does not allow firm conclusions to be drawn regarding which set performs better. All the experts now agree as well to exclude ABRI from the criteria. Whether hypovolemic shock would influence the performance of Baveno V criteria remains an issue, as it was not defined in the Baveno V conference. In the French study, hypovolemic shock was considered when a systolic blood pressure drop below 100 mmHg occurred or the heart rate increased over 100 bpm. In the Chinese study, it was not defined. The definition was probably different between the two studies, as 41 patients experienced hypovolemic shock in the French study and

only 1 patient in the Chinese study, whereas baseline systolic blood pressure and pulse rate did not seem to differ between the two studies. Including hypovolemic shock seems reasonable when defining failure to control bleeding; hence, Baveno V criteria are probably better in this regard. However, hypovolemic shock should be precisely defined.

A final consideration is whether 5-day treatment failure should be used as the primary endpoint in new trials for variceal bleeding in cirrhotic patients. Treatment failure, although not well defined, seems strongly associated with increased 6-week mortality. Some hemostatic drugs could have an effect on short-term survival [9], even if these drugs did not prove their efficacy in clinical trials and are not currently used in this setting. Nevertheless, a recent US Food and Drug Administration panel questioned the clinical relevance of treatment failure as a primary endpoint to assess the efficacy of drugs for VB [24]. This was based on the fact that treatment failure was not always associated to survival in old studies. One must keep in mind that these studies considered included Baveno II/III definitions, which we know now not to be accurate. However, this suggests that the approval of new treatments might face serious difficulties unless trials are designed with mortality as the principal endpoint. In that regard, mortality at 6 weeks seems to be a reasonable endpoint for RCTs.

The key endpoints for the design of future trials have to be redefined at this Baveno VI consensus conference. In our opinion, mortality should be the primary endpoint. The real question is how to identify patients who will be selected for new strategies. For this, we need early prognostic factors, not only to indicate early TIPS but also to test new drugs protecting or improving liver function during acute bleeding.

Review Treatment of Treatment Failures: Tamponade/Stenting

Mortality rates from acute variceal bleeding have improved over recent years due to the widespread use of vasoactive drugs, prophylactic antibiotics, variceal banding, and tissue adhesives [25–28]. However up to 20 % of patients may prove refractory to endoscopic and pharmacological treatment during the acute bleeding episode, and the management of these patients remains challenging and associated with a high mortality [4].

For patients fulfilling definition of failure according to Baveno IV/V criteria, the recommended treatment options are repeat endoscopy and insertion of PTFE-TIPS or BT as a “bridge” to more definitive therapy [4].

Balloon tamponade (BT) and transjugular intrahepatic portosystemic shunts (TIPS) are effective modalities for the control of refractory variceal bleeding. Balloon tamponade (BT) is usually performed with a Sengstaken-Blakemore tube and is highly effective in patients who fail conventional treatment (control of bleeding >80 %), but is not recommended for use longer than 24 h due to the risk of mucosal ischemia. Additionally the use of BT is associated with risks related to misplacement, esophageal rupture, and aspiration pneumonia [29–31].

TIPS is associated with a risk of hepatic encephalopathy of up to 48 % when applied as salvage therapy and can cause deterioration in liver function due to diversion of portal blood flow away from the liver parenchyma. Despite control of bleeding in up to 90 % of cases, mortality rates are in excess of 35 % when TIPS is used as salvage treatment [32, 33]. This is especially the case when TIPS is used in advanced liver disease. Paradoxically, it is patients with more advanced disease (high HVPG, Child–Pugh C) that are likely to have failure to control bleeding and hence require salvage TIPS. Strategies to improve the outcome for patients undergoing TIPS for variceal hemorrhage include the use of "early" TIPS (discussed elsewhere) and the prioritization of patients for liver transplantation following TIPS insertion [1, 8, 34].

Given the limitations of TIPS and BT, there appears to be an unmet need for a therapy in patients with refractory bleeding from esophageal varices that can be easily and effectively applied with a lower risk of complications. One alternative to the use of BT and TIPS for refractory bleedings is the use of self-expanding metal stents (SEMS).

Role of SEMS in the Management of Acute Variceal Bleeding

SEMS are potentially useful in the management of variceal bleeding for a number of reasons. Firstly, SEMS can provide rapid control of bleeding by tamponade of varices in the distal esophagus, but unlike TIPS, there is no risk of deterioration of liver function associated with placement; thus, SEMS could be used in patients with more advanced disease who may not be suitable candidates for TIPS. Secondly, unlike BT which is recommended as short-term therapy (<24 h), SEMS can stay in place for a number of days thus preventing early rebleeding and allowing the institution of effective secondary prophylaxis to prevent rebleeding on stent removal. Thirdly, unlike BT which is recommended only for intubated patients, SEMS do not require the patient to have airway protection and thus could facilitate a more rapid discharge from the intensive care unit. An additional potential benefit is that SEMS are used widely for other indications in gastroenterology (malignant obstruction, fistulae); thus, unlike TIPS, their use in variceal bleeding is not restricted to specialist centers.

The introduction of SEMS for variceal bleeding was facilitated by the development of removable stents, and early experience utilized a number of different stent designs. However, most experience has now been gained with the use of the SX-Ella Danis stent (Ella CS, Hradec Kralove, Czech Republic).

The SX-Ella Danis stent is a removable, covered, self-expanding mesh-metal stent designed specifically for the treatment of acute esophageal variceal bleeding. It is 135 mm long and has a diameter of 25 mm, allowing tamponade of bleeding vessels in the distal esophagus. Insertion of the SX-Ella Danis stent is technically unchallenging; the stent can be deployed without endoscopic or radiological fluoroscopic guidance, although most are placed over an endoscopically inserted guidewire.

The stent can remain in situ for up to 7–14 days and is easily removed endoscopically.

Early Experience with the Use of SEMS for Variceal Bleeding

Initial preclinical animal studies showed that stent insertion was not associated with adverse effects on esophageal histology or micro-circulation even after 2 weeks of deployment [35]. Following these initial encouraging animal data, a pilot study involving a cohort of 20 patients with massive bleeding from esophageal varices, who had failed endoscopic and pharmacological treatment, was performed [36]. In all patients except 1, the placement of the stent was satisfactory, and bleeding was immediately controlled. The patient who continued to bleed was found on further endoscopic examination to have bleeding from gastric varices. There was no rebleeding reported at follow-up after 30 days. All the stents were removed within 14 days (range 2–14 days), with migration only documented in two patients. Following placement, two patients subsequently died from bleeding-related complications (multi organ failure). Of note, one patient who was treated with SEMS had previously sustained an esophageal rupture as a complication from BT.

This original study was subsequently extended to include 39 patients (20 of these had been included in the original report) [37]. As previously demonstrated, insertion of SEMS in these patients was uncomplicated, and bleeding was controlled in all patients. There was a higher rate of stent migration into the stomach (seven patients), but there were no adverse effects from this. Mortality at 30 days was 26.5 %, and there was no rebleeding following hemostasis with SEMS. The majority of patients went on to receive definitive treatment (TIPS, band ligation, surgical shunt, or listing for transplant).

A further series of SEMs was published by Wright et al in 2009 [38]. The study cohort consisted of patients with uncontrolled variceal bleeding and contraindications to TIPS or BT. 2 out of the 10 patients had esophageal perforation secondary to BT use, and the others were not TIPS candidates due to hepatocellular carcinoma (HCC), multiorgan failure, or severity of liver disease. In this report, SEMS deployment failed in one patient due to failure of the balloon to inflate. Of the nine patients actively bleeding at the time of insertion, hemostasis was achieved immediately following SEMS application in seven. The other two patients were later demonstrated to be bleeding from gastric, rather than esophageal varices. The stents were extracted after a median of 9 days (range 6–14 days) following insertion, with no associated complications. Survival at 42 days was 50 % with only one episode of rebleeding at 60 days following stent removal.

Three further small series in patients with refractory bleeding have subsequently been reported [39–41]. These series describe excellent control of bleeding with low rates of stent migration. However, mortality was very high with rates of 67–75 % at 42–60 days. The current status of SEMS insertion for esophageal variceal bleeding is summarized in Table 27.1.

These initial pilot data confirm that the SX-Ella Danis stent can be deployed without complication in the setting of acute variceal bleeding and is effective at providing rapid hemostasis. Mortality in the published series is however disappointingly high reflecting at least in part the underlying severity of liver disease and severe comorbidities in the patients included.

Table 27.1 Current status of SEMS insertion for esophageal variceal bleeding

Author	Stent used	*N*	Indications	Length of insertion (days)	Hemostasis of esophageal varices by SEMS	Mortality (days)	Complications/notes
Hubmann et al. [36]	Choo in 2 Ella-Boubella in 3 SX-Ella Danis in 15	20	FTCB in 19 FTCB and esophageal perforation in 1	6 (2–14)	100 %	10 % 30 days 20 % 60 days	Minor ulceration in 1 patient Migration in 2 patients
Zehetner et al. [37]	SX-Ella Danis Choo in 2 Ella-Boubella in 3	39	FTCB	5 (1–14)	100 %	26.5 % 30 days 29.4 % 60 days	Migration in 7 patients Bleeding form gastric varices in 1 patient Contains 20 patients from Hubmann et al. [36]
Dechene et al. [39]	SX-Ella Danis	1	FTCB	6	100 %		Stent extracted at day 6 due to tracheal compression
Mishin et al. (2010)	SX-Ella Danis	1	FTCB (EBL ulcer)	8	100 %	0 % 10 days	Outcome following 10 days not reported
Wright et al. [38]	SX-Ella Danis	10	FTCB in 8 BT-induced esophageal tear in 2	6 (6–14)	100 %	50 % 42 days	Ongoing bleeding found to be from gastric varices in 2 patients Technical failure in 1 patient
Dechene et al. [39]	SX-Ella Danis	9	FTCB	11 (7–14)	100 %	56 % 30 days 67 % 60 days	
Holster et al. (2013)	SX-Ella Danis	5	FTCB	6–214	100 %	Not reported	1 rebleed at 7 days with stent in situ
Zakaria et al. [42]	SX-Ella Danis	16	Primary therapy for acute bleeding	2–4	100 %	25 %	Technical failure in 1 patient Uncontrolled bleeding in 1 patient from gastric varix
Fierz et al. [41]	SX-Ella Danis	7	FTCB	0.5–5	85 %	77 % 60 days	Stent migration in 2 patients

Areas for Further Study: SEMS as Primary Therapy for Oesophageal Variceal Haemorrhage in Patients at High Risk of Treatment Failure

The excellent control of active bleeding in the early series using SEMS suggests that they may have a role in the primary management of variceal bleeding. There has only been one study performed addressing this issue [42]. This was a nonrandomized study comprising 16 patients presenting with acute esophageal variceal bleeding (active spurting or presence of stigmata of recent hemorrhage with blood in the stomach and no other source of bleeding identified). The majority of patients were of Child–Pugh B/C class and underwent stent insertion at the time of diagnostic endoscopy. Stent insertion was successful in 15/16 patients, and control of bleeding was achieved in 14/16 patients. Failure to control bleeding was observed in two patients due to device failure in one and ongoing bleeding from gastric varices in one. Overall survival in the cohort was 75 % with only 1 death related to ongoing bleeding. Although this study was small and uncontrolled, the data supports the notion that SEMS may be effective as primary therapy in esophageal variceal hemorrhage especially in those with a high risk of failure to control bleeding and rebleeding. Further studies to define the role of stenting in this situation are clearly needed, and a prospective randomized trial of the SX-Ella Danis stent as primary therapy is currently underway in the United Kingdom.

SEMS as an Alternative to Balloon Tamponade in Refractory Variceal Bleeding

Given the limitations of BT as salvage therapy for refractory bleeding, there may be a role for SEMS as an alternative to BT. A randomized controlled trial of SEMS versus BT has reported results in 2013 in abstract form. 28 patients were randomized, 15 to BT, and 13 received SEMS. The primary outcome measure was survival at 15 days with control of bleeding and absence of serious adverse events. Using intention to treat analysis, the authors reported a significant difference in the probability of "remaining free from failure," which was also termed "therapy success" in favor of SEMS (46 % v 13 %, $p = 0.04$). There was however no difference in survival at 15 days or 6 weeks. The principal advantage of treatment with SEMS was the reduction in the number of adverse events associated with BT, particularly aspiration [40].

In summary, refractory esophageal bleeding and its attendant mortality remain a challenging condition. Existing data strongly suggest that, particularly in patients who have failed to achieve hemostasis endoscopically and for whom other procedures (e.g., TIPS) are contraindicated or not immediately available, SEMS insertion is highly effective at controlling bleeding. SEMs can facilitate control of bleeding over a longer time period (up to 2 weeks), after which other treatment options, including TIPS, transplantation, etc., may become viable. SEMS may have advantages over BT in the setting of refractory bleeding. Insertion can be done without direct

visualization, and the gastric balloon has a specially designed safety valve designed to minimize the risk of inflation in esophagus, thus minimizing the chances of rupture. As an alternative to BT, SEMS have been associated with less complications and appear to be a safe treatment option for patients with refractory esophageal bleeding.

There are however significant limitations in the use of SEMS for refractory bleeding based on currently available data. Firstly, unlike BT, they have no role in the management of bleeding from gastric varices. Secondly, there is a small but significant chance of stent migration, which can result in failure. Current data do not allow a strong recommendation to be made as to the role of stents in the management of acute variceal bleeding, and further studies comparing stents to other salvage therapies such as BT and TIPS are urgently needed.

Review Data on the Use of Early TIPS: Before Failure

Because of implementation of specific treatment and improvement of nonspecific management of patients with cirrhosis and acute variceal bleeding, the mortality has dropped from 40 to 20 % between the 1980s and 2000 [25] and 16 % in 2014 [7]. However, in high-risk patients (15–25 %), 6-week mortality remains high (30 %), and acute variceal bleeding is still considered a life-threatening complication [9].

The concept of "early TIPS" has emerged for several reasons:

- The control of bleeding is crucial for survival.
- Portal decompression proved to be the more effective method to stop bleeding.
- However, the experience of salvage TIPS showed that, while a hemostasis was achieved in 95 % of the patients, 6-week mortality remained consistently high close to 50 % [43]. TIPS, as a rescue in such patients, is performed after several episodes of bleeding, several endoscopic treatments, and in patients with sepsis, renal impairment, severe hemodynamic, and coagulation disorders. They die from "multiorgan failure" even though bleeding has been stopped. Treating patients earlier by TIPS in order to prevent early rebleeding could avoid further deterioration and improve survival.
- Obviously all patients may not benefit from early TIPS, and parameters defining high-risk patients are needed to facilitate the concept of the risk stratification and tailored therapy. Different criteria were identified in the last decades giving the opportunity to Monescillo et al. [8] to conduct the first randomized study comparing early TIPS with standard treatment in high-risk patients.

In this study, all the patients with variceal bleeding were treated by a single injection of sclerotherapy during the first endoscopic procedure, and HVPG was measured within the first 24 h after admission. Patients with a HVPG >20 mmHg, a strong predictor of negative outcome [44], were classed in the high-risk group and randomized either in early TIPS arm ($n=52$) or standard treatment ($n=52$). Standard treatment was applied to patients with a low risk of failure defined by a HVPG <20 mmHg ($n=64$).

The main findings were that high-risk patients treated by early TIPS had the same prognosis as low-risk patients and a better outcome as compared to high-risk patients treated by standard treatment (treatment failure: 12 % vs 50 %; 1-year survival 69 % vs 35 %). It is noteworthy that 2 of 3 failures in the TIPS group occurred before patients could be treated by TIPS.

Some years later this approach needed to be reassessed with an updated standard of care for the management of variceal bleeding but also considering the improvement of shunt patency by using covered stent [45]. Furthermore the use of HVPG is not widely available, and easier criteria defining high-risk patients were awaited. An international RCT coordinated by the Barcelona group [1] confirmed the efficacy of the concept of early TIPS. High-risk patients were defined as Child C (<14) patients or Child B patients with active bleeding at endoscopy. The baselines characteristics of the 63 patients included were quite similar (Table 27.2) except for the proportion of patients with active bleeding at endoscopy (71 % in the Garcia–Pagan study). Patients were either allocated to early TIPS group using PTFE-covered stent or in the standard treatment group (EBL + beta-blocker). The main endpoint was a combined criterion: 5-days treatment failure + rebleeding at 1 year. Early TIPS improved the control of the bleeding (97 % vs 50 %) and overall survival (86 % vs 61 %) without increasing the rate of hepatic encephalopathy (28 % vs 40 %). Interestingly, 7 patients from the medical treatment group had a rescue TIPS, of whom 4 (57 %) died. This strongly suggests early treatment is a key prognostic factor in high-risk patients.

Subsequently, an observational study was conducted in the centers participating to this previous European trial [2]. In this retrospective study, all patients with cirrhosis admitted for acute variceal bleeding were considered and included if they met the same criteria of the previous RCT. Two periods of inclusion were defined: the first one was between March 2007 (the date after the inclusion of the last patient in the RCT) and the date when the conclusions of the RCT became known, and thus early TIPS was applied in all high-risk patients. The second period was from the end of the first period to January 2011. Hence 30 patients with high-risk bleeding were included in the first period and constituted the control group (standard treatment), while 45 were included in the early TIPS group. Twelve percent (75/659) of patients met the inclusion criteria. Nearly half of the patients had Child A cirrhosis or Child B without active bleeding at endoscopy or Child–Pugh C score >13 and were therefore excluded. The baseline characteristics of patients were not different between the two periods and similar to those of the RCT (Table 27.2). The primary endpoint was reached in 50 % (15/30) of patients of the standard treatment group, validating once again the accurate selection of high-risk patients. A failure occurred in 7 % (3/45) of early TIPS group ($p < 0.05$ vs standard treatment group). These results were perfectly the same as reported in the RCT. There was a trend toward a higher mortality in the standard treatment group (1-year mortality actuarial rates 30 % vs 14 % $p = 0.056$). Furthermore, the incidence of other PHT-related complications and the length of stay in hospital were found to be lower in the early TIPS group as compared to the standard treatment group, while the risk of encephalopathy was not increased.

Table 27.2 Published studies addressing the issue of early TIPS in acute variceal bleeding in cirrhosis

	Monescillo (2004) [5]	Garcia–Pagan (2010) [7]	Garcia–Pagan (2013) [8]	Rudler (2014) [9]
Study design	Prospective randomized	Prospective randomized	Retrospective with historic control group	Retrospective with historic control group
Definition of high-risk patients	Child A, B, and C(<14) If HVPG>20 mmHg	Child B if active bleeding at initial endoscopy and Child C <14	Child B if active bleeding at initial endoscopy and Child C <14	Child B if active bleeding at initial endoscopy or Child C <14
Number of high-risk patients	52	63	75	62
Previous variceal bleeding	22,00 %	*0 %*	*0 %*	26 %
Shock at admission	19 %	22 %	23 %	*50 %*
Active bleeding at endoscopy	35 %	71 %	67 %	47 %
Child C patients	46 %	49 %	63 %	*77 %*
MELD score	ND	16	17	*21*
History of encephalopathy	11 %	9 %	7 %	ND
TIPS procedure	Uncovered stent within first 24 h	Covered stent within first 72 h	Covered stent within first 72 h	Covered stent within first 72 h
Composite endpoint[a]	23 % vs 70 %	3 % vs 50 %	7 % vs 50 %	3 % vs 42 %
5-day failure	12 % vs 50 %	3 % vs 13 %	2 % vs 13 %	3 % vs 35 %
1-year mortality	31 % vs 65 %	14 % vs 39 %	14 % vs 30 %	33 % vs 26 %
Encephalopathy during follow-up	23 % vs 19 %	28 % vs 40 %	52 % vs 49 %	45 % vs 48 %
Pooling Composite endpoint Death	TIPS $n=134$ 8 % 20 %		Standard treatment $n=131$ 49 % 36 %	

[a]Composite endpoint is defined as failure to control bleeding or failure to prevent significant rebleeding within 1 year

[b]Patients with previous variceal bleeding (26 %) were included while patients with secondary prophylaxis (beta-blocker + band ligation) were excluded in both Garcia–Pagan trials

A second observational study was also performed [34] by a French independent group. In this study, the same inclusion criteria as Garcia–Pagan's studies were used except that patient already under secondary prophylaxis with banding were enrolled. This explains the difference regarding the rate of previous episodes of bleeding (Table 27.2). The rate of Child C patients was higher in the Rudler study than in the other 3. The 31 patients in the TIPS group were matched for gender, age, MELD score, and Child–Pugh class with an historical cohort of patients treated by standard treatment.

The 1-year actuarial rate of remaining free of variceal rebleeding was 97 % vs. 51 % in the early TIPS group and standard treatment group, respectively. These figures are similar to those of the previous studies. However in the latter study, survival was the same in high-risk patients treated by early TIPS or standard treatment. Meta-analyses of the four studies are currently ongoing in order to allow subgroup analyses.

Finally a large French survey, including prospectively 914 patients in 59 centers, showed that 25 % of patients could be considered as eligible for an early TIPS. Among eligible high-risk patients, only 22 (9 %) patients were actually treated by early TIPS. In high-risk patients, mortality was of 7.7 % in patients who underwent TIPS vs 18.3 % in patients who did not ($p=0.05$) [46].

As previously mentioned, the clinical criteria used in these studies to define high-risk patients eligible for early TIPS have some drawbacks: some are hampered by subjectivity (such as active bleeding and some components of the Child–Pugh), while the prognostic value of these criteria has not been confirmed in observational studies [10]. Future studies should clarify whether more objective criteria (such as MELD) may improve the applicability of early TIPS and even the results of this strategy.

Conclusion

Failure to control bleeding remains challenging to define, despite many attempts by the community of experts. Even if it is associated with survival, regulatory agencies will not consider this endpoint as a reliable one for clinical trials. Moreover, identifying patients before early rebleeding or at risk of refractory bleeding is probably the most important issue. Mortality at 6 weeks seems to be a reasonable endpoint for RCTs. Refractory bleeding and its attendant mortality remains a challenging condition. Some therapeutic options, besides salvage TIPS, are currently developed, but need to be tested in RCTs. Up to date, most prognostic variables and scores lack external validation, and a majority include subjective or time-dependent variables and are, therefore, inconsistently evaluated. Identification of solid and unbiased predicting factors of treatment failure and rebleeding has become an urgent need, especially after the demonstration that placement of a TIPS improves survival in patients with acute variceal bleeding and high risk of failure. Identifying the best prognostic factors defining high risk should be our priority. The greatest improvement in the last years in the management of acute variceal bleeding is early TIPS in selected high-risk patients. Selection of patients needs to be refined. Most patients die from liver failure. In the future, developing drugs protecting or improving liver function during acute bleeding should be a priority.

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Consensus Statements: Management of the Acute Bleeding Episode

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Juan Carlos Garcia-Pagàn, Lars Aabakken, Christophe Bureau, Ian Gralnek, Gin Ho Lo, Frederik Nevens, James O'Beirne, Puneeta Tandon, Candid Villanueva, and Dominique Thabut

J.C. Garcia-Pagàn, MD, PhD
Barcelona Hepatic Hemodynamic Lab, Liver Unit, Hospital Clinic, IDIBAPS and CIBERehd, University of Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain
e-mail: jcgarcia@clinic.ub.es

L. Aabakken
Department of Cancer, Surgery and Transplant Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway
e-mail: Lars.aabakken@medisin.uio.no

C. Bureau
Service d'Hépato-Gastroentérologie, CHU de Toulouse, Toulouse, France

I. Gralnek, MD, MSHS, FASGE
Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Institute of Gastroenterology and Liver Diseases, Ha'Emek Medical Center, Afula, Israel
e-mail: ian_gr@clalit.org.il

G.H. Lo
Division of Gastroenterology, Department of Medical Research, E-DA Hospital, School of Medicine for International Students,
I-Shou University 1, Yi-Da Road, Kaohsiung County 824, Taiwan
e-mail: ghlo@kimo.com

F. Nevens, MD, PhD
Division of Liver and Biliopancreatic Disorders, University Hospitals Leuven, KU Leuven – University of Leuven, Leuven, Belgium
e-mail: frederik.nevens@uzleuven.be

J. O'Beirne
The Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK

P. Tandon, MD, FRCP(C), MSc (Epi)
Division of Gastroenterology, Department of Medicine, Cirrhosis Care Clinic, Edmonton, AB, Canada
e-mail: ptandon@ualberta.ca

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C. Villanueva
Gastrointestinal Bleeding Unit, Department of Gastroenterology, Hospital de Sant Pau, Barcelona, Autonomous University, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain

D. Thabut (✉)
Liver ICU, Service d'Hépato-Gastroentérologie, Hôpital de la Pitié-Salpétrière, APHP, UPMC, Paris, France
e-mail: dthabut@gmail.com

Definitions of Key Events Regarding the Bleeding Episode

- Six-week mortality should be the primary end point for studies for treatment of acute variceal bleeding (5;D).
- Five-day treatment failure is defined using Baveno IV/V criteria without ABRI and with a clear definition of hypovolemic shock (1b;A).
- Baveno IV/V criteria correlate with 6-week mortality (1b;A) and should be included in future studies as a secondary end point to allow further validation (5;D).
- Additional end points should be reported including the need for salvage therapy (tamponade, additional endotherapy, TIPS, surgery, etc.), blood transfusion requirements, and days of ICU/hospital stay (5;D).

Blood Volume Restitution

- The goal of resuscitation is to preserve tissue perfusion. Volume restitution should be initiated to restore and maintain hemodynamic stability.
- PRBC transfusion should be done conservatively at a target hemoglobin level between 7 and 8 g/dL, although transfusion policy in individual patients should also consider other factors such as cardiovascular disorders, age, hemodynamic status, and ongoing bleeding (1b;A).
- Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data (5;D).
- PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis (1b;A).

Antibiotic Prophylaxis

- Antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis presenting with upper gastrointestinal bleeding and should be instituted from admission (1a;A).
- The risks of bacterial infection and mortality are very low in patients with Child-Pugh class A cirrhosis (2b;B), but more prospective studies are needed to assess whether antibiotic prophylaxis can be avoided in this subgroup of patients.

- Individual patient risk characteristics and local antimicrobial susceptibility patterns must be considered when determining appropriate first-line acute variceal hemorrhage (AVH) antimicrobial prophylaxis at each center (5;D).
- Intravenous ceftriaxone 1 g/24 h should be considered in patients with advanced cirrhosis (1b;A), in hospital settings with high prevalence of quinolone-resistant bacterial infections, and in patients on previous quinolone prophylaxis (5;D).

Prevention of Hepatic Encephalopathy

- Recent studies suggest that either lactulose or rifaximin may prevent hepatic encephalopathy in patients with cirrhosis and upper GI bleeding (1b;A). However, further studies are needed to evaluate the risk/benefit ratio and to identify high-risk patients before a formal recommendation can be made (5;D).
- Although there are no specific studies in acute variceal bleeding, it is recommended to adopt the recent EASL/AASLD HE guidelines which state that episodic HE should be treated with lactulose (25 mL/q 12 h until 2–3 soft bowel movements are produced, followed by dose titration to maintain 2–3 soft bowel movements per day) (5;D).

Assessment of Prognosis

- Child-Pugh class C, the updated MELD score, and failure to achieve primary hemostasis are the variables most consistently found to predict 6-week mortality (2b;B).

Pharmacological Treatment

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before endoscopy (1b;A).
- Vasoactive drugs (terlipressin, somatostatin, octreotide) should be used in combination with endoscopic therapy and continued for up to 5 days (1a;A).
- Hyponatremia has been described in patients under terlipressin, especially in patients with preserved liver function. Therefore, sodium levels must be monitored (1b;A).

Endoscopy

- Following hemodynamic resuscitation, patients with upper GI bleeding and features suggesting cirrhosis should undergo esophagogastroduodenoscopy (EGD) within 12 h of presentation (5;D)

- In the absence of contraindications (QT prolongation), pre-endoscopy infusion of erythromycin (250 mg IV 30–120 min before endoscopy) should be considered (1b;A).
- The availability of both an on-call GI endoscopist proficient in endoscopic hemostasis and on-call support staff with technical expertise in the usage of endoscopic devices enables performance of endoscopy on a 24/7 basis and is recommended (5;D).
- Patients with acute variceal hemorrhage should be considered for ICU or other well-monitored units (5;D).
- In patients with altered consciousness, endoscopy should be performed with protection of the airway (5;D).
- Ligation is the recommended form of endoscopic therapy for acute esophageal variceal bleeding (1b;A).
- Endoscopic therapy with tissue adhesive (e.g., N-butyl-cyanoacrylate) is recommended for acute bleeding from isolated gastric varices (IGV) (1b;A) and those type 2 gastroesophageal varices (GOV2) that extend beyond the cardia (5;D).
- To prevent rebleeding, consideration should be given to additional glue injection (after 2–4 weeks), beta-blocker treatment, or both combined or TIPS (5;D). More data in this area are needed.
- EVL or tissue adhesive can be used in bleeding from type 1 gastroesophageal varices (GOV1) (5;D).

Early TIPS Placement

- An early TIPS with PTFE-covered stents within 72 h (ideally <24 h) must be considered in patients bleeding from EV, GOV1, and GOV2 at high risk of treatment failure (e.g., Child-Pugh class C <14 points or Child class B with active bleeding) after initial pharmacological and endoscopic therapy (1b;A). Criteria for high-risk patients should be refined.

Balloon Tamponade

- Balloon tamponade, given the high incidence of its severe adverse events, should only be used in refractory esophageal bleeding, as a temporary "bridge" (for a maximum of 24 h) with intensive care monitoring and considering intubation, until definitive treatment can be instituted (5;D).

Use of Self-Expandable Metal Stents

- Data suggest that self-expanding covered esophageal metal stent may be as efficacious and a safer option than balloon tamponade in refractory esophageal variceal bleeding (4;C).

Management of Treatment Failures

- Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by PTFE-covered TIPS (2b;B).
- Rebleeding during the first 5 days may be managed by a second attempt at endoscopic therapy. If rebleeding is severe, PTFE-covered TIPS is likely the best option (2b;B).

Research Agenda

- Trials of preventative strategies in acute kidney injury (AKI) in variceal bleeding should be undertaken.
- Treatment and prevention of HE.
- Optimal use of glue obliteration in variceal bleeding.
- Role of EUS in variceal injection therapy.
- Alternative endoscopic hemostasis techniques in EVB, e.g., hemostatic powders.
- Improve prognostic models: better stratification of risk to determine applicability of updated MELD or other potential new models to improve stratification of risk to determine type of treatment.
- Applicability of models to determine other issues such as timing of the initial endoscopy, duration of the drug therapy, and type of treatment.
- Use of early TIPS in gastric varices.
- Use of balloon-occluded retrograde transvenous obliteration (BRTO) in IGV.

Part VII

Controversies and Challenges in Pediatrics

Portal Hypertension in Pediatrics: Controversies and Challenges 2015 Report

29

Benjamin L. Shneider

Introduction

Portal hypertension remains a major clinical issue for children with chronic liver disease. This report updates progress in the understanding and management of portal hypertension in children since Baveno V [1, 2]. Approaches to the management of complications of portal hypertension in children are frequently driven by expert opinion and not fully evidence based [3]. Practical issues in the conduct of rigorous clinical trials of therapies in pediatric portal hypertension have impeded advances. For instance, it is estimated that ~35,000,000 pediatric lives (~½ of the children in the United States) would need to be accounted for in the catchment of a powered study of primary prophylaxis of variceal hemorrhage in children [4]. Despite these limitations, progress is being made in this very important field; highlights of that progress are summarized here.

Portal hypertension is well described in a wide range of pediatric disorders, many of which are fundamentally distinct from the diseases that afflict adults (Table 29.1). Those differences have profound implications for diagnosis and management. Two common causes of portal hypertension, biliary atresia, and extrahepatic portal vein obstruction (EHPVO, also known as portal vein thrombosis) have a myriad of critical differences from the common hepatocellular-based disorders that lead to portal hypertension in adults. Most notable is the fact that portal hypertension is an early manifestation of these disorders at a time when hepatic function

B.L. Shneider, MD (✉)
Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Houston, TX, USA

Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Houston, TX, USA
e-mail: Benjamin.Shneider@bcm.edu

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Table 29.1 Pediatric disorders commonly associated with portal hypertension

Primarily intrahepatic disorders
Primarily biliary or portal based
Alagille syndrome
Biliary atresia
Congenital hepatic fibrosis
Cystic fibrosis
Portal venopathy
Progressive intrahepatic cholestasis (e.g., Byler disease)
Sclerosing cholangitis
Primarily hepatocellular or sinusoidal
Alpha-1 antitrypsin deficiency
Autoimmune hepatitis
Chronic viral hepatitis (B and C)
Fatty liver disease
Glycogen storage disease
Wilson disease
Other
Venoocclusive disease
Primarily extrahepatic disorders
Budd-Chiari syndrome
Choledochal cyst
Congestive heart failure (e.g., Fontan related)
Extrahepatic portal vein obstruction (EHPVO – also known as portal vein thrombosis)
Splenic vein thrombosis

Table 29.2 Major clinical sequelae of portal hypertension in children

Variceal hemorrhage
Hepatopulmonary syndrome
Portopulmonary hypertension
Ascites and related complications
Hypersplenism – activity restrictions
Encephalopathy – learning disability

is relatively intact. Technical issues arise related to the small size of many children with portal hypertension. The range of complicated diseases that lead to portal hypertension in children continues to expand. Interesting recent case series of Fontan-related liver disease and obliterative portal venopathy have been published since Baveno V [5, 6].

A variety of very important clinical sequelae arise from the consequences of portal hypertension (Table 29.2). Recent reports highlight the prevalence of some of these issues in children. Variceal hemorrhage is clearly an issue for children and can be a dramatic mode of presentation. A comprehensive literature review identified

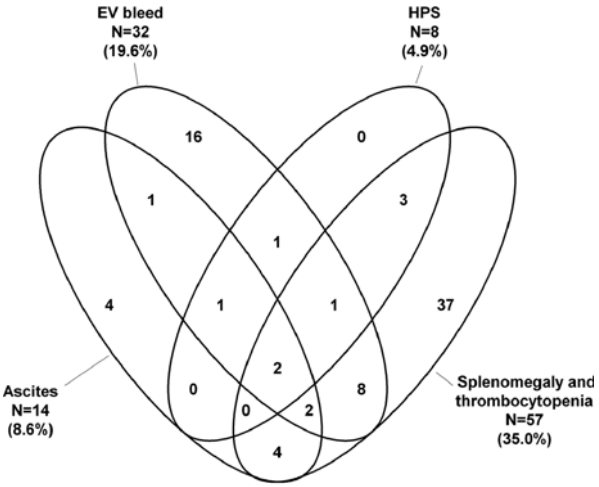

Fig. 29.1 Features of portal hypertension in biliary atresia. Overlapping manifestations of portal hypertension in a cross-sectional multicenter investigation of children with biliary atresia (Reproduced with permission from the publisher, Shneider et al. [10])

reports of bleeding from varices in a large number of children with congenital hepatic fibrosis [7]. When surveilled, esophageal varices are commonly found in congenital hepatic fibrosis in the setting of autosomal recessive polycystic kidney disease [8]. More than 50 % of children with EHPVO presented with variceal hemorrhage [9]. A multicenter cross-sectional analysis of children and young adults with biliary atresia identified a history of variceal hemorrhage in 20 % of those children [10]. This number likely underestimates the prevalence of this problem in biliary atresia as children who had undergone liver transplantation early in life were not captured in the analysis. The overlapping manifestations of portal hypertension in biliary atresia are nicely illustrated in a complicated Venn diagram from that cross-sectional investigation (Fig. 29.1). A similar analysis of children with alpha-1 antitrypsin deficiency identified portal hypertension as a major clinical issue [11]. In both of these studies, chronic ascites was not common. This complication is often a harbinger of advancing liver disease in children leading to considerations for liver transplantation. Hepatopulmonary syndrome may be relatively common in children with portal hypertension. The prevalence identified may be very much dependent upon the implementation of screening techniques. Transcutaneous oxygen saturation measurement in an upright position is easily employed although there is controversy about its sensitivity [12]. Arterial blood gas measurement is not straightforward in children and is even more difficult to accomplish in an upright position. Despite these limitations, Sari identified arterial hypoxemia in 9 of 40 children with portal hypertension [13]. Formal documentation of hepatopulmonary syndrome was made in four of these children. Portopulmonary hypertension has been described in children, although difficulties in its identification may limit our understanding of the scope of this issue in pediatrics [14, 15]. Quality of life in children with EHPVO is reduced and related to the degree of hypersplenism and failure to thrive [16]. All domains of quality of life including physical, emotional, social, and school function

are affected. Variceal eradication and/or portosystemic shunt surgery does not necessarily resolve these quality-of-life issues. Overt hepatic encephalopathy is uncommon in children with chronic liver disease. In contrast, minimal hepatic encephalopathy may be underappreciated, although it is not easy to identify in children [17].

Since Baveno V, progress has been made in deriving quality evidence to serve as the basis for clinical decision-making in Pediatric Hepatology. The scope of advancement has been quite variable with respect to fundamental aspects of the management of varices in children. It is interesting that the relative security in decision-making appears to increase as one moves from screen and primary prophylaxis to secondary prophylaxis of variceal hemorrhage. As is the case in the care of adults, endoscopic band ligation is clearly preferable to sclerotherapy for secondary prophylaxis of variceal hemorrhage [18]. In most recently reported case series, general anesthesia is required for the conduct of endoscopic management of varices in children. The ramifications of repeated general anesthesia in young children with chronic liver disease may not be fully realized [19, 20]. Anesthesia exposure in children less than 3 years of age may be associated with subsequent language and abstract reasoning deficits [21]. Unfortunately, size limitations may require injection sclerotherapy in children who are less than 10 or 15 kg. In a broad-ranging pediatric experience, 16 of 55 children required sclerotherapy for secondary prophylaxis for variceal hemorrhage [22]. In this cohort, there was ~90 % success in obliterating varices, although rebleeding occurred at a mean of 13 months from the initial hemorrhage. Focused efforts in biliary atresia, where bleeding can occur fairly early in life, necessitate a greater reliance on sclerotherapy (25 out of 30 children [23]). Four to five sessions of sclerotherapy were required for attempted variceal obliteration in these children with biliary atresia. Eradication was reported in 73 %, with relapse of varices in 45 % and rebleeding in 2 of 22 children. Nearly 50 % of these children went on to liver transplantation with 12 months of the initial bleeding episode. Treatment and secondary prophylaxis of gastric varices in children are not well described. Balloon-occluded retrograde transvenous obliteration and endoscopic cyanoacrylate injection have been successfully employed in a limited number of children [24–27]. Twenty-one children with gastric varices were successfully treated with endoscopic injections of ~0.3 ml of a 1:1 mixture of n-butyl-2-cyanoacrylate and lipiodol. Initial rates of hemostasis were high, 96 %, although rebleeding events occurred in nearly half of the children often within one year of treatment [27].

The use of nonselective ß-blockers (NSBB) in the management of portal hypertension in children remains quite controversial and poorly informed by solid evidence of optimal approaches and efficacy. Propranolol is the most widely used agent in pediatrics, even though it is not approved for use in children by the US Food and Drug Administration for any indication, let alone for portal hypertension. Variable basal heart rate during normal development and difficulties in accurate measurement of heart rate in younger children have hampered the use of a standard reduction in heart rate as a guide to pediatric NSBB dosing. Hepatic venous pressure gradient has been measured in a limited number of children with some technical issues and not in

support of assessing the potential efficacy of NSBB [28, 29]. Propranolol was used in combination with endoscopic secondary prophylaxis of variceal bleeding in 25 of 43 children [30]. In this nonrandomized retrospective analysis of clinical practice, there did not appear to be a major benefit of adding NSBB to endoscopic therapy in terms of recurrence of either varices or variceal hemorrhage.

In light of the relatively intact hepatic function and lack of significant comorbidities in many children who bleed from varices, portosystemic shunt surgery may be an interesting and underutilized approach. Distal splenorenal shunts were performed in 20 children, ten of whom had intrinsic liver disease [31]. Children selected for this approach had compensated liver disease manifest by an absence of significant ascites, an average INR of 1.3, and direct bilirubin of 0.5. The average age at shunt procedure was 11 years and with a mean follow-up of 3.5 years shunt patency was 100 %. No overt hepatic encephalopathy was noted although specific testing for minimal hepatic encephalopathy was not performed. A long-term risk of pulmonary complications of portosystemic shunting may exist in these patients, and ongoing monitoring after a successful procedure is probably warranted. Portosystemic shunt surgery for EHPVO was associated with a nonstatistically significant increase in the prevalence of minimal hepatic encephalopathy [32]. Long-term patency of these shunts has been demonstrated in children with EHPVO [33]. With the advent of polytetrafluoroethylene-coated endografts, one also wonders about the utility of transjugular intrahepatic portosystemic shunting as a method of secondary prophylaxis [34–36]. In a cohort, primarily consisting of teenagers with chronic liver disease, there was 100 % success in shunt placement [34]. Pressure gradients fell as would be expected from ~16 to ~6 mmHg. Varices were coil embolized in five children. In midterm follow-up, patency was high at mean follow-up of 20 months. One child developed encephalopathy. No revisions of shunts were required and there was a small increase in platelet counts after the procedure.

Clinical decision-making related to secondary prophylaxis of variceal hemorrhage in children with EHPVO is unique due to the availability and success of the mesoRex bypass procedure [37]. In this interesting procedure, the extrahepatic portal vein thrombosis is typically bypassed using a jugular vein graft connecting the superior mesenteric vein to the intrahepatic left portal vein within the Rex recessus (Fig. 29.2). This is distinct from a shunting procedure as it restores normal blood flow to the liver and is not associated with portosystemic shunting. When successful, this procedure reverses many of the abnormalities associated with EHPVO. In a retrospective comparison of mesoRex bypass to distal splenorenal shunting, significantly better improvement in thrombocytopenia, coagulopathy, and hyperammonemia were observed in children who underwent the mesoRex procedure. In some cases, anastomotic stenosis requires endovascular dilatation [38]. Neurocognitive testing has been previously shown to be better after mesoRex compared to distal splenorenal shunting [39].

The response to mesoRex bypass procedures suggests a remarkable plasticity of the intrahepatic portal system. This plasticity is no more evident than in recent and fascinating clinical experiences with congenital portosystemic shunts. Congenital portosystemic shunts, also known as Abernethy malformation, are rare vascular

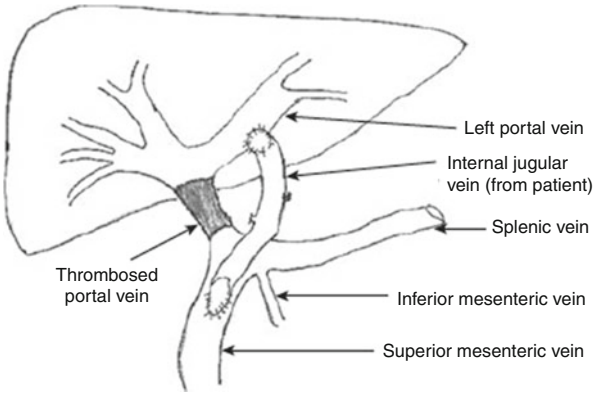

Fig. 29.2 Diagram of mesoRex bypass diagram of the mesoRex bypass procedure (Reproduced with permission from the publisher, Emre et al. [31])

malformations where there is direct shunt from the portal to the systemic circulation [40]. These malformations are likely the result of lack of appropriate developmental changes in fetal mesenteric vasculature. The clinical sequelae of these rare malformations are related to portosystemic shunting directly and not from intrinsic liver disease or portal hypertension per se. Hepatopulmonary and pulmonary hypertension are relatively frequent clinical manifestations of this disorder [41–44]. The development of liver tumors with potential for malignant transformation is an important complication of abnormal portal blood flow in these children. In many cases, there is no apparent extrahepatic portal vein – even when the congenital shunt is temporarily balloon occluded. Liver transplantation has been performed in some cases, and review of explanted liver may reveal an absence of intrahepatic portal vein structures [45]. It would be reasonable to presume that closure of these shunts would lead to intractable and severe portal hypertension. Surprisingly, this is not the case [41]. Staged closure of congenital portosystemic shunts is associated with development of intrahepatic portal blood flow [41, 46]. The staging typically includes interventional or operative shunt narrowing that is associated with a temporary increase in portal pressure. It is unclear if this increase in portal pressure is the key factor leading to remodeling of the portal vasculature. After a few months, with development of the intrahepatic portal venous system, complete occlusion can be undertaken. This approach can lead to resolution of sequelae of portosystemic shunting including decrease of liver tumor size, resolution of hepatopulmonary syndrome, and stabilization of pulmonary hypertension. This unique pediatric experience indicates a heretofore unappreciated plasticity of the portal vasculature in children.

There is a remarkable paucity of high-quality reported literature on the event of acute variceal hemorrhage in children. Endoscopic information has been presented, but details of clinical course and related morbidity are almost nonexistent in the pediatric literature. Mortality after variceal hemorrhage can be extracted from a number of published experiences, although strict application of Baveno definitions related to timing is not generally employed. This information is absolutely critical for informed decision-making related to primary prophylaxis, yet the data is primarily unavailable.

The utility of primary prophylaxis of variceal hemorrhage in children is controversial [23, 47, 48]. Surveys of clinical experts demonstrate this controversy [49]. There have been several recent reports of primary prophylaxis in pediatrics. A Finnish study focused on 47 children with biliary atresia [47]. The plan was to begin surveillance and intervention at 12 months of age. Six children had bled before primary prophylaxis could be initiated. In 16 children, endoscopic sclerotherapy was initiated – four subsequently had variceal hemorrhage. The risk of developing varices and bleeding from those varices was highly related to the response to the Kasai procedure performed for the underlying diagnosis of biliary atresia. In those whose jaundice did not clear, defined by a cutoff total bilirubin of 40 μM, the odds ratio of bleeding was 17. In a similar experience, 36 children with biliary atresia underwent primary endoscopic prophylaxis at a mean age of 22 month and weight of 11 kg [23]. Sclerotherapy was required in 21 of the children. Interestingly, the mean platelet count in these infants and young children with varices was 167,000. Four endoscopic treatments were required, with early rebleeding occurring in only two patients and rebleeding in only four. Varices relapsed in 13. Of great interest in this cohort was the finding that survival with native liver was nearly identical in those who underwent primary or secondary prophylaxis. For biliary atresia, one of the competing therapies is liver transplantation. Some suggest that liver transplantation is indicated for children with biliary atresia who have poor bile flow after the Kasai hepatoportoenterostomy [50]. This recognizes the relatively poor short-term prognosis for these children [51]. Many of the children who have required early primary prophylaxis for varices are those with biliary atresia and poor bile flow after Kasai hepatoportoenterostomy. One wonders if liver transplantation may be a better approach for these children [48]. A single-center experience from Kolkata has reported the use of NSBB for primary prophylaxis of variceal hemorrhage [52]. Sixty-two children with varices, 41 of whom had sinusoidal disease, were randomized to either propranolol or carvedilol. In a 2-year follow-up, only three children had variceal hemorrhage. No major difference in response to one therapy over another could be determined, although there may be theoretical and technical advantages to the use of carvedilol.

Significant efforts have led to advances in determining methods to predict the presence of and risk of bleeding from varices in children with portal hypertension. All of these investigations require surveillance endoscopy for the gold standard assessment of the presence or absence of esophageal varices. Interestingly, the number of these studies is much greater than reports of primary prophylaxis. Simple assessments like spleen size and platelet counts can be informative as a predictor of varices [53, 54]. Platelet count may not be informative in younger children for reasons that are not clear. Spleen size may be difficult to standardize as a measure and must be normalized to age-specific criteria. Clinical prediction rules have been developed to predict the presence of varices [55–57]. Parameters that are typically assessed include AST, platelet count, albumin, and spleen maximal linear dimension by sonography. In general, platelet count and spleen size measurements are fairly good predictors of varices. More complex predictor rules do not add a great deal to the predictive power. AUROCs for most of these parameters range between

Table 29.3 Clinical decision-making in biliary atresia and extrahepatic portal vein obstruction

Diagnosis	Biliary atresia		Extrahepatic portal vein obstruction	
Status	Drainage after Kasai hepatoportoenterostomy		Favorable anatomy of intrahepatic portal vein	
	No	Yes	No	Yes
Surveillance	No	?	?	Yes
1^0 prophylaxis	OLT	?	?	MRB
2^0 prophylaxis	EVS/EVL OLT	EVL DSRS OLT	EVS/EVL MRB/DSRS	EVS/EVL MRB

Abbreviations: DSRS distal splenorenal shunt, *EVL* endoscopic band ligation, *EVS* endoscopic sclerotherapy, *MRB* mesoRex bypass, *OLT* orthotopic liver transplant

0.70 and 0.84. Liver stiffness as measured by transient elastography has also been investigated for its utility to predict varices in children with biliary atresia [58–60]. Children with varices typically have liver stiffness in the range of 17–38 kPa, while those without were in the range of 8–12 kPa. Spleen stiffness is being investigated as an alternative assessment [61]. Endoscopic findings that predict risk of bleeding in children are not well described overall. Red markings, gastric varices along the cardia, and varix size are predictive of subsequent variceal hemorrhage in children with biliary atresia [62, 63]. In one study, large varices were defined by their response to insufflation, with large varices (grade II and III) being those that did not flatten in response to insufflation [62].

Despite significant progress since Baveno V, clinicians caring for children with portal hypertension face difficult clinical decision-making. Strict evidence-based decisions are difficult to derive. Numerous summaries have been written, and concerted efforts to provide expert pediatric-oriented opinion on Baveno IV and V have been published [3, 64, 65]. In light of the current available information, a personal biased set of recommendations for the approach to biliary atresia and extrahepatic portal vein obstruction is presented in Table 29.3. For each disease, there are critical clinical parameters that influence decisions. For biliary atresia, the early response to the Kasai hepatoportoenterostomy is critical. In children where the surgery has not worked, as manifest by poor bile drainage, near-term prognosis is poor and liver transplantation should be actively considered. In this case, there may not be a role for surveillance, and if possible, liver transplantation would serve as primary prophylaxis. Secondary prophylaxis would typically include endoscopic therapy with subsequent liver transplantation. In children with good bile flow after surgery, the decision-making is more complicated. My own personal bias is against surveillance and primary prophylaxis, although expert clinicians do both along the lines of recommendations for adults. Secondary prophylaxis would be predominantly endoscopic with consideration for the use of distal splenorenal shunting for those with intractable problems and good hepatic reserve. For EHPVO, a key issue is whether the intrahepatic portal vasculature is patent, i.e., favorable for mesoRex bypass. When there is favorable anatomy, strong consideration for early mesoRex bypass should be

given. Surveillance in this case that reveals varices may be an indication for the surgery as primary prophylaxis. In the case of secondary prophylaxis when bleeding is the initial presenting problem, endoscopic therapy is typically a primary approach with mesoRex bypass as a definitive and favorable therapy. Decision-making in those with an unfavorable anatomy is more complicated. One of the amazing complexities of pediatrics is what to do with the myriad of other pediatric diseases that have their own special clinical issues. A complete understanding of the natural history of the particular disease along with understanding the pros and cons of potential interventions in children is critical for relatively informed decision-making.

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Part VIII

Prevention of Further Decompensation (Ascites, Spontaneous Bacterial Peritonitis, Hepatorenal Syndrome, Hepatic Encephalopathy)

Introduction and Survey Results

30

Guadalupe Garcia-Tsao, Cristina Ripoll, Salvador Augustin, Thomas Reiberger, Agustin Albillos, Richard Moreau, Francesco Salerno, and Juan G. Abraldes

G. Garcia-Tsao (✉)
Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA
e-mail: guadalupe.garcia-tsao@yale.edu

C. Ripoll
First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
e-mail: cristina_ripoll@yahoo.es

S. Augustin
Liver Unit - Department of Internal Medicine, Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

CIBERehd, Juan Rodés Grant Researcher, Instituto de Salud Carlos III, Madrid, Spain
e-mail: salva.augustin@gmail.com

T. Reiberger
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria
e-mail: thomas.reiberger@meduniwien.ac.at

A. Albillos
Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain
e-mail: agustin.albillosm@uah.es

R. Moreau
Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

F. Salerno
Internal Medicine and Hepatology, Policlinico IRCCS San Donato, University of Milan, Milan, Italy

J.G. Abraldes
Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada
e-mail: Juan.g.abraldes@ualberta.ca, juan.g.abraldes@gmail.com

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Introduction

The landscape of portal hypertension and variceal hemorrhage has changed since the last Baveno workshop. Randomized controlled trials (RCTs) examining therapies to prevent recurrent variceal hemorrhage have included all patients that have recovered from an episode of variceal hemorrhage, independent of stage of cirrhosis. Therefore, recommendations derived from these trials are blanket recommendations for all patients with cirrhosis.

It has become clear that cirrhosis is an entity composed of different prognostic stages and that results of RCTs in patients with variceal hemorrhage should be analyzed in the context of these stages. Moreover, specific therapies may be more relevant for some stages than for others depending on the prevailing pathophysiologic mechanism at any given stage.

At a minimum, cirrhosis needs to be stratified in two main stages: compensated and decompensated with decompensation being defined by a history or by the presence of variceal hemorrhage, ascites, encephalopathy, and/or jaundice. In fact, variceal hemorrhage can occur in the absence of other decompensating events or may occur in patients who are already decompensated (presence of ascites or encephalopathy) or who develop one of these complications during the episode of variceal hemorrhage. These different scenarios have a different prognosis and should be taken into account in the treatment and investigation of patients with variceal hemorrhage. Moreover, therapies used to prevent recurrent variceal hemorrhage may have an impact (negative or positive) on the course of other complications of cirrhosis. Conversely, therapies used to treat other complications of cirrhosis may have an impact (negative or positive) on the course of a patient that has bled from varices.

Therefore, the objectives of this session were: (a) to determine whether results of recommended therapy to prevent recurrent variceal hemorrhage differ depending on the severity of liver disease, (b) to examine whether recommended therapies to prevent rebleeding have an effect on other complications of cirrhosis, (c) to examine whether recommended therapies for other complications of cirrhosis have an effect on variceal hemorrhage, and (d) to set the bases for the design of future research studies aimed at patients who have recovered from an episode of variceal hemorrhage.

In anticipation to this session, a survey was developed taking into account the objectives of the session and distributed via SurveyMonkey to the 54 Baveno participants (moderators, panelists, speakers). The survey consisted of 14 questions in three key areas: (a) prevention of recurrent variceal hemorrhage (two questions) – current practice and subpopulations that are treated differently; (b) prevention of further decompensation (other than rebleeding) and death (four questions) – including the issue of the potentially deleterious effect of nonselective beta-blockers in patients with refractory; and (c) trial design and research agenda (six questions).

From a total of 54 Baveno participants, 49 (90.7 %) responded to the survey, an excellent response rate. For each question, respondents had opportunity to attach a comment. The most common/relevant comments are mentioned at the end of each question.

Part A. Prevention of Recurrent Variceal Hemorrhage

1. *Which is the therapy* (*or combination of therapies*) *that you most commonly prescribe to prevent recurrent variceal hemorrhage in a patient who has recovered from first episode of esophageal variceal hemorrhage*?

NSBB + EVL	**33**	**67** %
Carvedilol[a] + EVL	8	16 %
NSBB alone	4	8 %
EVL alone[b]	2	4 %
NSBB + nitrates[c]	1	2 %
NSBB + nitrates + EVL	1	2 %
Carvedilol alone	0	–
TIPS	0	–
Total respondents	49	100 %

[a]Not in child B/C, not if: ascites, hypotension, creatinine >1.5
[b]Pediatric population
[c]Patients do not tolerate nitrates

2. *Do you routinely use HVPG monitoring in the setting of secondary prophylaxis*?

No	35	71 %
Yes	14	29 %
Total respondents	49	100 %

Comments: not widely available/feasible, not routinely but whenever possible

3. *Are there any situations in which you would consider a different approach to prevent recurrent variceal hemorrhage than the one you regularly use*?

Yes	46	94 %
No	3	6 %
Total respondents	49	100 %

Comments: would consider TIPS earlier in special populations – fundal varices, patients who have bled while on adequate primary prophylaxis, varices that do not obliterate, and patients with portal vein thrombosis or refractory ascites

4. *If you answered "Yes" to the previous question, please specify the situations in which you would consider a different approach. Tick all that apply and please comment on how you would modify your approach.*

Bled from fundal gastric varices (GOV2)[a]	31	74 %
Refractory ascites	21	50 %
Bled from GOV1 gastric varices	11	26 %
Positive hemodynamic response[b]	10	24 %
Advanced HCC (BCLC stages C/D)	8	19 %
Achieved sustained viral response (HCV) or viral suppression (HBV) after the episode of VH[b]	7	17 %
Abstained from alcohol after the episode of VH[b]	5	12 %

Developed SBP at the time of variceal hemorrhage	5	12 %
Child A patients who continue to be entirely compensated after the episode of VH[b]	2	5 %
Total respondents	42	100 %

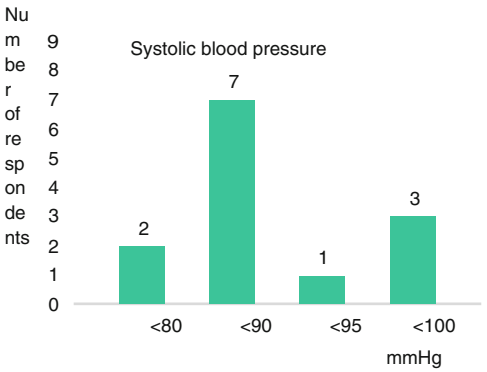
Comments: it is necessary to identify high-risk patients in whom TIPS should be considered earlier
[a]Glue plus NSBB or TIPS
[b]Consider NSBB alone (without EVL)

Part B. Prevention of Further Decompensation (Other than Rebleeding) and Death

5. *Would you discontinue NSBB* (*propranolol or nadolol*) *or carvedilol in an outpatient who has been receiving them but has now developed refractory ascites*?

If patient is more hypotensive than usual[a]	22	46 %
No	14	29 %
Yes	10	21 %
If patient has HRS-2 (stable increase in SCr)	2	4 %
Total respondents	48	100 %
Did not answer	1	

Comments: only if hypotension is symptomatic; would lower dose not discontinue
[a]Threshold systolic blood pressure selected by respondents is depicted in the next figure:



6. *Would you discontinue NSBB* (*propranolol or nadolol*) *or carvedilol in a hospitalized patient who has been receiving them but is now admitted with an episode of SBP*?

If patient is more hypotensive[a]	16	33 %
No	16	33 %
Yes	12	24 %
If patient has acute kidney injury	5	10 %
Total respondents	49	100 %

Comments: [a]would lower dose; no consensus on threshold blood pressure

7. *In a patient in whom beta-blockers or carvedilol have been discontinued for any of the above reasons*, *would you consider restarting them*?

Sometimes	22	48 %
Would consider restarting NSBB (nadolol or propranolol) but not carvedilol	15	33 %
Always	6	13 %
Never	3	6 %
Total respondents	46	100 %
Did not respond	3	

8. *Which of the following medications do you use regularly in a patient with cirrhosis to prevent further decompensation/death*?

Antibiotics to prevent first episode of SBP in high-risk patients[a]	29	59 %
Anticoagulants in patients with occlusive non-tumoral portal vein thrombosis	27	55 %
Simvastatin	3	6 %
Chronic midodrine in patients with refractory ascites	3	6 %
Pentoxifylline in child C patients	1	2 %
Low molecular weight heparin in patients without portal vein thrombosis	1	2 %
None of the above	9	18 %
Total respondents	49	100 %

[a]Per Fernandez et al. criteria, almost all mentioned quinolones/norfloxacin

Part C: Research Agenda and Trial Design

In future trials designed to prevent recurrent variceal hemorrhage:

9. *Which of the following do you think should be the primary endpoint* (*choose only one*)?

A composite of all complications of portal hypertension (ascites, SBP, HRS, HE) + mortality	22	45 %
A composite of rebleeding and mortality	16	33 %
Mortality	7	14 %
Rebleeding	4	8 %
Total respondents	49	100 %

Comments: key point is to treat portal hypertension not only one of its complications; in otherwise compensated patients, it would be difficult to achieve an appropriate sample size if mortality alone is chosen; in this group decompensation would be a better endpoint

10. *What do you think should be the standard treatment arm*?

NSBB (propranolol or nadolol) + EVL	34	74 %
NSBB (propranolol or nadolol)	4	9 %
NSBB (propranolol or nadolol) + nitrates + EVL	4	9 %
NSBB (propranolol or nadolol) + EVL+ simvastatin	4	9 %
NSBB (propranolol or nadolol) + nitrates	0	–
Total respondents	46	100 %
Did not respond	3	

Comments: some respondents added carvedilol + EVL

11. *Which, in your opinion, should be the main subgroup analysis* (*choose only one*)?

Child A vs. child B/C	13	27 %
Ascites vs. no ascites	12	25 %
Child A/B vs. C	8	17 %
Stratification by MELD	8	17 %
Child A vs. B/C	3	6 %
Alcoholic vs. nonalcoholic etiology	3	6 %
No subgroup analysis should be reported	1	2 %
Viral vs. nonviral etiology	0	–
Total respondents	48	100 %
Did not respond	1	

12. *Do you think phase III trials should include HVPG measurements*?

Yes	36	74 %
No	13	26 %
Total respondents	49	100 %

Comments: if the treatment affected is expected to be related to portal pressure changes, at least in a subgroup, variation in quality of measurement at multiple sites raises questions on validity of measurements

13. *Do you think we need new trials comparing covered TIPS vs. standard therapy*?

Yes	28	58 %
No	20	42 %
Total respondents	49	100 %

Comments: only in specific high-risk groups

14. *Do you think there are new drugs ready to be tested in phase III trials*?

No	27	59 %
Yes	19	41 %
Total respondents	46	100 %

For those who answered "yes," which drug(s)?

Specific drug	**n**
Statins/simvastatin	9
FXR agonists/obeticholic acid	4
Anticoagulants	4
Pentoxifylline	1
New terlipressin formulation	1
Antivirals	1

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Prevention of Variceal Rebleeding: Stratifying Risk and Individualizing Care

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Agustin Albillos, Juan G. Abraldes, Cristina Ripoll, Thomas Reiberger, Salvador Augustin, Francesco Salerno, Richard Moreau, and Guadalupe Garcia-Tsao

Introduction

Combination of drugs and endoscopic therapy is the currently recommended first-line treatment for the prevention of variceal rebleeding [1, 2]. The greater efficacy of the combination of drugs (beta-blockers ± nitrates) plus endoscopic therapy over treatment alone was demonstrated in a meta-analysis that included trials using either sclerotherapy or endoscopic variceal ligation (EVL) as endoscopic therapy [3]. This meta-analysis included 23 trials (1860 patients) and showed that combination therapy (drugs plus endoscopic therapy) led to lower overall rebleeding rates than either drugs [Relative risk (RR), RR 0.71; 95 % CI, 0.59–0.86)] or endoscopic therapy alone (RR 0.68; 95 % CI, 0.52–0.89). Variceal rebleeding rates were also lower in the combination therapy group. The beneficial impact of combination therapy on overall and variceal rebleeding did not translate into a reduction in mortality. Subgroup analysis concluded that the benefit of combination therapy was independent of the type of endoscopic therapy.

A. Albillos (✉)
Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain
e-mail: agustin.albillos@uah.es

J.G. Abraldes, MD, MMSc
Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada

C. Ripoll, MD
First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

T. Reiberger, MD
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria
e-mail: thomas.reiberger@meduniwien.ac.at

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S. Augustin, MD
Liver Unit - Department of Internal Medicine, Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

CIBERehd, Juan Rodés Grant Researcher, Instituto de Salud Carlos III, Madrid, Spain
e-mail: salva.augustin@gmail.com

F. Salerno, MD
Internal Medicine and Hepatology, Policlinico IRCCS San Donato, University of Milan, Milan, Italy

R. Moreau, MD
Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

G. Garcia-Tsao, MD
Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA
e-mail: guadalupe.garcia-tsao@yale.edu

Four subsequent meta-analyses including only trials that used EVL as endoscopic therapy have confirmed these findings [4–7]. Trials comparing combination therapy (EVL + drugs) vs. EVL alone address the effect of adding drugs to EVL (i.e., EVL acts as a control group), whereas trials comparing combination therapy (drugs + EVL) vs. drugs alone address the effect of adding EVL to drugs (i.e., drugs act as a control group). In the most recent of these meta-analyses by Puente et al., combination of drugs plus EVL was compared to EVL alone (five trials, 476 patients) or to drugs alone (four trials, 409 patients) [7]. Pooled analysis shows a statistically significant effect favoring combination therapy for reducing variceal rebleeding, when combination therapy was compared with either therapy alone. However, overall rebleeding was significantly reduced when combination therapy (RR, 0.44, 95 % CI 0.28–0.69) was compared with EVL alone, but not when compared with drugs alone (RR, 0.76, 95 % CI 0.58–1.00) [7]. Mortality was unchanged and similar between both comparisons. These data indicate that EVL and drugs are highly effective to prevent esophageal variceal rebleeding and provide further support to combination therapy as the standard of care in this setting.

Risk Stratification

The current standard of care, i.e., combination of EVL and drugs, is uniformly applied to all patients with cirrhosis who have recovered from an episode of variceal hemorrhage because, so far, randomized controlled trials have not included risk stratification strategies. Most trials identify severity of liver disease (Child class or presence of ascites) as independent predictors of death, but there is a lack of

information to stratify patients according to their rebleeding risk. Risk stratification would allow to tailor therapy and, for instance, to identify subpopulations of patients with a good response to drugs in whom EVL would not be necessary or patients unlikely to respond to combination therapy in whom other therapies (i.e., TIPS) could be a better choice.

Unfortunately, data on risk stratification cannot be obtained from published randomized controlled trials of prevention of variceal rebleeding, since none of the trials reported outcomes stratified by patient characteristics. Moreover, the unavailability of individual data precludes the possibility to analyze survival as a time-dependent variable. To overcome the limitations associated with the use of published data, in order to increase the power of the statistical analysis, we decided to perform a meta-analysis using individual patient data.

The current individual patient data meta-analysis was done to pool the data of patients included in randomized controlled trials comparing the efficacy of EVL and drugs (nonselective beta-blockers ± nitrates) with EVL or drugs alone to prevent variceal rebleeding. We revised electronic databases and conference proceedings to search for all randomized trials addressing this issue up to January 2015. Trials were selected according to the following criteria: (1) study design: randomized, controlled trials comparing combination therapy (EVL and drugs) with EVL or drugs alone; (2) study population: patients with cirrhosis and a prior episode of esophageal variceal bleeding; (3) publication type: full article; and (4) outcomes assessed: overall gastrointestinal bleeding and mortality.

We included three trials comparing combination therapy vs. drugs alone (398 patients) [8–10] and four trials comparing combination therapy vs. EVL alone (421 patients) [8, 11–13]. We excluded two trials that were published only in abstract form [14, 15], one trial that was designed to address the incidence of portal hypertensive gastropathy after EVL and lacked data on mortality [16], and one trial in which drug administration was HVPG guided [17].

The following results of the individual data meta-analysis should be considered preliminary. We stratified patients by Child-Pugh (A, B/C), which is concordant with the stratification suggested by most of the Baveno experts that answered the survey.

Combination therapy compared with drugs alone reduces significantly overall rebleeding in Child A [Odds ratio (OR) 0.39, CI 0.15–0.99)], but not in Child B/C (OR 1.03, CI 0.64–1.64) or in the whole population. On the contrary, combination therapy compared with EVL alone significantly reduces overall GI rebleeding in the whole population (OR 0.43, CI 0.27–0.67), as well as in Child A (OR 0.24, CI 0.06–0.95) and in B/C patients (OR 0.45, CI 0.27–0.74). This indicates that pharmacological therapy is an essential element in preventing rebleeding, particularly in patients with more severe liver disease.

Mortality was not different when combination therapy was compared with drugs alone in the whole population, as well as in Child A and B/C patients. On the other hand, combination therapy compared with EVL alone significantly reduced mortality in the whole population and in Child B/C patients (OR 0.41, CI 0.21–0.80), but not in Child A patients.

The preliminary results of the individual data meta-analysis indicate that the efficacy of these therapies on rebleeding and mortality is different between Child A and

Child B/C patients. In Child A, combination of drugs and EVL is associated with lower rebleeding rate, but without differences in survival. In Child B/C, and compared to EVL alone, combination therapy is associated with lower rebleeding and mortality.

Taken together, these data indicate that EVL and drugs are highly effective to prevent esophageal variceal rebleeding, but in the case of EVL, this benefit is offset by its effect in increasing upper gastrointestinal bleeding from other sources, such as post-banding ulcers, and its lack of impact on the natural history of cirrhosis. EVL alone is suboptimal and should not be used as monotherapy, unless there is intolerance or contraindication to beta-blockers. This contention is further supported by the superiority of drugs (beta-blockers ± nitrates) when compared to EVL regarding mortality on long-term follow-up [18]. Physicians should be aware that patients on combination therapy for variceal rebleeding prevention face an increased risk of rebleeding and death if beta-blockers are withdrawn.

Combination of drugs and EVL should continue to be the standard of care for variceal rebleeding prevention, but it should take into account that beta-blockers are the mainstay of such therapy.

TIPS as Second-Line Therapy

TIPS is recommended as second-line therapy for patients who have failed variceal rebleeding prevention with the combination of drugs and EVL. Meta-analysis of trials that compared TIPS with endoscopic therapy shows that TIPS is very effective in preventing rebleeding, although it markedly increases the risk of hepatic encephalopathy without an effect on survival [19, 20]. The only trial that compared TIPS with propranolol plus 5-isosorbide mononitrate to prevent rebleeding in patients with advanced cirrhosis (Child B or C) showed that patients allocated to TIPS had lower rates of overall and variceal rebleeding and a lower rate of ascites, but greater rates of encephalopathy and identical survival [21]. Covered endoprostheses with lower occlusion and encephalopathy rates have largely replaced uncovered stents [22] but these have not been used in RCTs of prevention of variceal rebleeding.

The lower occlusion rates of covered TIPS make it a good first-line option for the prevention of rebleeding in those patients likely to fail standard combination therapy or who present complications of portal hypertension other than bleeding. These include:

1. Patients presenting a variceal bleed while on primary prophylaxis with beta-blockers, which constitute a distinct high-risk subpopulation, with an especially poor response to combination therapy in terms of rebleeding risk and death. In this situation, current guidelines recommend adding EVL to beta-blockers [1]. However, information is meager, as these patients are excluded from most clinical trials. A recent observational study has shown that addition of EVL is particularly ineffective in this patient population, with higher rates of overall and variceal rebleeding and lower incidence of 2-year transplant-free survival compared to patients who were not undergoing primary prophylaxis with beta-blockers when presenting with the index episode of variceal hemorrhage [23].

2. Patients in whom beta-blockers are contraindicated, especially if they bleed while on EVL for primary prophylaxis.
3. Patients with recurrent or refractory ascites. TIPS eliminates ascites in two-third of the patients with refractory ascites, with a trend toward improved survival [24]. Besides, in this population, concern has recently been raised about the safety of beta-blockers [25].
4. Patients with non-tumoral portal vein thrombosis. Portal vein thrombosis, either occlusive or not, is found in about 15 % of patients with cirrhosis and likely worsens the outcome of complications of portal hypertension. TIPS placement is feasible, safe, and effective in most of these patients, being especially valuable in those eligible for liver transplantation, since extension of the thrombosis might complicate surgery [26, 27].
5. Patients with fundal varices. Patients bleeding from esophageal varices who simultaneously have large fundal varices constitute a difficult to treat population that can benefit from TIPS.

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Secondary Prophylaxis in Special Patient Populations

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Thomas Reiberger, Richard Moreau, Cristina Ripoll, Agustin Albillos, Salvador Augustin, Francesco Salerno, Juan G. Abraldes, and Guadalupe Garcia-Tsao

T. Reiberger (✉)
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria
e-mail: thomas.reiberger@meduniwien.ac.at

R. Moreau
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

C. Ripoll
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

A. Albillos
Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain

S. Augustin
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

Liver Unit - Department of Internal Medicine, Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

CIBERehd, Juan Rodés Grant Researcher, Instituto de Salud Carlos III, Madrid, Spain

R. de Franchis (ed.), *Portal Hypertension VI: Proceedings of the Sixth Baveno Consensus Workshop: Stratifying Risk and Individualizing Care*,
DOI 10.1007/978-3-319-23018-4_32

F. Salerno
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

Internal Medicine and Hepatology, Policlinico IRCCS San Donato, University of Milan, Milan, Italy

J.G. Abraldes
Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada

G. Garcia-Tsao
Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA

Secondary Prophylaxis of Variceal Bleeding in Special Patient Populations

The Baveno V guidelines recommended a combination of non-selective beta-blockers (NSBBs) and endoscopic band ligation (EBL) for secondary prophylaxis of variceal bleeding [1]. Hemodynamic responders to medical therapy (beta-blockers alone or in combination with nitrates) have a significantly lower incidence – not only of variceal rebleeding but also of other complications, including death [1]. NSBBs that were used in those studies were the "traditional" NSBB, propranolol or nadolol.

More recently, carvedilol, a NSBB with additional anti-alpha adrenergic activity, has been assessed both for primary [2, 3] and secondary prophylaxis [4, 5] of variceal bleeding. Given additional vasodilating effects (presumably decreasing intrahepatic resistance), it has a greater portal pressure-reducing effect compared to propranolol [2, 6]. In secondary prophylaxis studies, carvedilol has been shown to be equivalent to EBL with a tendency for lower mortality [5] and to the combination of nadolol + ISMN with lower side effects [4]. However, it has not been compared to standard of care (traditional NSBB + EBL). Additionally, vasodilatation induced by carvedilol occurs not only at the sinusoidal level but also in the systemic circulation, especially at doses above 12.5 mg/day [2, 6], it has a more pronounced effect on systemic blood pressure compared to propranolol [6, 7] and has been shown to lead to adverse effects such as sodium and water retention [6]. This is particularly concerning in patients with more advanced liver disease who are the primary focus of this section [8, 9]. In the absence of prospective trials addressing the efficacy/safety of carvedilol in comparison to currently recommended secondary prophylaxis with NSBB plus EBL, its use in secondary prophylaxis of variceal bleeding cannot be recommended.

Patients with Refractory Ascites, SBP, and HRS

Patients in need for prevention treatment of variceal rebleeding (secondary prophylaxis) usually present with more advanced disease – reflected by higher Child-Pugh or MELD scores – than patients receiving primary prophylaxis. Trials on secondary prophylaxis of variceal bleeding have consistently excluded patients with renal failure, refractory ascites, SBP, or hepatocellular carcinoma. Thus, it is uncertain whether Baveno recommendations to use a combination of endoscopic band ligation (EBL) and non-selective beta-blockers (NSBB) for prevention of variceal rebleeding also apply to these patients.

Recently, data have emerged showing that NSBB therapy in patients with refractory ascites or in case of SBP is associated with increased mortality rates. Potential explanations of this detrimental effect of NSBB include the window hypothesis suggesting that NSBBs – while being highly effective in compensated cirrhosis – might be detrimental in decompensated stages of cirrhosis. Ascites is the most common decompensation in patients with cirrhosis and is often accompanied by modest renal impairment. A sympathetic drive is needed when a patient with cirrhosis becomes more hypotensive in case of infection, bleeding, or progressive vasodilation. If hyperdynamic circulation is pronounced – as indicated by refractory ascites or renal dysfunction – NSBB therapy might impair the inotropic/chronotropic response and the upregulation of the sympathetic nervous system that is necessary for a compensatory hemodynamic adaptive response.

Before analyzing the effects of NSBBs in special patient populations in order to understand the pathophysiology and mechanisms by which NSBBs may negatively impact outcomes in cirrhosis, we reviewed the hemodynamic and cardiac effects of NSBB in heart failure and cirrhosis.

Beta-Blockers and Heart Failure

Beta-blockers (BBs) were initially developed to treat angina pectoris in order to "stop the effects of adrenaline on the heart" [10]. Further studies described the use of beta-blockers in other settings such as arterial hypertension, tachyarrhythmias, and acute myocardial infarction. Traditionally BBs were considered contraindicated in the setting of heart failure due to their negative inotropic effect. Nevertheless, nowadays the use of BB – especially carvedilol – represents an essential treatment option of heart failure, since clear benefits including increased survival have been demonstrated in various studies [11–14]. The actual hypothesis explaining the beneficial effect of BBs in heart failure is the neurohormonal hypothesis [15]. In heart failure, like in cirrhosis, there is an activation of the sympathetic nervous system (SNS). In heart failure, the chronic activation of the SNS leads to a desensitization of adrenergic receptors at different levels including

downregulation and uncoupling which leads to a loss of function of the receptor. This in turn leads to a switch from the predominant beta1-adrenergic receptors to beta2-adrenergic receptors [16]. Accordingly, BB would prevent structural and functional heart damage induced by upregulation of the SNS. Interestingly, desensitization of beta-receptors, reduced density of beta-receptors, and shift to a predominance of beta2 receptors have also been described as characteristics of cirrhotic cardiomyopathy [17]. Similar findings are also observed in cirrhotic cardiomyopathy compared to the sympathetic lesion described in heart failure, namely, cardiac myocyte edema, fibrosis, and exudation [18].

Although initial studies were focused on patients with mild to moderate heart failure, the tolerability and efficacy of BB in functional NYHA Class IV ($n=63$) compared to 167 patients with NYHA I–III have been evaluated [19]. In this study carvedilol was started at a very low dose (3.125 mg/day) and titrated up to a maximum of 25 mg twice a day (50 mg/day). Patients with baseline hypotension (80/50 mmHg or bradycardia HF <50 bpm) were not included. Those who had more severe heart failure had more frequent nonfatal adverse events (43 % vs. 24 %; $p<0.0001$) and more frequent permanent withdrawal of the drug because of adverse events (25 % vs. 13 % $p<0.01$). Nevertheless more patients with NYHA IV at baseline benefited from BB therapy than patients with NYHA I–III (59 % vs. 37 %). However, 29 % deteriorated or died under NSBB therapy in NYHA IV versus only 19 % in patients the less severe heart failure NYHA I–III. Clinical predictors of BB intolerance were hyponatremia (136 vs. 138 mmol/L; $p=0.0026$) and baseline hypotension (MAP 74 vs. 82 mmHg; $p=0.01$). Thus – although some patients benefit from BB therapy – there are patients who do not tolerate BB or who decompensate on BB due to a low cardiac output [20].

Heart failure with preserved ejection fraction (previously referred to as heart failure with normal ejection fraction, HFNEF) is a heterogeneous group of patients who have symptoms of heart failure and diastolic dysfunction in the absence of a reduced ejection fraction [21]. Although the use of BB in this group of patients has been questioned, a recent meta-analysis showed a decrease in all cause mortality in patients who had received BBs, although no decrease in hospitalization or a composite endpoint of hospitalization and mortality was demonstrated [22]. Although cirrhotic cardiomyopathy could be regarded as heart failure with preserved ejection fraction, there are no data regarding the effect of BB in the patient population with cirrhotic cardiomyopathy.

Effects of BB on Cardiac Output and Systemic Blood Pressure

BB therapy reduces cardiac output and heart rate and, thus, mean arterial pressure [23]. Due to the unopposed action of alpha antagonists, non-selective beta-blockers (NSBBs) lead to an increase in systemic vascular resistance [23]. Due to its additional alpha-1 antagonistic activity, carvedilol leads to a greater reduction in MAP than traditional NSBBs that lack alpha1 adrenergic activity. This was recently demonstrated in a meta-analysis comparing the hemodynamic effects of carvedilol

to propranolol that showed that both NSBBs and carvedilol lead to a decrease in MAP but with a greater effect of carvedilol [carvedilol mean weighted diff of −10.4 (−13.9–(−6.9)) mmHg vs propranolol. −6.4 (−9.9–(−2.8)) mmHg] [7]. It is considered that patients with cirrhosis have chronotropic incompetence that is the inability to adequately increase heart rate under stress conditions, which leads to inadequate exercise capacity. Chronotropic incompetence has also been observed in patients with heart failure, where its presence is associated with mortality [24].

Patients with heart failure on BB have more frequent chronotropic incompetence [25], although BB cessation is not associated with an improvement in exercise capacity [26]. Indeed, the positive or negative impact of BBs on exercise capacity in patients with heart failure is controversial [27]. In cirrhosis, impaired exercise capacity has been described and has been associated to chronotropic incompetence [28, 29]. Acute administration of BBs leads to a blunted increase of cardiac output and heart rate and a lack of increase of stroke volume in response to exercise compared to placebo [30]. These systemic hemodynamic effects lead in turn to a lack of increase in hepatic blood flow and therefore a lack of increase of the hepatic venous pressure gradient [30]. However, the effect of chronic BB administration on exercise capacity in cirrhosis is unknown.

Effects of NSBBs on Renal Function and Post-paracentesis Circulatory Dysfunction

Beta-receptors can be found on other structures besides the cardiovascular system, including baroreceptors and the macula densa in the kidney, so that BBs inhibit the secretion of renin [31]. This has been described in the setting of arterial hypertension [32] and also in patients with cirrhosis [33], although other studies have shown controversial results [34]. In cirrhosis, an increase in renin of at least 50 % from baseline after large-volume paracentesis defines post-paracentesis circulatory dysfunction (PPCD), which is associated with the development of renal impairment and hyponatremia [35]. The impact of BBs on the incidence of PPCD has been recently evaluated [36]. This study was developed in an attempt to explain the potential negative impact of NSBB in patients with refractory ascites [37]. This study included ten patients with refractory ascites who received NSBBs for primary ($n=9$) or secondary ($n=1$) prophylaxis. Measurements of renin were performed before and 1 week after a large-volume paracentesis. Beta-blockers were then discontinued, and then a second measurement was performed. The baseline values of renin were similar. After large-volume paracentesis (LVP), patients under NSBB therapy had a significant increase in "post-paracentesis" plasma renin and no change in heart rate indicating that regulation of arterial pressure in these patients depends mainly on activation of the renin-angiotensin system. After LVP, patients who were not receiving NSBB had a significant increase in heart rate and no changes in plasma renin showing that blood pressure regulation in this case depends on reflex tachycardia. However, due to the small sample size and the cross-over design of this study, more data is necessary to clarify the effect of NSBBs on PPCD.

Evidence for NSBB Therapy for Prophylaxis of Variceal Bleeding in Patients with Ascites

We have revisited the available literature on prophylaxis of variceal rebleeding and assessed evidence for efficacy and safety of NSBB therapy in the special populations of patients with ascites. As summarized in Table 32.1 of this chapter, only a small number of patients with (refractory) ascites were included in trials, and information on the proportion of patients with ascites/refractory ascites was often not provided. Interestingly, a meta-analysis including 598 individual patient data [38] has found that NSBB prevented variceal bleeding in a similarly effective way both in patients with or without ascites and in patients with a Child-Pugh lower or greater than 8. However, this meta-analysis still did not answer the question if other non-bleeding complications – such as renal failure or cardiac/circulatory dysfunction – are influenced by NSBB therapy, since the endpoint transplant-free survival was not assessed. The majority of studies excluded patients with renal failure and refractory ascites (such as those related to hepatorenal syndrome type 2) from prospective studies. Thus, the proportion of patients with ascites is underrepresented in prospective trials of prophylaxis of variceal bleeding, and the discrimination between ascites and refractory ascites (when cardiac chronotropic response is most needed) was often not made/reported. Even if patients with ascites were included in prospective trials of secondary prophylaxis showing efficacy of NSBB therapy, this does not essentially imply efficacy and safety in the subgroup of patients with ascites – especially in refractory ascites.

Studies Addressing the Effect of NSBB Therapy on Outcome in the Population of Patients with Refractory Ascites

The first study was published by Sersté et al. who prospectively evaluated a cohort of 151 consecutive patients with refractory ascites, of which 77 were receiving NSBBs for the prevention of bleeding or rebleeding. All NSBB patients were treated with propranolol (median dose: 80 mg). Patients taking NSBBs had a poorer condition at baseline, as shown by higher bilirubin, a slightly higher HVPG, and all had varices (as compared to only 4 % in those not taking NSBBs). Those on NSBBs had a much shorter median survival (5 months vs. 20 months). Kimer et al. [39] retrospectively studied 71 patients with refractory ascites (23 on NSBBs). Baseline characteristics were comparable between patients taking and not taking NSBB, except for a higher proportion of patients with varices in those taking NSBBs. There were no differences in survival between the two groups of patients. Robins et al reported another retrospective cohort of 114 consecutive patients defined as having diuretic-resistant ascites [40]. Thirty-six were on propranolol (mean dose 49 mg). Patients were comparable except for the proportion of patients with varices and of previous bleeders. Median survival was not significantly different between groups (NSBB: 18 months vs. no-NSBB: 11 months).

Table 32.1 Proportion of patients with ascites, refractory ascites, or Child-Pugh C in trials assessing NSBB therapy for secondary prophylaxis of variceal bleeding from 2000 to 2015

Study	Type	Total (*n*)	% Ascites	% Refractory ascites	% Child C
Lo, 2000, Hepatology	BB/sucralfate vs. EBL/sucralfate vs. EBL	122	56	?	34
Lo, 2001, GI Endosc	BB/EBL vs. EBL	77	?	?	?
Villanueva, 2001, NEJM	BB/Nx vs. EBL	144	67	?	22
Patch, 2002, Gastro	BB/N vs. EBL	102	?	?	50
Lo, 2002, Gastro	BB/N vs. EBL	121	62	?	21
Romero, 2006, APT	BB/N vs. EBL	109	67	?	24
Ahmad, 2009, JCPSP	BB vs. BB/N vs. EBL vs. BB/Nx/EBL	160	75	?	24
Sarin, 2005, Dig Dis Sci	BB/N vs. EBL	137	?	?	15
De La Pena, 2005, HEP	BB vs. BB/EBL	80	?	0	29
Romero, 2006, APT	BB/n vs. EBL(EST)	109	66	?	24
Garcia-Pagan, 2009, Gut	BB/N vs. BB/N/EBL	158	44	?	23
Kumar, 2009, Gastro	BB vs. BB/EBL	177	32	?	14
Ahmad, 2009, J Coll Physicians Surg Pak	BB/N vs. BB vs. EBL vs. EBL/BB/N	160	65	?	24

Another single-center retrospective cohort study evaluated 322 patients with ascites (117 refractory ascites) on the liver transplant waiting list [8]. One hundred and fifty-nine patients were on a NSBB, 119 on propranolol (median daily dose 80 mg), and 40 on carvedilol (median dose 6.25 mg). Patients on NSBBs showed higher serum sodium levels and a higher proportion of previous bleeders. The systolic blood pressure was lower in the NSBB group, though blood pressure data was only available in 25 % of the patients. Mortality was analyzed using a competing risk model, taking liver transplant as the competing event. To take into account the potential for indication bias, the final analysis was conducted in a subcohort of 104 patients on NSBB and 104 not on NSBB, matched by a propensity score. The use of NSBBs was associated with a lower mortality both in the overall series and also in the subgroup of patients with refractory ascites. An interesting aspect of this study is derived from the subgroup of patients on carvedilol who showed an intermediate survival that was worse than in the patients on propranolol but better than patients without NSBBs. This again suggests that carvedilol may not be the optimal choice in patients with ascites. However, these results might be biased due to a very selected cohort of patients on the liver transplant waiting list – indicating that these patients were probably thoroughly assessed and quite fit from a cardiovascular point of view and therefore that these results might not be generalizable to all patients with cirrhosis and refractory ascites.

This thorough assessment of the available evidence from the literature revealed no clear beneficial nor detrimental effects of NSBB on survival in patients with ascites. However, even if many statistical efforts were made in this study to match the subgroups of patients with/without NSBB therapy, some critical differences in baseline characteristics remain an issue (mainly the proportion of patients with varices but also the information if patients already had a history of variceal hemorrhage before or had a diagnosis of HCC). Ultimately, there seems to be a trend toward detrimental effects of NSBBs in patients with true refractory ascites.

To address the controversial issue of NSBB therapy in the special population of patients with ascites, we collected data from studies that were specifically designed to assess the effect of NSBB therapy in this subpopulation of cirrhotic patients. These studies did not aim to assess the efficacy of NSBB therapy on prophylaxis of variceal bleeding or rebleeding, they rather aimed at investigating survival as the main outcome parameter. Table 32.2 summarizes the five studies that were identified, four original articles and one letter to the editor. Reporting of important patient characteristics was generally sufficient, although not all relevant parameters could be obtained from the studies and/or from the authors.

Finally, we looked at recent studies that specifically addressed the controversial role of NSBB therapy in the specific population of patients with ascites and refractory ascites. We were able to obtained raw data of the studies by Sersté et al. [37] and Mandorfer et al. [9] and also received additional data of patients with ascites from Prof. Bernardi and Dr. Giovanni Vitale. We assessed potential indicators that may discriminate subgroups of patients who benefit from NSBB therapy from patients in whom NSBB are potentially associated with detrimental effects on their outcome/survival. Please see Table 32.3 and Figs. 32.1 and 32.2 below.

Summary and Conclusions

The lack of sufficient data from prospective studies and the conflicting results from observational studies make it difficult to reach a definitive conclusion on the efficacy and safety of NSBBs therapy for prophylaxis of variceal (re)bleeding in patients with ascites and refractory ascites. Prospective trials assessing the effect of NSBBs on cardiac function, systemic and splanchnic hemodynamics, and renal function in patients with refractory ascites are currently being conducted [https://clinicaltrials.gov/ct2/show/NCT02163512]. Until these results are available and based on the individual data analysis in patients with ascites, and to expert opinion (panelists of Baveno VI), it is concluded that in patients with refractory ascites and (1) arterial hypotension (SAP < 90 mmHg), (2) increasing serum creatinine, or (3) and hyponatremia (Na < 130 mmol/L), NSBB therapy should be reduced or discontinued. However, the net effect of NSBB reduction/discontinuation on mortality is

Table 32.2 Studies that assessed the influence of NSBB in ascites on outcome

	Sersté et al. Hepatology 2010		Kimer et al. Sc J Gastro 2015		Mandorfer et al. Gastro 2014		Robbins et al. Hepatology 2014		Leithead et al. Gut 2014	
	NSBB	noNSBB	NSBB	noNSBB	NSBB	noNSBB	NSBB	noNSBB	NSBB	noNSBB
N	77	74	23	38	245	362	36	78	159	163
NSBB	Prop	-	Prop	-	Prop/ Carv	-	Prop	-	Prop/ Carv	-
Dose Prop	80mg (40-160)	-	80mg (40-200)	-	40mg (20-160)	-	48.9mg	-	80mg (10-240)	-
Dose Carv	-	-	-	-	12.5mg (6.25-25)	-	-	-	6.25mg 3.125-12.5	-
Refr. Ascites	77 (100%)	74 (100%)	23[1] (100%)	38 (100%)	**78 (32%)**	**145 (40%)**	36 (100%)	78 (100%)	56 (35%)	61 (37%)
Varices	**77 (100%)**	**3 (4.1%)**	**19/20[2] (95%)**	**12/26 (46%)**	**220 (90%)**	**223 (62%)**	**36 (100%)**	**42 (54%)**	?	?
Previous Bleeding	?	?	?	?	44 (18%)	54 (15%)	**25 (69%)**	**25 (32%)**	**64 (40%)**	**40 (25%)**
HCC	**24 (31%)**	**17 (23%)**	?	?	55 (22%)	74 (20%)	7 (19%)	10 (13%)	15 (9.4%)	23 (14%)
SAP	103	123	?	?	114	117	117	116	115[3]	122
MAP	**83**	**89**	?	?	84	86	?	?	86[3]	89

Table 32.2 (continued)

Child C	57 (74%)	45 (61%)	?	?	121 (49%)	183 (51%)	23 (64%)	50 (64%)	?	?
MELD	18.8	18.9	15.0	15.5	17.2	17.8	?	?	16	17
Crea	0.89	0.86	0.94	0.90	1.14	1.14	?	?	1.01	1.00
Na	125	133	133	135	134	134	?	?	136	134
Followup	8m	8m	? (500d)	? (500d)	12.9m	10.6m	10m	9m	until OLT	until OLT
Hospital	?	?	4.17/p	4.26/p	26.7/PY	30.9/PY	?	?	?	?
Bleeding	?	?	14 (61%)	7 (18%)	0.06/PY	0.04/PY	?	?	?	?
SBP	?	?	8 (35%)	11 (29%)	0.07/PY 86 (35%)	0.12/PY 96(27%)	18 (50%)	34 (44%)	?	?
Death	63 (82%)	34 (46%)	15 (65%)	26 (68%)	156 (64%)	228 (63%)	9 (25%)	15 (19%)	35 (22%)	47 (29%)
NSBB effect	DETRIMENTAL		NEUTRAL		BENEFICIAL IN ASCITES, DETRIMENTAL AFTER SBP		NEUTRAL		BENEFICIAL, ALSO IN REFRACTORY ASCITES	

[a]Kimer: definition of refractory ascites, in need of paracentesis >1 a year despite diuretics
[b]Kimer: not all patients had data on endoscopy available
[c]Leithead: blood pressure data was only available for 81 patients; MAP was calculated

unclear, and thus, in case there was a clear precipitating event (such as SBP), re-initiation of NSBB therapy should be considered given the documented survival benefit with NSBB in secondary prophylaxis.

Special Populations of "Clinical Nonresponders" to Medical Therapy

The widespread use of NSBB makes that an increasing number of patients with cirrhosis experience their first episode of variceal hemorrhage while on NSBB. In Baveno V consensus conference, the recommendation for the prevention of rebleeding in these patients was to maintain the NSBB and to add endoscopic band ligation (EBL). However, these patients have been systematically excluded in most trials evaluating current standard treatments for the prevention of rebleeding. Indeed, only 4 % of the patients randomized in most recent trials [41–46] had received NSBB prior to the index bleeding. These patients can be considered the "worst" type of nonresponders to NSBB, i.e., "clinical nonresponders." These are different

Table 32.3 Characteristics of patients with ascites with and without NSBB therapy

	No NSBB	NSBB	*p* value
Patients	457	340	
Age	47 (23)	44 (26)	0.045
Male	74 %	69 %	0.064
FU [m]	13.4 (18.4)	13.5 (18.7)	0.377
RefrAsc	48 %	46 %	0.257
Mortality	58 %	66 %	0.010
MELD	18.9 (7.8)	18.2 (6.9)	0.100
Na	133.8 (6.4)	133.1 (6.9)	0.063
Varices	54 %	92 %	<0.001
High-risk varices	30 %	63 %	<0.001
Prior variceal bleeding	14 %	20 %	0.011
SAP	118 (17)	111 (16)	<0.001
MAP	87 (12)	83 (11)	<0.001
HCC	25 %	26 %	0.321

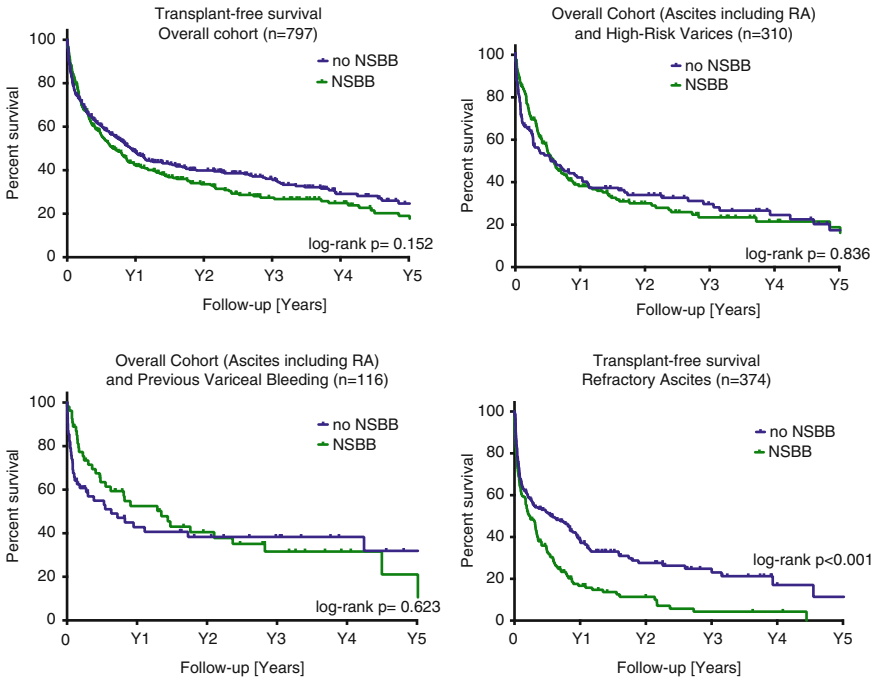

Fig. 32.1 Transplant-free survival according to NSBB therapy in the overall cohort, in the subgroup of patients on primary prophylaxis and on secondary prophylaxis, and in patients with "true" refractory ascites

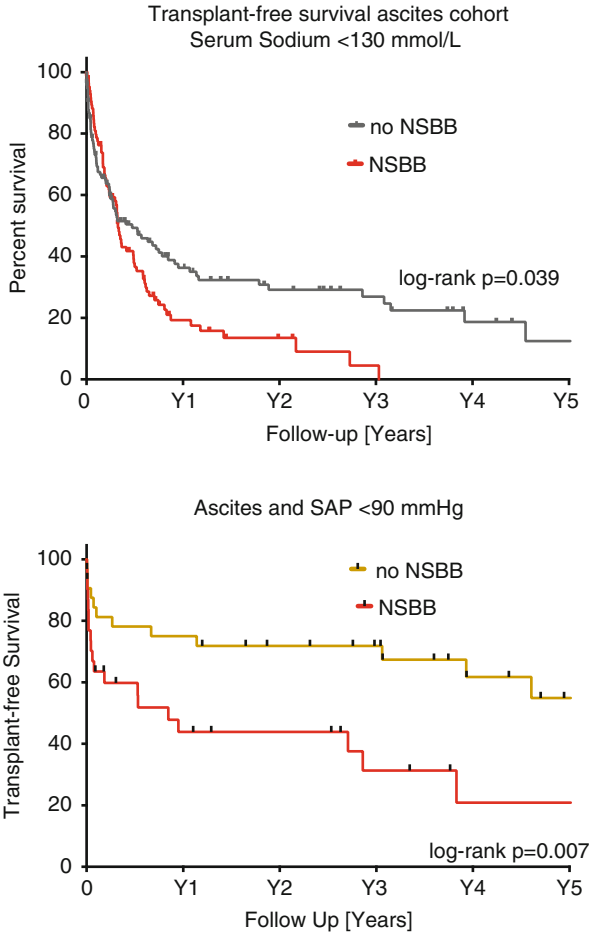

Fig. 32.2 Special situation in patients with ascites when NSBB seem to have a detrimental effect on transplant-free survival

from "hemodynamic nonresponders," who have an increased risk of bleeding, but still around 50 % will never have a hemorrhage over a long follow-up [47]. Importantly, the dose of the NSBB under which the actual bleeding episode occurred has to be taken into account before considering the patient a "clinical nonresponder," since some patients might have received insufficient doses of NSBBs such as less than 40 mg of propranolol or nadolol, respectively. This scenario is more likely a "clinical under dosing" than a "clinical nonresponse." However, if variceal bleeding occurs under sufficient beta blockade – as indicated by decreased heart rate or a sufficient dosing (such as 80–120 mg or more of propranolol or nadolol), then the patients should be considered as "clinical nonresponder" to NSBB therapy. Indeed, a recent cohort study assessing 89 patients with cirrhosis and portal hypertensive bleeding showed that the efficacy of the standard therapy to prevent rebleeding (combination of NSBB + EBL) was much worse in patients having their first bleeding while on NSBBs, than in those not treated before with NSBBs [48]. These patients had a greater risk of rebleeding (adjusted HR: 2.37; 95 % CI: 1.10–5.11)

and death or transplantation (adjusted HR: 4.24; 95 % CI: 1.31–13.71). Taken together, these data suggest that clinical nonresponders to drug therapy have an idiosyncrasy that renders them also likely poor responders to endoscopic therapy and therefore are at a higher risk of variceal rebleeding and death. This suggests that these patients may require an alternative, more effective treatment – such as TIPS, which should be evaluated in adequately designed prospective studies.

Special Population of Patients with HCC

Development of hepatocellular carcinoma (HCC) has a detrimental impact on the natural history of cirrhosis [49]. Indeed, patients with variceal hemorrhage and HCC show higher in-hospital mortality than patients with variceal hemorrhage without HCC (19 % vs. 9 %, $p<0.001$) on multivariate analysis [OR 2.15 (95 % CI 1.67–2.77)] [50]. Due to the study design, no information regarding the use of secondary prophylaxis on rebleeding and survival could be obtained.

A retrospective observational study compared the management and outcomes after variceal bleeding of patients with HCC compared to controls without HCC matched for age and Child-Pugh class [51]. Most patients included in this study had inoperable HCC with a BCLC stage B or greater in 78 % (114/146). Almost all patients who were BCLC B had secondary prophylaxis (96 %), whereas patients who were BCLC C and D had were less commonly treated with secondary prophylaxis (66 %). Lack of secondary prophylaxis was associated with poor survival (0.7 vs. 3 months, $p<0.001$) in patients with BCLC C and D. Multivariate analysis showed that among patients with HCC, secondary prophylaxis together with presence of portal vein thrombosis and BCLC classification and Child-Pugh score were independent predictors of death, while only the first three were independent predictors of failure of secondary prophylaxis.

Interestingly, standard secondary prophylaxis with beta-blockers and endoscopic ligation was used less frequently in these patients compared to controls without HCC. Whether standard secondary prophylaxis with beta-blockers and endoscopic ligation or only one of the two options results in beneficial effects on survival cannot be answered with the available data. Since initiation of prospective clinical trials in this setting seems highly unlikely, physicians managing patients HCC and varices should consider individualized prophylactic therapy of variceal bleeding, taking into account the survival benefit, as long as the clinical condition of the patient allows it.

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Effect of Current Therapies Aimed at Preventing Variceal Rebleeding on Other Complications of Cirrhosis

33

Cristina Ripoll, Salvador Augustin, Thomas Reiberger, Richard Moreau, Francesco Salerno, Agustin Albillos, Juan G. Abraldes, and Guadalupe Garcia-Tsao

C. Ripoll (✉)
First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
e-mail: cristina_ripoll@yahoo.es

S. Augustin, MD
Liver Unit - Department of Internal Medicine, Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

CIBERehd, Juan Rodés Grant Researcher, Instituto de Salud Carlos III, Madrid, Spain

T. Reiberger
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

R. Moreau
Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

F. Salerno
Internal Medicine and Hepatology, Policlinico IRCCS San Donato University of Milan, Milan, Italy

A. Albillos
Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain

J.G. Abraldes, MD, MMSc
Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada

G. Garcia-Tsao
Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA

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Introduction

Complications of cirrhosis are frequently approached as unique and independent events, without taking into account that complications often occur concurrently and that treatment for one complication may have an effect on other complications. In the setting of prevention of recurrent variceal hemorrhage, different treatment options are available [1, 2]. This section will review the effects of these treatments on the incidence of non-bleeding complications of cirrhosis, specifically ascites, hepatic encephalopathy, and hepatocellular carcinoma (HCC).

Nonselective Beta Blockers and Endoscopic Variceal Ligation (EVL)

Nonselective beta blockers (NSBB) have both hemodynamic and non-hemodynamic effects. Their hemodynamic effects are mediated by a reduction in cardiac output and an unopposed alpha-mediated splanchnic vasoconstriction. These effects lead to a protective reduction in hepatic venous pressure gradient, an estimation of portal pressure, in approximately 40–50 % of patients [3, 4]. The patients who achieve this hemodynamic response have a lower incidence of ascites [3, 4], spontaneous bacterial peritonitis [3, 4], hepatorenal syndrome [4], and hepatic encephalopathy [4] and have an improved survival [3–6].

On the other hand, it has been postulated that some beneficial effects of NSBB could be independent of their hemodynamic effect, such as an influence on intestinal transit time, intestinal permeability, and bacterial translocation [7, 8]. The effect of beta blockers on non-bleeding complications of cirrhosis in the setting of secondary prophylaxis, independent of hemodynamic response, is evaluated in this section.

All trials comparing NSBB versus placebo or NSBB versus EVL were evaluated [9–23]. Trials comparing NSBB to endoscopic sclerotherapy were excluded given the sustained rise of portal pressure that has been described after sclerotherapy [24]. The incidence of non-bleeding complications of cirrhosis has been inconsistently reported in these trials. The information on non-bleeding complications that can be obtained from the few trials which report this data is summarized in Table 33.1. However, given the small number of patients, no definite conclusion can be obtained from these studies regarding the influence of NSBB (independent of hemodynamic response) on the development of "de novo" or worsening ascites [11, 13, 20, 22, 23], spontaneous bacterial peritonitis [20, 22, 23], hepatorenal syndrome [22], and "de novo" or worsening hepatic encephalopathy [11, 20, 22].

In these trials, there seems to be a trend toward a lower incidence of HCC (which is a complication of cirrhosis, although not an event that defines decompensation) [13, 15, 20]. Indeed, a recently published meta-analysis including studies in the setting of primary or secondary prophylaxis of variceal hemorrhage observed a significant decrease in the incidence of HCC in patients who take NSBB [25].

Table 33.1 Non-bleeding complications reported in trials comparing NSBB with placebo or with endoscopic band ligation

Study	Patient population	Comparison groups	Follow-up	Ascites and related complications	Hepatic Encephalopathy	Hepatocellular carcinoma
Perez-Ayuso et al. *Lancet* (1991) [11]	Portal hypertensive gastropathy bleeding	Propranolol ($n=26$) Controls ($n=28$)	Propranolol mean 21 (11) months Control mean 18 (13) months	*Ascites*: *Propranolol 6/26 (23 %)* *Control 15/28 (54 %)* *$p<0.05$* *SBP*: ND *HRS*: ND	Propranolol 7/26 (27 %) Control 6/28 (21 %)	ND
Villanueva et al. *NEJM* (2001) [13]	Variceal bleeding	EVL ($n=72$) N+IMN ($n=72$)	EVL median 22 months (1–68) N+ IMN median 20 months (1–65)	*Ascites*: EVL 47/72 (65 %) N+IMN 39/72 (54 %) *SBP*: ND *HRS*: ND	ND	EVL 13/72 (18 %) N+IMN 9/72 (12 %)
Patch et al. *Gastroenterology* (2002) [15]	Variceal bleeding	EVL ($n=51$) Propranolol +/− IMN ($n=51$)	Median 307 days (1–1396)	ND	ND	EVL 6/51 (12 %) Propranolol+ IMN 1/51 (2 %)
Lo et al. *Hepatology* (2008) [20]	Variceal bleeding	EVL ($n=60$) N+IMN ($n=61$)	EVL: mean 82 months (range 10 days to 8 years) N+IMN: mean 81 months (range 15 days to 8 years)	*Ascites*: EVL 39/60 (65 %) N+ IMN: 44/61 (72 %) *SBP*: EVL 11/60 (18 %) N+IMN:11/61 (18 %) *HRS*: ND	EVL 17/60 (28 %) N+IMN 19/61 (31 %)	EVL 25/60 (42 %) N+IMN 19/61 (31 %)

(continued)

Table 33.1 (continued)

Study	Patient population	Comparison groups	Follow-up	Ascites and related complications	Hepatic Encephalopathy	Hepatocellular carcinoma
Kumar et al. *Gastroenterology* (2009) [22]	Variceal bleeding[a]	EVL ($n=89$) EVL+propranolol +IMN ($n=88$)	Mean 15 (12) months	*De novo Ascites*: EVL 5/83 (6 %) EVL+ drugs 4/84 (5 %) *SBP* EVL 2/83 (2 %) EVL+ drugs 2/83 (2 %) *HRS* EVL 3/83 (4 %) EVL+drugs 3/84 (4 %)	EVL 7/83 (8 %) EVL+drugs 8/84 (10 %)	ND
Stanley et al. *J Hepatol* (2014) [23]	Variceal bleeding	Carvedilol ($n=33$) EVL ($n=31$)	Carvedilol median 30.7 months (IQR 7.9–47.1) EVL median 23.5 months (IQR 10.3–44.8)	*Worsening Ascites* Carvedilol 2/33 (6 %) EVL 5/31 (16 %) *SBP* Carvedilol 0/33 (0 %) EVL 1/31 (3 %) *HRS* ND	ND	ND

The only statistically significant result is shown in italics. Unless otherwise specified, results are expressed as median (with interquartile range) or mean (standard deviation). Unless otherwise specified, the development of ascites and hepatic encephalopathy refers to the de novo onset of these complications or worsening of previous ascites and hepatic encephalopathy

EVL endoscopic variceal ligation, *N* nadolol, *IMN* isosorbide mononitrate, *ND* not described, *yrs* years, *mos* months, *d* days, *IQR* interquartile range

[a]Patients with non-cirrhotic portal hypertension were also included. Patients with cirrhosis (EVL+ drugs $n=76$; EVL $n=75$)

Transjugular Intrahepatic Portosystemic Shunt

The transjugular intrahepatic portosystemic shunt (TIPS) was developed as an alternative to surgical shunts in the setting of variceal hemorrhage [26]. It was initially observed that this procedure was not only successful in controlling variceal hemorrhage but also could successfully control ascites. However, patients treated with TIPS showed an increased incidence of hepatic encephalopathy. Initial studies were performed using bare stents that had a high incidence of dysfunction, so that the effects on other complications of cirrhosis were largely dependent on the maintenance of stent patency [27].

The development of ePTFE-covered endoprosthesis substantially reduced the incidence of TIPS dysfunction and led to a significant improvement of outcomes after TIPS [28, 29]. Patients in whom TIPS was placed using ePTFE endoprostheses had lower recurrence of bleeding or ascites and even a nonsignificant trend toward reduced hepatic encephalopathy and an improved survival in comparison to the uncovered stents [29]. Since the introduction of ePTFE-covered endoprostheses, there have been no studies evaluating TIPS in the setting of secondary prophylaxis. Data regarding the impact of TIPS on non-bleeding complications of cirrhosis can only be derived from the "early TIPS" studies, which include a very special population of patients deemed to have a high risk of rebleeding (Child C with a score <14 and Child B with active bleeding) in the context of an acute variceal bleed, with TIPS placement within 72 h of index bleed [30–32]. In the "early TIPS" study [31], there were no significant differences in the 1-year actuarial probability of hepatic encephalopathy [28 % for early TIPS vs 40 % for the pharmacotherapy/EVL group with an absolute risk reduction of 12 % (95 % CI −18 to 40 %, $p=0.13$)]. Most of the hepatic encephalopathy episodes occurred in the context of the initial variceal bleed. Similar results were observed in the two subsequent observational studies [30, 32].

The "early TIPS" study described also a nonsignificant reduction in the incidence of de novo ascites or worsening of previous ascites during follow-up in the TIPS group as compared to the combined medical/endoscopic therapy group [13 % vs 33 % with an absolute risk reduction of 20 % (95 % CI −8 to 47 %, $p=0.11$)] [31]. Similar results, which achieved statistical significance, were observed in the European early TIPS observational study [32]. When data from these two studies are combined [31, 32], the incidence of complications associated with ascites, specifically HRS (3 % vs 10 %) and SBP (1 % vs 10 %), also seems to be lower among patients who had "early" TIPS placement compared to patients assigned to standard rebleeding prophylaxis. Only one study [32] reported the incidence of HCC, which was lower (albeit nonsignificantly) among patients with early TIPS (4 % vs 10 %).

Lastly and most importantly, the use of ePTFE TIPS, in this group of high-risk patients included in the early TIPS studies, led to an improvement in overall survival in two of the three studies with a combined hazard ratio of 0.27 CI 95 %(0.13–0.54) ($p=0.0002$) [31–33].

In conclusion, although patients with hemodynamic response to NSBB seem to have a reduction in both bleeding and non-bleeding complications of cirrhosis, little conclusive information can be obtained from published studies on secondary

prophylaxis regarding the effects of different therapies to prevent rebleeding on non-bleeding complications of cirrhosis. Early TIPS in high-risk patients could improve the incidence of ascites and survival. Nevertheless, outside of the early TIPS studies, there is no data regarding the incidence of non-bleeding complications of cirrhosis after TIPS using covered endoprosthesis.

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Impact of Treatment of Non-bleeding Complications of Cirrhosis on the Risk of Variceal Bleeding

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Salvador Augustin, Agustin Albillos, Cristina Ripoll, Juan G. Abraldes, Francesco Salerno, Richard Moreau, Thomas Reiberger, and Guadalupe Garcia-Tsao

S. Augustin, MD (✉)
Liver Unit - Department of Internal Medicine, Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

CIBERehd, Juan Rodés Grant Researcher, Instituto de Salud Carlos III, Madrid, Spain
e-mail: Salva.augustin@gmail.com

A. Albillos, MD
Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain

C. Ripoll, MD
First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg Halle, Saale, Germany

J.G. Abraldes, MD, MMSc
Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada

F. Salerno, MD
Internal Medicine and Hepatology, Policlinico IRCCS San Donato, University of Milan, Milan, Italy

R. Moreau, MD
Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

T. Reiberger, MD
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

G. Garcia-Tsao, MD
Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA

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Introduction

Complications of cirrhosis are frequently approached as if they were unique and independent events, without taking into account that complications often occur concurrently and that treatment for one complication may have an effect on other complications.

This chapter will review available evidence and current research efforts on the observed and/or potential effects of treatments currently recommended for non-bleeding complications of cirrhosis on variceal hemorrhage. The aim of this review is to try to identify, among these commonly used treatments, potential new therapies that could improve current strategies for the prevention of variceal rebleeding.

The focus is set on published evidence relating the direct effect of such therapies on the incidence of variceal rebleeding, but also on their potential prophylactic effect based on their ability to lower portal pressure or to demonstrate an effect on well-known drivers of portal pressure and bleeding. This knowledge could serve for the design of therapeutic trials as well as for the interpretation of results from observational studies.

The observed or potential effects of some of these therapies on portal hypertension are extensively covered in other chapters in this book (mainly antibiotics and other therapies used in hepatic encephalopathy with effects on the gut microbiome). Therefore, these therapies are succinctly addressed here. For all other therapeutic options, a concise review of available evidence of their effects on portal pressure and/or variceal hemorrhage is provided, and potential further applications are briefly discussed.

Methodology

As starting point for the present review, a systematic list of recommended therapies for non-bleeding complications of cirrhosis, specifically ascites (and complications, hyponatremia, spontaneous bacterial peritonitis, and hepatorenal syndrome), hepatic encephalopathy, and HCC, was abstracted from the most current practice guidelines of international hepatology societies [1–3]. Additionally miscellaneous drugs used to treat decompensated cirrhosis (specifically anticoagulants and pentoxifylline) were added to the list. A systematic search of studies was then conducted exploring published evidence of a direct effect of each of these therapies on variceal hemorrhage. In addition, the search also aimed at identifying potential therapies for the variceal hemorrhage based on indirect data, i.e., either an observed direct effect on lowering portal pressure or a positive effect on the main mechanisms driving portal hypertension and variceal bleeding.

To perform the systematic search, each item of the matrix therapy list was cross-referenced with four key terms ("portal pressure," "HVPG," "variceal bleeding," "variceal hemorrhage") in three different search engines (pubmed.gov, clinicaltrials.gov, and google.com). As a result, a total of 88 studies (11 published only in abstract form), 5 book chapters, and 49 clinical trial records (from clinicaltrials.gov)

were reviewed looking for specific data on the incidence of variceal or unspecified gastrointestinal bleeding (which were commonly addressed as secondary or safety outcomes in studies designed to address effects on other complications of cirrhosis), as well as for data on an observed or suggested effect on portal pressure. Only the studies in which relevant information (relative to the aim of this review) was found are referenced throughout the chapter.

Impact of Treatment of Ascites, Spontaneous Bacterial Peritonitis, Hepatorenal Syndrome, and Hepatic Encephalopathy on the Risk of Portal Hypertensive Bleeding

Diuretics and Aquaretics

First-line therapy in patients with cirrhosis and ascites consists of dietary sodium restriction and *oral diuretics* (spironolactone +/– furosemide) [1–3]. The combination of a low-sodium diet and spironolactone has been shown to significantly decrease hepatic venous pressure gradient (HVPG) compared to sodium restriction alone in patients with compensated cirrhosis, although this effect is mediated by volume depletion and reduced cardiac output and mean arterial pressure, which could be deleterious in advanced cirrhosis [4]. The potential effect of spironolactone on the risk of variceal bleeding was tested in a pilot study comparing the use of nadolol + placebo vs. nadolol + spironolactone for the prevention of a first variceal bleeding in non-ascitic cirrhotic patients [5]. In the study, the use of nadolol + spironolactone was associated with a lower incidence of a first episode of clinical ascites, but not with significant reductions in either the HVPG or the risk of variceal bleeding.

Vaptans (vasopressin receptor antagonists) have been shown to ameliorate hyponatremia in patients with cirrhosis and ascites [6]. Satavaptan was specifically studied to determine its efficacy in treating ascites in a large randomized trial in 1200 patients with cirrhosis [7]. However, the study failed to show a beneficial effect of satavaptan in ascites management, and it did show that its use was associated with an increased mortality compared to placebo (subsequently, approval for the drug has been withdrawn). Although data from that trial suggested an increased risk of variceal bleeding as cause of death in patients treated with satavaptan, a recent meta-analysis suggests that the use of vaptans in cirrhosis has no effect on the risk of variceal bleeding [6]. Additional data from an ongoing study of tolvaptan and midodrine in refractory ascites in which variceal bleeding is a secondary end point (NCT02173288) are eagerly awaited.

Albumin

Albumin is commonly used in cirrhotic patients with ascites. It has been shown to improve outcomes after large-volume paracentesis [8] and to reduce mortality (in

addition to antibiotics) in patients with spontaneous bacterial peritonitis (SBP) [9, 10]. Albumin is also useful in the treatment of hepatorenal syndrome (HRS), in combination with vasoactive drugs.

Recent advances in the knowledge of albumin biology [11, 12] have led to studies assessing the efficacy of albumin administration on other complications of cirrhosis, such as hepatic encephalopathy (HE), infections other than SBP [13], pruritus, and liver failure (the last two indications in the form of albumin dialysis through liver support devices) [14, 15]. Most of these efforts have failed to show clinically relevant benefits of albumin infusion for these indications, and therefore its use remains investigational. Notably, in a recent randomized trial, the use of albumin infusions failed to accelerate the resolution of episodic hepatic encephalopathy (HE) as compared to isotonic saline, but it was unexpectedly associated with a significant increase in 90-day survival (*ALFAE trial*) [16]. The exact cause of this improvement in survival was unclear in that study. Although it has been shown that albumin improves endothelial function in experimental models and therefore a potential beneficial effect of albumin on portal hypertension cannot be excluded, indirect experimental and clinical data suggest that the effect might be related to improved systemic and renal hemodynamics and/or immunomodulatory functions rather than to a direct decrease in portal pressure [17–19]. In the ALFAE trial, four patients died from gastrointestinal bleeding, one in the saline group and three in the albumin group [16]. Four ongoing large, multicenter, randomized trials in different clinical scenarios in patients with advanced cirrhosis (ANSWER, Italy (NCT01288794); MACHT, Spain (NCT00839358); BETA, Spain (NCT02401490); ATTIRE, UK (ISRCTN14174793)) will provide also indirect data on the incidence of variceal bleeding in patients treated with periodical infusions of albumin.

Oral Vasoactive Drugs

Different oral vasoactive agents have been studied in advanced cirrhosis to treat recurrent or refractory ascites. The last update in the AASLD practice guidelines for ascites includes *midodrine* (an alpha-1 adrenergic agonist) as a potential adjuvant therapy in refractory ascites [20]. The recommendation is based on a small ($N=40$ patients) randomized pilot study in which adding midodrine to usual therapy increased urine volume, urine sodium, mean arterial pressure, and survival [21]. These effects on ascites control and systemic hemodynamics were reproduced in another small study [22]. Midodrine is also recommended (combined with octreotide and albumin) for the treatment of type 1 HRS in the USA (where terlipressin is not available) [20]. There are no direct data on the effect of midodrine on portal pressure or on the risk of variceal bleeding. However, some insights on the potential effects of midodrine on portal pressure could be gained by extrapolation from studies using drugs with similar pharmacologic effects in patients with cirrhosis. Methoxamine, another alpha-1 adrenergic antagonist that has been used in alcoholic hepatitis, was shown to induce, on the one hand, significant increases in blood

pressure and, on the other hand, decreases in the HVPG similar to that of propranolol in patients with cirrhosis. Nonetheless, the use of methoxamine was associated with a significant decrease on portal blood flow and an increase in azygos blood flow in these patients. Further data on the effects of alpha-1 agonists on portal hemodynamics is required [23].

Clonidine is an alpha-2 adrenergic agonist with sympatholytic effects, and its use alone or combined with midodrine has also been evaluated in patients with refractory ascites. Data from two randomized studies [24, 25] suggest that clonidine increases the diuretic response in these patients. The only comparison with midodrine comes from a small study showing a nonsignificant superiority of midodrine over clonidine on ascites control [22], and its use is not addressed in current guidelines. In the case of clonidine, unlike midodrine, abundant direct data on the effect on portal hemodynamics is available from a number of published studies [26–29]. Clonidine administration (both short term (intravenous or oral) and long term (oral)) has been shown to induce significant decreases in HVPG in several small pilot studies in patients with cirrhosis. However, the sympathetic inhibitory effect also induced marked reductions in cardiac output and mean arterial pressure in the majority of these patients. This systemic hypotensive effect has limited the research on the use of this potent portal hypotensive drug for patients with advanced cirrhosis after a variceal bleeding, although new evidence showing a potential benefit in advanced cirrhosis could reignite the interest in this drug to treat portal hypertension.

Droxidopa is an oral synthetic norepinephrine precursor that is indicated in patients with orthostatic hypotension. In animal models of cirrhosis, it has been shown to improve systemic and splanchnic hemodynamics and to induce marked increases in diuresis [30, 31]. However, despite its splanchnic vasoconstrictive effect, portal pressure reduction in these models was mild, probably due to a norepinephrine-induced increase in intrahepatic vascular resistance. A pilot study with droxidopa in patients with cirrhosis and refractory ascites is ongoing, although the expected effect on portal pressure and its potential use for the prophylaxis of rebleeding seem limited.

Oral Antibiotics

Recent breakthroughs in the knowledge of the biology of the gut microbiome and its potential implications in liver disease have renewed the interest on the effects of oral antibiotics as potential agents for the management of portal hypertension and its related complications in patients with cirrhosis, including variceal hemorrhage. It has been accepted for long, based on clinical and experimental data, that bacteria and their direct (endotoxin, DNA) or indirect products (cytokines) can worsen the hyperdynamic circulation, increase intrahepatic vascular resistance and portal pressure, alter coagulation, and trigger variceal bleeding in patients with cirrhosis [32]. In fact, the administration of a 7-day course of antibiotics in patients with cirrhosis and gastrointestinal bleeding has been shown to improve survival [33] and is

recommended in all guidelines as a cornerstone in the management of acute variceal bleeding [1–3]. However, the potential effect of longer (beyond the 7 days recommended during acute variceal hemorrhage)-term antibiotics on the incidence of variceal bleeding has not been addressed until recently, in part because of the mild effect on HVPG shown in the first reported studies (see below) and partly due to the concern of long-term antibiotic use leading to the emergence of resistant bacterial strains in cirrhotic patients. Long-term oral antibiotic administration (the therapeutic modality more suited to be explored for use in the prophylaxis of rebleeding) has currently only two accepted indications in patients with cirrhosis. First, long-term oral norfloxacin is recommended for the prophylaxis of SBP in high-risk patients, those who have recovered from an episode of SBP (secondary prophylaxis), and those with low-protein ascites and additional risk factors (primary prophylaxis) [1–3]. Second, long-term oral rifaximin has been recently incorporated to clinical guidelines for the prevention of the recurrence of overt HE episodes [1–3].

The specific effect on portal hemodynamics of oral antibiotics in patients with cirrhosis has been evaluated in six studies. Regarding *norfloxacin*, one noncontrolled small study ($N = 14$ patients with alcoholic cirrhosis) showed a nonsignificant decrease in HVPG after a 4-week course of 400 mg bid oral norfloxacin [34]. However, two placebo-controlled pilot studies failed to show any effect of the same therapeutic regimen on the HVPG of patients with cirrhosis and clinically significant portal hypertension [35, 36]. Regarding *rifaximin*, there are three published studies. The first study, a noncontrolled pilot study in 30 patients with decompensated alcoholic cirrhosis, showed a significant drop in HVPG (which was directly correlated with a decrease in plasma endotoxin) after 1 month of oral rifaximin 1200 mg/day [37]. In a follow-up case–control study from the same group, the 23 hemodynamic responders from the previous cohort received long-term oral rifaximin at the same doses [38]. Each case was matched to two controls from the same center. The median follow-up for patients in the study was 36 months (range 5–60 months). Patients receiving long-term rifaximin showed a significantly reduced incidence of variceal bleeding, HE, SBP, HRS, and mortality. Finally, the last study was recently published as an abstract [39] and reported a beneficial effect on the risk of first variceal bleeding of the concurrent administration of rifaximin for management of HE in a retrospective cohort of patients with varices undergoing therapy for primary prophylaxis of rebleeding. Based on these and other preliminary results [39], there are currently four registered large trials studying the effects of long-term rifaximin in patients with cirrhosis. Two of them have clinical primary outcomes: these are large, randomized, placebo-controlled trials studying the effects of a 24-week treatment with different doses of oral rifaximin on all-cause mortality and clinical decompensation (including variceal bleeding as a secondary outcome) in early decompensated cirrhotic patients (NCT02190357 (China), estimated completion by 2016, and NCT01904409 (USA), estimated completion by June 2015). The two remaining trials are also randomized, placebo-controlled trials and have a smaller sample size, and their primary outcome is changes in HVPG after a shorter (4–6 weeks) course of oral rifaximin in patients with clinically significant portal

hypertension (NCT01769040 (Denmark) and NCT01897051 (South Korea), the latter comparing propranolol plus rifaximin vs. propranolol plus placebo).

Some preliminary experimental and clinical studies suggest potential benefits in the management of portal hypertension of other drugs currently used in the treatment or prophylaxis of overt HE, such as *prebiotics* (such as lactulose) and *probiotics*. The implications on portal hypertension of these promising therapies are extensively discussed elsewhere in the book.

Impact of Treatment of Hepatocellular Carcinoma and Graft Rejection After Liver Transplant on the Risk of Bleeding

Sorafenib has been shown in placebo-controlled trials to significantly improve survival in patients with advanced hepatocellular carcinoma (HCC) and compensated liver disease (BCLC stage C) [41, 42] and remains the only approved systemic treatment for unresectable HCC. Sorafenib is an oral multi-kinase inhibitor with potent anti-angiogenic properties. Angiogenesis is crucial in mediating increased splanchnic blood flow and development of collateral vessels and represents a hallmark in the development of portal hypertension in animal models [43]. The ability of sorafenib to inhibit angiogenesis has been shown in experimental models of portal hypertension to improve the splanchnic and systemic circulatory dysfunction, inducing significant decreases in portal pressure [44, 45]. In addition to the inhibition of extrahepatic angiogenesis, sorafenib has also been shown to induce intrahepatic attenuation of fibrosis and inflammation [44, 46]. With this experimental background, the effect of sorafenib in portal hypertension in patients with compensated cirrhosis and advanced HCC has been tested in several small pilot studies. In two of these trials, sorafenib was associated with an improvement of indirect noninvasive markers of portal hypertension (portal vein area measured by Doppler US and portal venous flow measured by MRI) [47, 48], suggesting a potential clinical benefit in portal hypertension. However, the effect of a short course of sorafenib therapy on portal pressure as assessed by HVPG measurements is moderate and clinically relevant in only a small proportion of patients (overall 8/24, 33 %) [49, 50]. Overall, the promising beneficial effects of sorafenib on portal hypertension in experimental models have not yet been reproduced in the few available pilot studies in patients with advanced HCC and compensated cirrhosis. It is unclear whether the effect of sorafenib on portal hypertension would be different in patients without HCC, but the safety profile and costs of sorafenib and the modest efficacy in patients shown so far make it difficult to design adequate trials to answer this question.

Although several other targeted systemic therapies have been investigated for advanced HCC in cirrhosis, to date, none have shown better outcomes than sorafenib in randomized controlled trials. The risk of variceal bleeding has been addressed as safety outcome in some of those trials [51], but the overall incidence is low, and results are inconclusive.

Mammalian targets of rapamycin (*mTOR*) *inhibitors* (such as everolimus or sirolimus, also known as rapamycin) are oral drugs with potent anti-angiogenic and

immunosuppressive properties that have been proven ineffective to arrest the progression of HCC. However, everolimus has been recently approved for use (in combination with a reduced dosage of tacrolimus and corticosteroids) for the prophylaxis of organ rejection in adult liver transplant recipients. The potent anti-angiogenic and antifibrotic effects of this drug class have also been tested from the perspective of its potential use in portal hypertension. Rapamycin has been shown in experimental models to ameliorate inflammation and fibrosis and to lower portal pressure at early stages in the development of portal hypertension [52] but also, at advanced stages, decreasing splanchnic neovascularization, portosystemic collaterals, and portal pressure even in fully established portal hypertension in rats ("reversing" the angiogenic drive in these later stages) [53]. The potential effects of mTOR inhibitors on portal pressure and the risk of variceal bleeding in patients with cirrhosis have not been studied so far.

Miscellaneous

Anticoagulant Therapy

In patients with portal vein thrombosis without cirrhosis, long-term treatment with anticoagulant therapy is currently recommended in patients with permanent thrombotic risk factors and/or extensive involvement of the porto-mesenteric axis [1]. In patients with cirrhosis, data on the benefits and risks of long-term anticoagulation therapy are less abundant, and guidelines do not provide definite recommendations for or against its routine use. Nonetheless, the interest on the use of anticoagulants in advanced cirrhosis has been recently sparked by the publication of a pilot study on the safety and efficacy of prophylactic anticoagulation in reducing the incidence of acute PVT and improving clinical outcomes in decompensated cirrhotic patients [54]. In this non-blinded, randomized, single-center prospective study, a fixed-dose 12-month course of enoxaparin was safe and effective versus no treatment in preventing PVT in patients with cirrhosis and a Child–Pugh score of 7–10. In addition, enoxaparin was able to decrease the risk of clinical decompensation at 1 year (59 % vs. 12 %; $p < .001$) and to improve survival (60 % vs. 40 %; $p = .02$). However, there were no differences in the development of variceal hemorrhage between groups (1/36 controls and 2/34 enoxaparin, $p = 0.521$). The limited sample size, lack of a blinded control arm, and inability to reliably assess the degree of anticoagulation currently preclude a generalization of this approach into management. However, the study provides exciting preliminary data regarding the potential use of prophylactic anticoagulation in improving clinical outcomes in cirrhosis, beyond the prevention of portal vein thrombosis.

The underlying mechanisms that could account for the improvement in the risk of further decompensation in these patients are unclear. It is currently widely accepted that in patients with cirrhosis, the hemostatic mechanisms are set to an unstable balance and that prothrombotic phenomena are enhanced. This activation of prothrombotic mechanisms could have an effect in the progression of portal hypertension

through different pathways. It has been shown that thrombin can directly activate hepatic stellate cells, promoting fibrosis and endothelial dysfunction [55]. It has also been suggested that the occurrence of microthrombi in small venules and sinusoids in the liver could lead to progressive ischemic injury, hepatocyte apoptosis, and further endothelial dysfunction [55, 56]. All these effects would lead to an increase in intrahepatic vascular resistance to portal blood flow worsening portal hypertension in these patients. From this perspective, anticoagulant therapy could counteract this cascade of effects ignited by prothrombotic mechanisms, attenuating the progression of intravascular resistance. These effects could be directly reversed by enoxaparin or, as hypothesized in the clinical trial by Villa et al. [54], indirectly through a decrease in microbial translocation and inflammation induced by the use of enoxaparin (it was associated with a significant reduction in biomarkers of intestinal integrity, bacterial DNA, and inflammatory cytokines compared to controls). In an unpublished experimental study, the use of enoxaparin for 1 week in CCl4 cirrhotic rats was associated with a significant reduction of fibrosis, improving the structural component of increased liver vascular resistance and leading to a significant decrease in portal pressure [57]. These promising results highlight the current need of evaluating the effects of anticoagulants on portal hypertension in patients with cirrhosis in large trials. One of the main concerns for the use of anticoagulants in cirrhosis, especially in decompensated patients, is the risk of increasing the severity of eventual variceal bleedings in these patients. In this regard, a small pilot study in patients with variceal bleeding within the context of portal thrombosis did not show an increased risk of bleeding in patients receiving acute low-molecular-weight heparin [58]. A recent multicenter, retrospective, matched study showed that the outcome of upper gastrointestinal bleeding in patients with cirrhosis receiving anticoagulant therapy was related to the degree of multi-organ failure and comorbidities (mainly cardiac disease), rather than to the anticoagulant therapy itself [59].

In summary, anticoagulant therapy represents a promising therapeutic approach to ameliorate portal hypertension and prevent clinical decompensation (including variceal rebleeding) in patients with early decompensated cirrhosis. More data from adequately designed studies are needed to establish its benefit-to-risk ratio. In this regard, a randomized, placebo-controlled, multicenter study from Spain is ongoing, studying the safety and effect of a new oral anticoagulant, rivaroxaban, in preventing portal hypertensive complications and improving survival in patients with early decompensated cirrhosis (*Cirroxaban* study). The study will also include HVPG measurements that hopefully would provide further mechanistic insights on the effects on anticoagulants.

Pentoxifylline

Pentoxifylline is an oral phosphodiesterase inhibitor with antioxidant properties that also inhibits the production of TNF, among other cytokines. Its use has been studied in different conditions in patients with liver disease. However, so far the only accepted use of pentoxifylline in liver disease is as therapy of severe acute

alcoholic hepatitis as an alternative to corticosteroids, especially in the case of ongoing sepsis [1–3]. In these patients, pentoxifylline improved short-term survival in a placebo-controlled pilot trial [60]. In that study, pentoxifylline also seemed to have a protective effect against the hepatorenal syndrome, but with no significant effect on pro-inflammatory cytokines or liver tests. Based on the results of this and other clinical and experimental data, it has been suggested that the antioxidant and anti-inflammatory properties of pentoxifylline could be beneficial in improving outcomes in patients with advanced cirrhosis. A large randomized trial in 335 patients with Child–Pugh class C studied the effect of 6 months of pentoxifylline vs. placebo in survival and risk of further clinical decompensation [61]. The study failed to show differences in survival or gastrointestinal bleeding, but patients receiving pentoxifylline experienced fewer complications, mainly bacterial infections, renal failure, and hepatic encephalopathy. Data on bleeding from other studies with pentoxifylline is very scarce [62, 63]. Some experimental data suggested that pentoxifylline can lower portal pressure in animal models [64], although this effect was not replicated in a pilot study in patients with alcoholic cirrhosis with varices [65] receiving either pentoxifylline or thalidomide (another oral unspecific TNF-alpha inhibitor). In that study, administration of pentoxifylline had no effect on HVPG (thalidomide did have a lowering effect of HVPG, although it was poorly tolerated). Overall, the effect of pentoxifylline on portal pressure and its potential applicability for the prevention of rebleeding is unclear, although available clinical data suggests that this effect is probably mild to none.

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Issues in Trial Design and Areas Needing Further Research

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Juan G. Abraldes, Francesco Salerno, Salvador Augustin, Cristina Ripoll, Thomas Reiberger, Richard Moreau, Agustin Albillos, and Guadalupe Garcia-Tsao

J.G. Abraldes, MD, MMSc (✉)
Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada
e-mail: Juan.g.abraldes@ualberta.ca; juan.g.abraldes@gmail.com

F. Salerno, MD
Internal Medicine and Hepatology, Policlinico IRCCS San Donato, University of Milan, Milan, Italy

S. Augustin, MD
Liver Unit - Department of Internal Medicine, Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

CIBERehd, Juan Rodés Grant Researcher, Instituto de Salud Carlos III, Madrid, Spain
e-mail: Salva.augustin@gmail.com

C. Ripoll, MD
First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg Halle, Saale, Germany

T. Reiberger, MD
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

R. Moreau, MD
Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

A. Albillos, MD
Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain

G. Garcia-Tsao, MD
Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA

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The Clinical Complexity of the Patient with Cirrhosis

Variceal bleeding is a life-threatening complication of cirrhosis, but it is only one among several complications that develop in these patients. This means that the therapeutic goal in a patient that recovers from an acute variceal bleeding episode cannot be limited to the prevention of rebleeding but should aim at preventing all complications of cirrhosis and at improving survival. The implications for trial design of this clinical complexity were extensively discussed in the Baveno V consensus conference [1]. We will specifically discuss how this applies to the design of trials for the treatment of patients that recover from acute variceal bleeding.

Issues in Trial Design for the Management of Patients After Variceal Bleeding

Standard Treatment Arm for Future Trials

The combination of nonselective beta-blockers and endoscopic banding ligation (EBL) is the standard therapy for preventing rebleeding and should be the standard therapy with which new treatments should be compared. In patients with contraindications or intolerance to beta-blockers or experiencing NSBB-related adverse events necessitating discontinuation of drug therapy, the standard treatment arm should be EBL.

Time Frame for Randomization in Trials of Secondary Prophylaxis

After an index variceal bleeding, the risk of rebleeding and death is maximal during the first 5 days [2, 3], and this led to define the time frame of the bleeding episode as 5 days. This reflects also the time period in which i.v. therapy with vasoactive drugs is maintained in most centers. On this basis we recommend to randomize patients from the 5th day after the index hemorrhage. After this period the risk of rebleeding progressively decreases and therefore a maximal time from bleeding to randomization should be set. We propose a time frame for randomization between day 5 and 10 after the index hemorrhage.

Definitions of Rebleeding

The definition of rebleeding has been heterogeneous across trials. Most trials have used variceal rebleeding, whereas two recent trials used all-cause upper-GI bleeding [4, 5]. The rationale for using all-cause rebleeding was the difficulties in assigning a specific source of bleeding in some cases with the ensuing potential bias in the context of non-blinded trials (such as those with only one endoscopic arm). The competing risk of portal hypertension-unrelated bleeding was minimal in both trials

(only 1 event reported in the trial by Garcia-Pagan et al. [4] and none in Kumar et al. [5]). An additional problem is how to consider the hemorrhages due to post-banding ulcers. In some trials these were defined as variceal rebleeding [6, 7]. However, in most trials, these are reported separately and not counted as variceal rebleeding. If the primary end point is "all-cause rebleeding," they would be counted as events toward the primary end point.

In the opinion of the panel, adopting "all-cause rebleeding" is a good solution to avoid bias in unblinded trials.

Definition of the Primary End Point in Trials for the Management of Patients with Cirrhosis After a Variceal Hemorrhage

Traditionally the design of randomized trials has been based on the definition of a single primary end point and hypothesized effect size. The expected effects of the tested therapy on the primary end point drive sample size calculation. However, cirrhosis is a complex disease, and several complications occur as the result of portal hypertension. Therefore, if the assessment of the effects of an intervention is limited to just one complication (rebleeding), it will provide a very limited view of the overall impact of the intervention on the overall prognosis and well-being of patients with cirrhosis. In addition, natural history studies have shown that rebleeding is not the most frequent complication after a first episode of variceal bleeding [8, 9]. Thus, the primary end point in trials for secondary prophylaxis should take into account this complexity.

Another layer of complexity derives from the fact that the prognosis of patients with acute variceal bleeding is very different if bleeding is the only complication (1-year mortality: 8–18 %), or bleeding occurs in the presence of ascites (1-year morality: 38–50 %) [10–12] or any additional complication of cirrhosis (1-year mortality of 29 %) [11]. Therefore, patients with variceal bleeding with or without other complications are two very different populations in terms of prognosis, and this should be reflected in the design of future trials.

Patients with Variceal Bleeding Without Other Complications

As discussed above, medium-term risk of mortality is low in patients with variceal bleeding as the only complication. Therefore, mortality would be an impractical primary end point. Powering a study to assess changes in mortality would require a huge sample size and a very long follow-up. These patients, however, are at a higher risk of developing a second complication of cirrhosis (1-year probability: 21 %) (in order of frequency: ascites, rebleeding, and jaundice/encephalopathy) [9]. The occurrence of a second complication has strong prognostic implications, since it places the patient at a high risk for short-term death. Thus, the occurrence of that second complication could constitute a meaningful primary end point for the design of therapeutic trials in patients who recover from acute variceal bleeding and do not have other complications of cirrhosis. In addition, in this group of patients with low mortality, patient-reported outcomes (PROs) should be assessed and considered an important secondary outcome.

A relevant practical problem with this design is whether the experimental treatment should be stopped upon the development of a non-bleeding complication. This question would need to be defined according to the specific treatment being tested and the definition of therapeutic failure of that specific treatment.

Patients with Variceal Bleeding and Other Complications

Patients in whom variceal bleeding occurs together with other complications of cirrhosis or in patients already decompensated have a much higher risk of death [9]. Therefore, mortality in these patients is the most appropriate primary end point, and sample size calculation should be powered to detect differences in survival.

Strategies to Deal with Patients' Heterogeneity

Trials in Patients with Bleeding With and Without Other Complications

With the relatively high efficacy of current therapies for preventing rebleeding, the expected difference between treatment arms in future trials would be predictably small. A potentially weak signal would have to be detected in the context of prognostic factors (such as liver function or the presence of other decompensating events) that have a much stronger influence on outcomes than the treatment itself (and would constitute "noise" in the trial). Therefore, the view of the panel is that, taking into account the different prognosis and complications between patients with or without additional complications, trials for the prevention of variceal rebleeding should be conducted as independent trials in these two populations, with different end points for each of these subgroups (with or without additional complications). This would greatly increase the "signal to noise" ratio within these trials and would allow more flexibility in the design of the trial than a single trial with subsequent subgroup analysis. This flexibility includes the possibility of testing different treatments in patients with or without additional decompensation.

Stratified Randomization

Even within these two classes of patients (especially in the group of patients with additional decompensations), there might be significant heterogeneity regarding prognostic factors. Stratified randomization based on one or more of these prognostic factors facilitates balancing of these factors between treatment arms.

Subgroup Analysis

Subgroup analysis traditionally had a low reputation, mainly due to lack of a sound methodological approach and over-interpretation of results. However, subgroup analyses have regained momentum in the era of "precision medicine." Unfortunately, there has been no formal reporting of subgroup analyses in trials of secondary prophylaxis of variceal bleeding. The panel recommends conducting and reporting preplanned subgroup analysis based on meaningful risk categories. This would allow a better understanding of potential heterogeneity of treatment effects in different

subgroups of patients, which might inform clinical practice and subsequent trial design. These should adhere to accepted methodological standards [13].

The Issue of Liver Transplant as a Competing Event

Patients with variceal bleeding and other decompensations are usually candidates for liver transplant. Liver transplantation can be considered both a "failure" – since the native liver needs replacement – or a success, since the patient has been effectively bridged to a life-saving therapy. Therefore, the use of a composite end point defined as "death or liver transplantation" (transplant-free survival) does not have a direct interpretation – as in this case patients would be censored at the time of liver transplantation. If the rate of transplantation is high during the trial, this should be analyzed within the framework of competing risk analysis. This provides information on the effects of a given treatment specifically on the rate of death and on the rate of transplant and prevents the possibility of equivocal interpretations.

Time Frame for Defining the Study End Points

In patients with variceal hemorrhage occurring in the absence of any other decompensating event, the incidence of other decompensating events is relatively high (around 30 % per year [11]), and therefore, a time frame of 2 years would be a reasonable follow-up period. In these patients, however, mortality is low, and therefore, for assessing mortality, designs with longer follow-up periods would be required. In patients with additional decompensating factors at the time of variceal hemorrhage, the risk of death within 2 years is high, allowing a relatively short follow-up (2 years) in the design of therapeutic trials with death as the primary end point.

Reporting the Incidence of Hepatocellular Carcinoma (HCC)

Although it was considered an event independent from portal hypertension, it has been recently suggested that treatments for portal hypertension may also impact the incidence of HCC [14]. Therefore, HCC should be included as a secondary end point in trials for secondary prophylaxis of bleeding.

The Use of Hepatic Venous Pressure (HVPG) Response as a Surrogate End Point

Several studies have demonstrated that achievement of HVPG response (more than 20 % from baseline or less than 12 mmHg) to drug therapy (nonselective beta-blockers ± nitrates) is associated with decreased risk of rebleeding and other

complications of cirrhosis and with improved survival [15, 16]. Therefore, HVPG response has been considered a validated surrogate for the treatment of portal hypertension. Thus, HVPG response would be a useful surrogate in clinical settings in which the rate of end points is low. However, in the setting of secondary prophylaxis of bleeding – in which relevant clinical end points are frequent – its relevance is lower. Thus, trials in secondary prophylaxis can be efficiently designed and conducted based on relevant clinical end points, without the need for surrogates such as HVPG response. However, HVPG studies remain essential in trials assessing HVPG-guided therapy and in proof-of-concept studies to assess the effect of new drugs and provide useful additional explanatory information to understand the effects (or lack thereof) of novel drugs in trials with clinical end points.

Impact of an Early-TIPS Strategy in the Design of Trials of Secondary Prophylaxis

If the use of early TIPS in high-risk patients with acute variceal bleeding (Child-Pugh B with active bleeding or Child-Pugh C) becomes a widespread practice [17, 18], this would have a major impact on secondary prophylaxis of variceal bleeding. The highest risk patients would have already received a portal-hypotensive therapy that would not only decrease (or even eliminate) the risk of rebleeding but would also improve other complications such as ascites. Trials in this area would probably be aimed at decreasing the rate of encephalopathy and predicting the risk of triggering heart failure. This may be another area where patient-related outcomes (such as quality of life) may be explored. This would have an impact both on clinical practice and for trial design. The impact would be limited to the group with bleeding and additional decompensations, since patients with bleeding without other decompensations very rarely meet criteria for early TIPS.

Areas Needing Further Research

The Use of Covered-TIPS as First-Line Therapy to Prevent Rebleeding

TIPS has been shown to be more effective than endoscopic therapy or drug therapy for the prevention of rebleeding. However, it is associated with a higher rate of hepatic encephalopathy and does not decrease mortality. These data were obtained in trials performed with uncovered TIPS, which are associated with a much higher risk of TIPS dysfunction than the newer covered TIPS. Indeed, in an initial trial, the rate of hepatic encephalopathy was lower with the covered stents [19, 20], although this was not confirmed in a subsequent trial [21]. As of today, no trials have compared ePTFE-covered TIPS with the current standard therapy to prevent variceal rebleeding, and in the view of the panel, this requires further investigation. This should not be limited to high-risk situations. On the one hand, patients without other

complications of cirrhosis are more likely to tolerate a TIPS than more advanced patients. On the other hand, patients with variceal bleeding and other complications might be more prone to develop further decompensation if recurrent bleeding occurs, and therefore, a highly effective therapy to prevent rebleeding such as TIPS might prevent further deterioration of these patients. This was already shown in the setting of acute variceal bleeding [18]. Therefore, there is rationale to assess the effects of ePTFE-covered TIPS as compared to standard therapy both in patients with and without other complications of cirrhosis.

Optimal Treatment for Special Populations

The current recommendation is to treat all patients after a first episode of variceal bleeding in the same way, with repeated EBL and NSBB if tolerated. There is currently no evidence to support a different approach (less or more aggressive) to patients at lower or higher risk of rebleeding. Future studies should evaluate whether different treatment approaches outperform standard therapy in specific groups of patients including: pediatric patients, patients with bleeding as the sole complication, patients with bleeding and additional complications, patients having a first bleeding while on NSBB, patients with refractory ascites, patients with persistent varices despite repeated EBL, and patients with lack of HVPG response (either acute or chronic) to drug therapy for portal hypertension. In some of these areas, randomized trials are logistically challenging due to the reduced number of patients fulfilling these characteristics and would require innovative trial design strategies. In some of these situations, the answers might only be provided by well-designed large collaborative comparative research effectiveness studies. The methodological advances in the design and analysis of these studies have increased the ability to control for confounding, but at the same time, this makes them increasingly unintelligible for clinicians.

The Effects of Current Treatments in Patient-Reported Outcomes

The effects of first-line standard therapies for preventing rebleeding on patient-reported outcomes (PROs) have received little attention. Indeed, none of the trials comparing EBL + drug therapy with either therapy alone included assessments of health-related quality of life (HRQL). This is likely due to the fact that the relevance of PROs is lower in situations with high mortality, such as decompensated cirrhosis [22]. Still, these might be especially relevant in trials studying populations at low risk of death but with high morbidity (such as those with bleeding without other complications of cirrhosis) or in cases in which two treatments might have similar efficacy, but one might have advantages in terms of health-related quality of life or the treatments have a different profile of adverse events (such as TIPS when compared with medical/endoscopic therapy). In these cases HRQL assessments should be included as secondary end points.

New Drugs in the Pipeline for Secondary Prophylaxis for Treating Patients After Variceal Bleeding

In these patients, new drug therapies could improve overall prognosis by preventing episodes of rebleeding and/or additional complications of portal hypertension or by improving or preventing a further deterioration in liver function. Unfortunately, since the introduction more than 30 years ago of nonselective beta-blockers for the treatment of portal hypertension, no new class of drugs have been added to the armamentarium for treating patients after a variceal bleeding. This has occurred despite a very high number of drugs showing efficacy in animal models of cirrhosis. Many of them were never tested in proof-of-concept studies in humans or failed at that stage.

In our survey to Baveno VI faculty, the three new drugs that were identified as having greatest potential for the management of patients after variceal bleeding were: (i) simvastatin, (ii) obeticholic acid, and (iii) anticoagulants. A thorough description of the effects of these drugs and other potential new treatments for patients with portal hypertension can be found elsewhere in this book.

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Consensus Statements: Preventing Recurrent Variceal Hemorrhage and Other Decompensating Events

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Juan G. Abraldes, Augustin Albillos, Salvador Augustin, Richard Moreau, Thomas Reiberger, Cristina Ripoll, Francesco Salerno, and Guadalupe Garcia-Tsao

J.G. Abraldes, MD, MMSc
Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada

A. Albillos, MD
Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, University of Alcalá, IRYCIS, CIBERehd, Madrid, Spain

S. Augustin, MD
Liver Unit - Department of Internal Medicine, Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), CIBERehd, Juan Rodés Grant Researcher (ISCIII), Barcelona, Spain

R. Moreau, MD
Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

UMRS1149, Université Paris Diderot, Paris, France

Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France

T. Reiberger, MD
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

C. Ripoll, MD
First Department for Internal Medicine, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

F. Salerno, MD
Department of Internal Medicine and Hepatology, Policlinico IRCCS San Donato, University of Milan, Milan, Italy

G. Garcia-Tsao, MD (✉)
Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Section of Digestive Diseases, VA-CT Healthcare System, West Haven, Connecticut, USA
e-mail: Guadalupe.garcia-tsao@yale.edu

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Prevention of Recurrent Variceal- Hemorrhage

- First-line therapy for all patients is the combination of non-selective beta-blockers (NSBB= propranolol or nadolol) + endoscopic variceal ligation (EVL) (1a; A).
- EVL should not be used as monotherapy unless there is intolerance/contraindications to NSBB (1a; A).
- NSBB should be used as monotherapy in patients with cirrhosis who are unable or unwilling to be treated with EVL (1a; A).
- Coated transjugular intrahepatic portosystemic shunt (TIPS) is the treatment of choice in patients that fail first-line therapy (NSBB + EVL) (2b; B).
- Because carvedilol has not been compared to current standard of care, its use cannot be recommended in the prevention of rebleeding (5; D).

Secondary Prophylaxis in Patients with Refractory Ascites

- In patients with cirrhosis and refractory ascites, NSBB (propranolol, nadolol) should be used cautiously with close monitoring of blood pressure, serum sodium, and serum creatinine (4;C).
- Until randomized trials are available, NSBB should be reduced/discontinued if a patient with refractory ascites develops any of the following events (5; D):
  - Systolic blood pressure <90 mmHg
  - Hyponatremia (<130 mEq/L)
  - Acute kidney injury
- [This assumes that drugs that could precipitate these events (e.g., non-steroidal antiinflammatory drugs, diuretics) have been removed.]
- The consequences of discontinuing NSBB in the setting of secondary prophylaxis are unknown.
- If there was a clear precipitant for these events (e.g., spontaneous bacterial peritonitis, hemorrhage), reinitiating NSBB should be considered after these abnormal parameters return to baseline values after resolution of the precipitant (5; D).
- If reinitiating NSBBs, dose should be re-titrated, starting at the lowest dose (5; D).
- If the patient continues to be intolerant to NSBB and is an appropriate TIPS candidate, coated TIPS placement may be considered (5; D).

Secondary Prophylaxis of Portal Hypertensive Gastropathy (PHG)

- PHG has to be distinguished from gastric antral vascular ectasia (GAVE) because treatments are different (4; C).
- NSBBs are first-line therapy in preventing recurrent bleeding from PHG (1b; A).

- TIPS might be considered in patients with transfusion-dependent PHG in whom NSBB and/or endoscopic therapies fail (4; C); coated TIPS placement may also be considered (5; D).

Trial Design (5; D)

- Primary end points in patients after variceal hemorrhage depend on the presence of other complications (ascites, encephalopathy, jaundice):
  - Patients without additional complications (low risk of death): end point should be the development of an additional complication, including variceal rebleeding.
  - Patients with an additional complication (high risk of death): end point should be mortality.
- The use of "all-cause rebleeding" is a good strategy to minimize bias in definition of rebleeding.
- Patients in these trials should be randomized 5–10 days after the index bleed.
- Hepatic venous pressure gradient (HVPG) response assessment is needed as a surrogate marker in trials where a low rate of events is expected.
- Sample size and outcomes should be assessed by using competing risk analyses in settings where transplant rates are predictably high.
- The impact of comorbidities and successful treatment of the underlying etiology on disease progression and mortality requires further evaluation.

Research Agenda

- Efficacy/safety assessment of promising drugs (statins, FXR agonists, anticoagulants, and rifaximin) and nutritional optimization
- HVPG-guided therapy
- Role of coated TIPS as first-line therapy after variceal bleeding (secondary prophylaxis)
- Noninvasive predictors of drug response
- Effect of current therapies on patient-reported outcomes, particularly in low-mortality patients
- Innovative trials for small subpopulations of patients who have bled from varices (e.g., children, fundal varices, HCC, patients who have bled while on NSBB prophylaxis)

Part IX

Vascular Diseases of the Liver in Cirrhotic and Non-cirrhotic Portal Hypertension: Coagulation, Anti-coagulation, Anti-platelet Drugs

Results of the Questionnaire

37

Massimo Primignani

General Issues on the Use of DOACs and of Anti-platelet Agents in Vascular Diseases of the Liver

Four questions concerned the use of DOACs and of anti-platelet drugs in patients with vascular liver diseases, either cirrhosis or not.

To the question "Do you use DOACs in your patients with vascular liver disease?", 89 % of respondents ($n=24$) answered no [*consensus*].

To the question "Do you think that liver cirrhosis is a contraindication for the use of DOACs?", 78 % of respondents ($n=21$) answered no [*consensus*].

To the question "When do you use anti-platelet agents (e.g. aspirin) in patients with splanchnic venous thrombosis?", no consensus was reached. The responses were scattered among never (48 %), only in patients with myeloproliferative neoplasms (22 %), only in patients with myeloproliferative neoplasms and a re-thrombosis event despite anticoagulation (15 %) or only in patients with a re-thrombosis event despite anticoagulation regardless of underlying prothrombotic disease (15 %). None of the respondents used antiplatelet agents as primary treatment of splanchnic venous thrombosis.

To the question "In patients with EHPVO and myeloproliferative neoplasms, the anti-thrombotic prophylaxis should be made with: anticoagulants, antiplatelet drugs, anticoagulants plus antiplatelet drugs?", 78 % of respondents ($n=21$) answered "anticoagulants [*consensus*], other responses being antiplatelet drugs ($n=1$; 4 %) or anticoagulants plus antiplatelet drugs ($n=5$; 19 %).

Massimo Primignani, MD (on behalf of the panellists of Session VI)

M. Primignani, MD
Division of Gastroenterology and Hepatology,
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
Milan, Italy
e-mail: Massimo.primignani@policlinico.mi.it

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Comment

The registration studies of the DOACs did not include patients with liver diseases, so that very little experience is currently available on their safety profile in such patients. This is, at present, the main limitation to their usage. Yet it appears that, among experts, there is little concern on their safety in patients with liver disease, since most respondents felt that liver cirrhosis should not be considered as a contraindication to their use. As to the antiplatelet drugs, it was remarked that no consensus exists on their use as add-on treatment, while their sole usage in patients with liver disease is not currently implemented. It was settled that studies on the efficacy and safety of the DOACs in patients with vascular disorders of the liver, either cirrhosis or not, and on the role of anti-platelet drugs as add-on antithrombotic treatment are needed.

Aetiology of Primary Vascular Diseases of the Liver

Two questions regarded the need for bone marrow biopsy in the diagnostic workup of primary splanchnic vein thrombosis in the JAK 2 era and the indication to search for the calreticulin mutation, a recently recognized biomarker of chronic myeloproliferative Ph–neoplasia (MPN).

To the question "In which of the following cases do you perform bone marrow biopsy in patients with BCS or EHPVO?", none of the possible answers reached the level required for consensus. The responses, for BCS and EHPVO, respectively, were as shown in Table 37.1.

To the question "Would you include Calreticulin mutations test in the diagnostic work up of splanchnic venous thrombosis?", none of the answers reached consensus: never (33 %), routinely (0 %), only if JAK2 mutation is absent (41 %), only if blood counts are abnormally high (0 %) and no, if other prothrombotic conditions are present (22 %).

Comment

It was recognized that the JAK2 V617F mutation is highly specific but less sensitive for MPN. When undetectable, although the search for other somatic mutations, such as calreticulin, MPL and exon 12 mutations, may detect few further cases of

Table 37.1 Question: in which of the following cases do you perform bone marrow biopsy in patients with BCS or EHPVO?

Possible answers	BCS (%)	EHPVO (%)
Routinely	52	33
Only if JAK2 mutation is present	7	7
Only if JAK2 mutation is absent	4	4
Only if blood counts are abnormally high	11	7
No, if other prothrombotic conditions are present	15	33
Other	11	7

V617F JAK2-negative MPN, it was agreed to leave the decision for further aetiologic investigation to the haematologist. The key role of bone marrow biopsy to rule out the diagnosis of MPN in patients without any biomarker of MPN, or, in patients with any positive biomarker, to characterize the MPN phenotype, was remarked.

A third question considered the indication of liver biopsy in patients with non-cirrhotic, non-neoplastic EHPVO. To the question "Should liver biopsy be performed in patients with non-cirrhotic EHPVO?", 78 % of respondents ($n=21$) answered "Yes, if liver is dysmorphic on imaging or liver tests are persistently abnormal" [*consensus*], other responses being "never" ($n=3$, 11 %) or always ($n=3$, 11 %). Based on the consensus achieved on survey, the consensus statement on liver biopsy in patients with non-cirrhotic EHPVO was as follows:

> Liver biopsy and HVPG are recommended if liver is dysmorphic on imaging or liver tests are persistently abnormal to rule out cirrhosis or idiopathic non-cirrhotic portal hypertension (1b; B). Liver stiffness by transient elastography may be useful to exclude cirrhosis (5, D).

Duration of Anticoagulation Treatment in Patients with Primary Splanchnic Vein Thrombosis

Two questions regarded the duration of anticoagulation in patients with BCS/HVOTO or EHPVO, with or without a persistent prothrombotic condition. As for BCS/HVOTO, there was consensus on the need of long-term anticoagulant treatment in patients with a persistent prothrombotic state but no consensus on the duration of anticoagulation in patients without an underlying recognized prothrombotic condition. In fact, 48 % of respondents ($n=13$) felt that long-term anticoagulation was needed, but the other responses were distributed among 3 months (4 %), 6 months 19 %, 1 year (19 %) or "until recanalization" (11 %). As for patients with EHPVO, the answers were similar to those for BCS/HVOTO. In fact, for patients with a persistent prothrombotic state, 93 % ($n=25$) [*consensus*] of respondents felt that long-term anticoagulation was necessary, whereas, for patients without a persistent prothrombotic state, only 7 % of respondents were in favour of a long-term anticoagulation. The majority of respondents preferred a limited duration of anticoagulation of 6 months (30 %) or 12 months (41 %) or "until recanalization" (22 %).

Comment

The rationale for changing the duration of anticoagulation in patients with recent EHPVO from 3 months (as in the Baveno V statements) to 6 months stands in the study by Plessiér et al., Hepatology 2010, which demonstrates that portal vein can recanalise after up to 6 months of anticoagulation, and splenic vein (SV) and superior mesenteric vein (SMV) after up to 12 months of anticoagulation.

Prevention of Bleeding in Patients with Large Oesophageal Varices Prior to Anticoagulation

A question was devoted to the prevention of bleeding in patients with large oesophageal varices prior to anticoagulation and regarded either BCS/HVOTO patients or cirrhotic or non-cirrhotic EHPVO patients. To the question "In patients with large EV which is your choice for prophylaxis before starting anticoagulants?", there was no consensus on the treatment to choose, as the answers were widely dispersed among beta-blockers, banding alone or plus beta-blockers or TIPS, as shown in Table 37.2.

Management of Non-cirrhotic, Non-neoplastic Acute (Recent) EHPVO: Anticoagulation

To the question "In patients with acute EHPVO (or acute portal vein thrombosis), which is your choice for treatment as initial therapy?", all respondents agreed that anticoagulants are the first-choice treatment.

Management of Non-cirrhotic, Non-neoplastic Chronic EHPVO: Anticoagulation

To the question "In patients with chronic non-cirrhotic EHPVO (portal cavernoma) do you use anticoagulants?", 81 % of respondents ($n = 22$) answered "only in case of recognized/persistent prothrombotic state" [*consensus*], whereas for patients without underlying persistent prothrombotic state, there was no consensus on the indication for anticoagulant therapy.

Questions on Anticoagulation Treatment in Cirrhotic Patients with Portal Vein Thrombosis (PVT)

Some questions regarded the use of anticoagulants in cirrhotic patients with PVT, taking into account the aim of anticoagulation, the indication to liver transplant or not, the extension of thrombosis and the platelet count.

Table 37.2 Question: in patients with large EV, which is your choice for prophylaxis before starting anticoagulants?

Possible answers	BCS (%)	Non-cirrhotic EHPVO (%)	Cirrhotic EHPVO (%)
Beta-blockers	30	37	37
Banding	19	19	19
Banding plus beta-blockers	30	30	33
TIPS	22	15	11

To the question "By giving anticoagulation, are you aiming to… (to which more than one answer was possible)?", 81 % of responders ($n=22$) felt that anticoagulation could facilitate recanalization and prevent extension, whereas 26 % ($n=7$) thought that their aim in giving anticoagulation was also to improve liver condition prior to liver transplantation or to improve the outcome after liver transplantation.

To the question "In cirrhotic patients with portal vein thrombosis do you use anticoagulants?", most of the responses (93 %) were confirmatory. There was a wide consensus on the treatment of candidates to liver transplant with PVT but no consensus as far as noncandidates are concerned. In such case, the responses ranged from 3 months (4 %, $n=1$) to long-term (7 %, $n=2$), with most respondents indicating 6 months (22 % $n=6$), 1 year (19 %, $n=5$) or "until recanalization" (37 %, $n=10$).

Moreover and particularly in noncandidates to liver transplant, some concern appears to exist about the safety of anticoagulation in patients with severe thrombocytopenia. In fact, for patients with a platelet count lower than 50×10^9/L, around half respondents would not treat, and for a platelet count lower than 30×10^9/L, 80 % would not treat.

As to the indication of anticoagulants according to the extent of portal vein thrombosis, most of the responses (96 %; $n=24$) were affirmative in case of PVT occlusive or partial if involving the spleno-mesenteric confluence. Around half of the respondents (56 %; $n=15$) favoured treating PVT even if partial and not involving the spleno-mesenteric confluence. Therefore, there was a large consensus on treating cirrhotic patients with PVT with anticoagulants, either occlusive or partial if involving the spleno-mesenteric confluence but no consensus for treating partial PVT not extended to that site.

To the question "Which anticoagulants do you use in cirrhotic patients with portal vein thrombosis?", none of the answers reached the level required for consensus. In fact, 56 % of respondents ($n=15$) indicated low molecular weight heparin, while 29 % ($n=8$) indicated vitamin K antagonists without further specification ($n=4$) or unless platelet count is below 50×10^9/L ($n=2$) or below 30×10^9/L ($n=2$).

Comment

There is no consensus on which anticoagulation treatment should better be used. Protocols including low molecular weight heparins (LMWH) and vitamin K antagonists (VKAs) have been adopted. LMWH is as safe and effective as VKAs but is less practical for patients because of the need for subcutaneous injections. LMWH can be used until transplantation and does not interfere with the MELD score.

VKA can be administered orally. Anticoagulation can be reversed rapidly at the time of transplantation by the administration of fresh frozen plasma. Monitoring may be difficult in patients with a baseline increase in INR. A platelet count $<50\times10^9$/L and the use of VKA were the only factors more frequently observed in patients with a bleeding episode suspected to be related to anticoagulation therapy.

Thrombin inhibitors and inhibitors of activated factor X (dabigatran, rivaroxaban) have the advantages of oral administration and no need of laboratory monitoring. Moreover, their mechanism of action is independent of antithrombin. These drugs do not interfere with the MELD score. At present, anticoagulation with these drugs cannot be rapidly reversed. Data on their efficacy and safety in patients with cirrhosis are not available yet.

Extrahepatic Portal Vein Obstruction (EHPVO) and Idiopathic Portal Hypertension: East Versus West

38

Shiv K. Sarin and Cyriac Abby Philips

Extrahepatic Portal Vein Obstruction

Definition

Portal vein thrombosis refers to complete or partial obstruction of portal venous blood flow due to presence of a thrombus in the lumen of the vein. Even though, as earlier described, PVT and EHPVO are sometimes used interchangeably, it is preferable to use the term EHPVO when the obstruction is particularly in the extrahepatic portion of the portal vein. EHPVO is an inclusive term, encompassing PVT, when the thrombus is no longer present in the lumen and is replaced by portal cavernoma. Portal cavernoma is defined as the replacement of the normal single channel of the portal vein with a number of tortuous venous channels that function as a porto-portal shunt system characterized by hepato-petal flow, leading eventually to complications of portal hypertension. Extrahepatic portal vein obstruction (EHPVO) forms part of the umbrella term, splanchnic vein thrombosis – which also encompasses mesenteric vein thrombosis, splenic vein thrombosis, Budd–Chiari syndrome or a combination of each other. EHPVO is particularly used when there is an obstruction of the extrahepatic portal vein with or without involvement of the intrahepatic part. Earlier, general classification of EHPVO into acute and chronic forms considerably depended on duration of symptoms, presence of portal cavernoma or complications of portal hypertension (PHT) [1].

S.K. Sarin, MD, DM, DSc, FNA (✉) • C.A. Philips
Department of Hepatology, Institute of Liver and Biliary Sciences, D-1, Vasant Kunj, New Delhi 110070, India
e-mail: shivsarin@gmail.com; abbyphilips@gmail.com

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Classification (Fig. 38.1)

Portal vein thrombosis could have protean manifestations depending on the age, underlying status of the liver (healthy or diseased), co-morbidities, precipitating events and procoagulant genetic predisposition [2]. It is therefore important to grade and classify PVT/EHPVO. As a consequence of thrombosis, the liver can lose up to a half of its blood supply. In such a scenario, the hepatic arterial buffer response rapidly helps maintain the total hepatic blood flow and allows time for rapid development of collaterals to bypass the obstruction. This collateral system generally gets fully established within a 3–5-week period. Even though not fully understood, acute EHPVO is considered to be present when symptoms are present 2 months prior to diagnosis, in the absence of portal cavernoma or PHT. Hyperkinetic circulation develops in the systemic region with low systemic vascular resistance and high cardiac output as seen in patients with compensated cirrhosis. Hepatic homeostasis is disrupted leading to increase in hepatocyte apoptosis and decreased proliferation of viable hepatocytes. Progressive loss of parenchymal tissue ensues in the long term a condition termed parenchymal extinction leading to features similar to end-stage cirrhosis [3]. Chronic EHPVO is defined when there is accompanying portal cavernoma and/or PHT or its complications (variceal bleeding, ascites, hypersplenism) [4, 5]. Time to development of a thrombus may not be equivalent to the symptomatic period; a thrombus can form much before symptoms occur. The presence of portal cavernoma need not always define chronicity – rapid development of portal

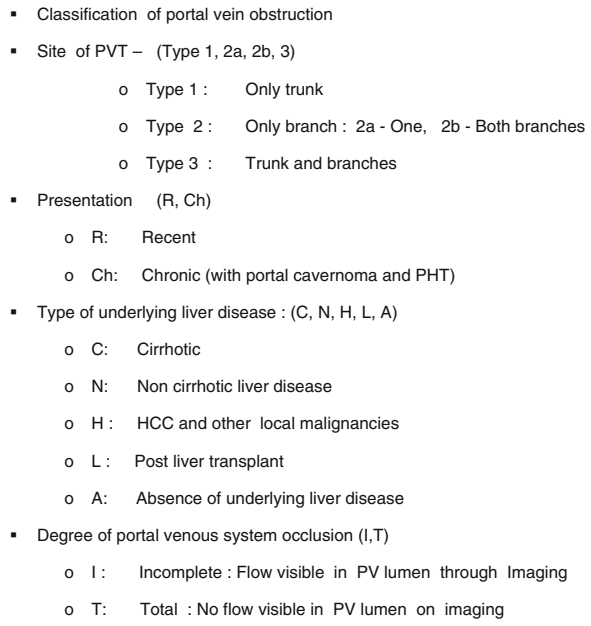

Fig. 38.1 Classification of extrahepatic portal vein obstruction

cavernoma is seen in as early as few days in patients who develop complete acute thrombosis. On the other hand, cavernomatous transformation may not always be seen even after a 2-month period in some patients [6]. Further, development of portal hypertension after formation of cavernoma also is quite variable; not all patients with cavernoma may develop PHT and the reverse may also be true. For the distinct clinical disease entity of EHPVO, development of PHT is integral.

These issues were addressed in the Baveno VI conference in reference to the consensus of Baveno V, and it was agreed that EHPVO be generally divided into recent (no cavernoma) and chronic forms that differ in symptoms but not in time. In a recent study, Jingqin Ma and co-workers [7] proposed a classification for patients with PVT who were asymptomatic. The asymptomatic PVT patients become considerably symptomatic once the thrombus extends into the mesenteric system, in which case a classification of acute PVT would be falsely made and, in some cases, acute PVT can lead to development of cavernoma in as short as 0–2 days, leading to a false diagnosis of chronic PVT. The authors proposed a new classification system as follows: type I, partial PVT without cavernoma; type II, partial PVT with cavernoma; type III, complete PVT without cavernoma; and type IV, complete PVT with cavernoma. This classification system could help in deciding on treatment modality, prognostication and treatment follow-up. Early on, most of the commonly used classifications of PVT based on degree and extension of thrombus rather than a clinical classification which would encompass aetiology and hence, modality of treatment, severity and prognosis [7]. In Baveno VI, after deliberations, it was suggested that the grading system for PVT which was agreed upon in the Baveno V is most appropriate, but, instead of grading, it should be called classification of PVT. This holistic classification system would bring homogeneity in stratifying this group of patients. In this system, EHPVO was divided based on site (trunk, one branch, both branches, trunk and branches), symptoms (recent, chronic), underlying liver disease (cirrhotic, non-cirrhotic, hepatocellular carcinoma and other local malignancy-related, post-liver transplant and idiopathic), degree of occlusion (incomplete, complete) and extent into extrahepatic portal venous system (splenic vein, mesenteric vein or both) [8].

In a clinical setting where the status of the underlying liver disease is not known, additional investigations need to be done to provide a comprehensive clinical assessment. The classification system should initially start with the underlying liver disease or malignancy, progress towards aetiology and, finally, presentation and site. Such a system that could be utilized by clinicians in the East and West was proposed in Baveno V and was endorsed again in Baveno VI.

Clinical Features

Patients with recent EHPVO are usually asymptomatic, more so in the presence of partial PVT. In acute portal vein thrombosis, a condition more commonly seen in adults at any age, the clinical features range from an asymptomatic presentation to that of an of acute abdomen with fever, vomiting, pain abdomen and abdominal

sepsis in the presence of extension of the thrombus into the vasculature of the bowel. Acute and toxic symptoms develop with rapid progression/extension of the thrombus. Pylephlebitis needs to be considered when the patient has persistent spiking fever, abdominal tenderness, signs of peritonitis, shock and sepsis-related cholestasis. It is important to investigate for thrombosis in other regions of the body.

Chronic EHPVO/PVT presents with features of portal hypertension, notably variceal bleeding. Compared to cirrhotics, EHPVO patients have more extensive esophageal and gastric varices formation, often with ectopic varices in the duodenum, anorectal, bile duct and gall bladder regions. EHPVO patients in the chronic phase can also present with features of acute abdomen if the thrombus extends into the mesenteric venous system, sometimes associated with intestinal bleeding, haemoperitoneum or shock. About 7–10 % of the patients could present with features of cholestasis and obstructive jaundice, especially in the presence of portal biliopathy.

In chronic EHPVO, symptoms are mostly related to complications of PHT – self-limiting ascites, variceal bleeding and hypersplenism. In patients who develop EHPVO associated with cirrhosis or malignancy, the severity and eventual complications may stem from underlying disease rather than PVT itself.

Diagnosis

Diagnosis of EHPVO or its complications relies on imaging modalities (Fig. 38.2. and 38.3). Ultrasonography with Doppler imaging is the most useful non-invasive method to diagnose thrombosis. It can be ideally used to look for the presence of a thrombus in the lumen and cavernoma formation. To diagnose the extension of the thrombus into the spleno-mesenteric system, computed tomography or magnetic resonance imaging is a better modality. The latter also helps in diagnosing bowel infarction and involvement of surrounding organs. Upper gastrointestinal endoscopy is helpful in looking for features of portal hypertension such as the presence of varices. In acute PVT, varices are usually not seen, but there could be evidence of portal hypertensive gastropathy. In chronic EHPVO/PVT, the presence of portal hypertensive gastropathy is very rare, but that of varices is quite frequent. Diagnosis of portal biliopathy can be achieved using non-invasive methods such as magnetic resonance cholangiography or endoscopic retrograde cholangiography, the latter of which is helpful in therapeutic management also [9–11].

Prevalence and Aetiology of Extrahepatic Portal Vein Obstruction

The population prevalence of PVT was shown to be 1 % of all general population in a study by Ogren et al., conducted in Sweden [12]. This prevalence ranges from 0.6 to 26 % in patients with cirrhosis without hepatocellular carcinoma in various studies from the West. Amitrano and co-workers reported a prevalence of de novo PVT in 16 % of cirrhotics who were followed up for a year. In patients with

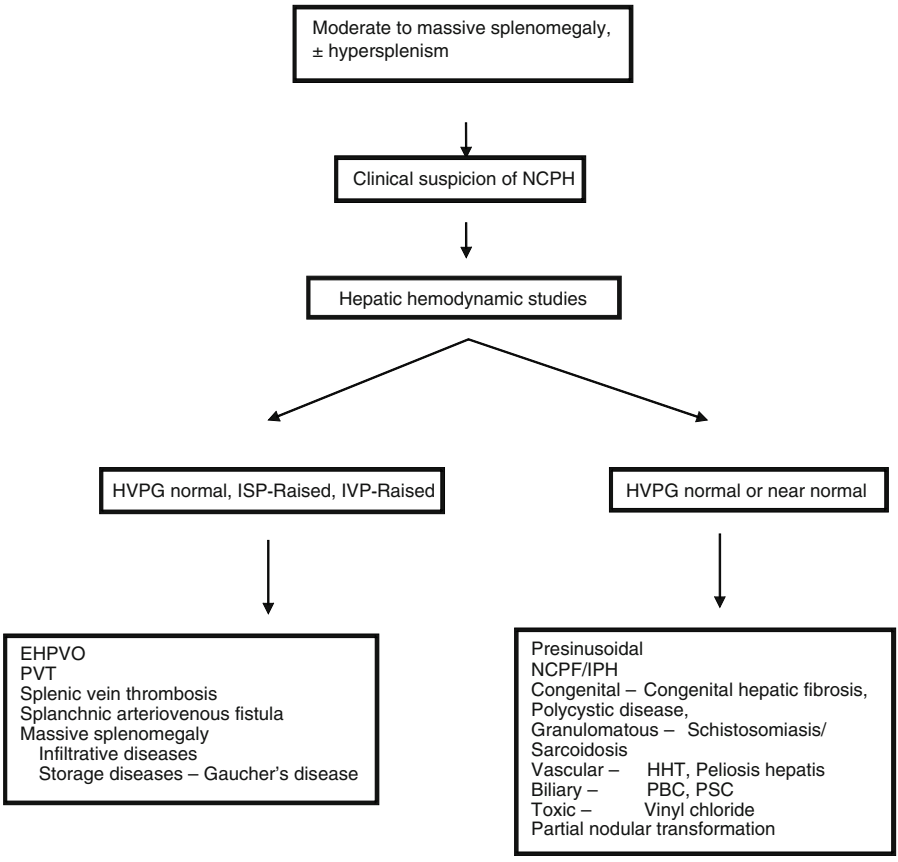

Fig. 38.2 Clinical suspicion, diagnosis and aetiology of EHPVO and IPH

hepatocellular carcinoma, associated PVT is seen in approximately 44 % of patients and this increases in the presence of cirrhosis [12–15].

Prevalence of PVT varies from region to region and also among populations and disease states. By way of angiographic, ultrasonography, computed tomography and magnetic resonance imaging modalities, PVT is seen to occur in 0.6 %, 4.4 % and 10–12 % of patient with cirrhosis, respectively [16, 17]. The modality used for diagnosis, the populations screened and the disease under consideration associated with PVT have varied influences on the prevalence of the condition. Hence, a universal prevalence of PVT cannot be commented upon in a broad and generalized sense, and this variability still prevails between the East and the West, even though the aetiologies that lead to PVT do have some common ground. One of the reasons for discrepancies could be delayed presentation and diagnosis of the patients in the East.

EHPVO in the absence of liver disease occurs only in 10 % of cases of portal hypertension in patients from Western regions. Aetiological cause for EHPVO can

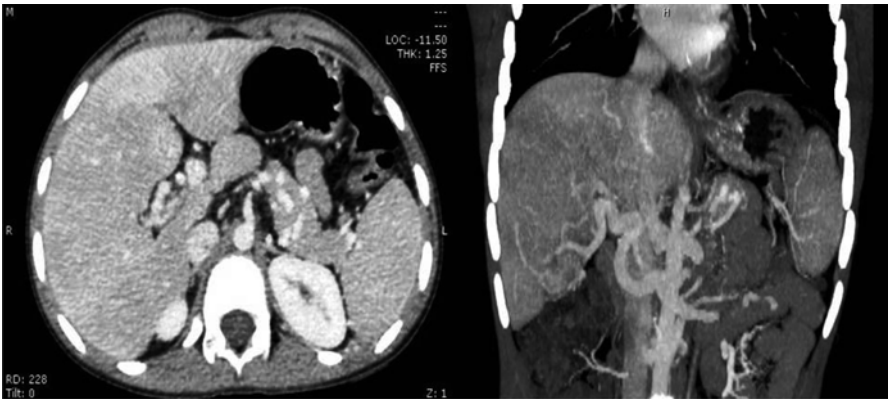

Fig. 38.3 Contrast-enhanced computed tomography of abdomen showing portal cavernoma formation and extensive portosystemic collaterals in a young male with extrahepatic portal vein obstruction

be divided based on local and systemic risk factors. Local factors include cirrhosis, hepatobiliary malignancies, intra-abdominal infections, abdominal surgeries such as splenectomy and those that cause injury to the portal vein. Systemic risk factors mainly include inherited or acquired thrombophilic factors. In adults, cirrhosis of the liver and hepatobiliary malignancies used to be the most commonly associated conditions, but a changing trend that has been seen in the last few years is that, with detailed screening and better diagnostics, myeloproliferative diseases (secondary thrombophilic syndromes) have been shown to be more common in this group. In children, the commonest causes include local infections such as omphalitis and umbilical sepsis that would have occurred during umbilical catheterization during birth. Local risk factors are identified in 30 % of patients and systemic risk factors in 70 %. Local factors include solid organ malignancies; inflammatory diseases, such as diverticulitis, appendicitis, pancreatitis, cholecystitis and Crohn's disease; iatrogenic causes, such as surgical or endovascular procedures; and cirrhosis of the liver. Systemic factors most commonly include myeloproliferative diseases, factor V Leiden mutation, factor II mutation, protein C and S deficiency, antiphospholipid antibody syndrome, hyperhomocysteinaemia and paroxysmal nocturnal haemoglobinuria. At present, thrombophilic disorders still prevail as the commonest cause for EHPVO in adults in both East and West among non-cirrhosis, non-malignant cases. In the Western EHPVO population, thrombophilia related to congenital mutations prevails as the commonest cause of EHPVO [18]. The risk factors for PVT in cirrhosis, mainly in the Western countries, have been reported to be due to factor V Leiden mutation, MTHFR mutation and prothrombin gene mutation in association with liver disease, even though literature from the East has not validated such an association between PVT and mutations in cirrhosis. Another study from the Asian region has also confirmed that factor VIII level increase with decrement in protein C levels in cirrhosis also predisposes to PVT development. However, recently, in patients with cirrhosis, it was shown in a large patient series from a single centre

that PVT is not associated with progression but with severity of liver disease. Independent risk factors for development of PVT were portal vein flow velocity <15 cm/s, grade of varices and prothrombin time and were not associated with underlying genetic mutations [19–21]. In Western countries, cirrhosis is the cause of portal hypertension in 90 % of patients, but in countries like India, EHPVO has been found to be the cause in almost 33 % of portal hypertensive cases in adults and more than 50 % in children [22, 23].

Treatment

Treatment of acute PVT/EHPVO aims at reversal of thrombosis, prevention of extension of thrombus, prevention of recurrence of thrombosis and treatment of established thrombosis to prevent long-term complications. Anticoagulation is the mainstay of treatment in the acute scenario. Low molecular weight heparin is as effective as unfractionated heparin, and in the absence for need of interventions, this can be safely switched to oral anticoagulation. However, there is limited data comparing the efficacy of low molecular weight heparin (LMWH) and vitamin K antagonists (VKA) in patients with vascular diseases of the liver. Spontaneous recanalization is quite rare in the setting of PVT and hence early initiation of anticoagulation is the thumb rule. If anticoagulation is initiated in the second week rather than the first week, the rates of recanalization could drop from 69 to 25 % [24, 25].

Anticoagulation and Re-permeation

In EHPVO, there is no consensus on the role or indication of anticoagulation therapy. In non-cirrhotic acute PVT, there is a strong role of anticoagulation and re-permeation therapy, and in the presence of prothrombotic risk factors, anticoagulation is continued for life and, in the absence of prothrombotic factors, anticoagulation is continued for at least 6 months [26, 27].

Variceal Bleeding

Variceal bleeding is a life-threatening complication of EHPVO. There is limited data on the use of vasoactive drugs, beta blockers, endoscopic therapy or shunt surgery in the management of these patients. Currently, recommendations of Baveno V apply to clinical practice. Medical management using vasopressors such as somatostatin, octreotide or terlipressin should be started as early as possible. In a study by Sarin and co-workers, equal efficacy was shown between propranolol and endoscopic band ligation for prevention of re-bleeding [28]. Endotherapy along with vasoactive drug utilization is more effective in preventing re-bleeding episodes. Endoscopic sclerotherapy and band ligation have comparable efficacy

for variceal eradication. However, band ligation achieves faster variceal eradication rates with fewer complications as compared to sclerotherapy, but the recurrence rate of varices is increased with EVL. Endotherapy using glue (N-butyl-cyanoacrylate) is useful for bleeding gastro-esophageal varices type 2 or isolated gastric varices type 1. Endotherapy is repeated every 3 weeks until variceal eradication. In patients who have failed endotherapy, use of surgical shunt procedures needs to be contemplated [29].

Portal Biliopathy

Portal biliopathy is defined as abnormalities of the extrahepatic and intrahepatic bile ducts (most commonly left system) and gall bladder wall in patients with portal cavernoma. These changes are a result of the development of portal hypertension and large collateral channels in and around the bile ducts. In fact, these patients develop indentations on the biliary ducts due to compression by paracholedochal collaterals which may lead to focal stricturing due to ischemia, dilatations of the bile ductal system, narrowing and clustering, stasis, development of choledocholithiasis and intrahepatic ductal stones. These changes in the long term can lead to progressive obstructive jaundice, coagulation abnormalities, cholelithiasis and choledocholithiasis, haemobilia, cholangitis and secondary biliary cirrhosis [30, 31]. Morphological changes have been reported in 80 to 100 % of patients with EHPVO, but the majority of patients remain asymptomatic. In the adult population, the reported frequencies range from 5 to 17 % depending on duration of follow-up. The most common clinical presentation is recurrent abdominal pain with fever and jaundice with partial or complete biliary obstruction. Elevation in alkaline phosphatase is seen in almost 80 % of patients and increased transaminases are seen predominantly with cholangitis and sepsis and in advanced stages of the disease. Chandra et al. [32] classified portal biliopathy on the basis of endoscopic retrograde cholangiography (ERC) as type I, involvement of extrahepatic bile duct; type II, involvement of intrahepatic bile ducts only; type IIIa, involvement of extrahepatic bile duct and unilateral intrahepatic bile duct (left or right); and type IIIb, involvement of extrahepatic bile duct and bilateral intrahepatic ducts. Magnetic resonance cholangiography is the diagnostic modality of choice and ERC is done when endotherapy is contemplated concomitantly. An appropriate treatment algorithm is to start patients on high-dose ursodeoxycholic acid in combination with biliary tract instrumentation as needed. But it is important to decompress the portal system with a portosystemic shunt procedure (surgical or radiological) when the anatomy permits [32].

Growth Retardation

In the natural history of EHPVO, because the insult occurs early, the course is complicated by the presence of growth retardation, slow and progressive parenchymal extinction and impaired life quality. Some patients also develop features of minimal

to overt encephalopathy in the long term. Stunting and wasting is seen in around 54 % of children with EHPVO. The growth failure is progressive, despite adequate calorie intake. Impairment of growth is secondary to multiple factors, such as reduction in portal blood supply and reduction in hepatotrophic factors, poor energy utilization, malabsorption secondary to portal enteropathy and growth hormone resistance along with hypersplenism. Early shunt surgery or liver transplant has been advocated by some in the presence of growth failure and to improve quality of life in these patients [33].

Salient Features of Extrahepatic Portal Vein Obstruction: East Versus West

(a) In the East, the incidence of EHPVO is much higher than that seen in the West. In children, the aetiology has been attributed to umbilical sepsis after birth or due to portal pyemia after intra-abdominal sepsis. Most of these patients belong to the lower economic strata. There is strong association between levels of hygiene and poverty with incidence of EHPVO. This disease entity was common in the late nineteenth century in the West and has almost disappeared from there in the current era with development and economic growth [34].

(b) In the West, intrahepatic causes of portal hypertension are common in children, whereas in the East, PH is due to EHPVO. In children in the West, biliary atresia is the commonest cause of portal hypertension, and the spectrum of portal hypertension is well known, contrary to the East where this knowledge is lacking.

(c) Clinically, upper digestive tract bleeding or splenomegaly is commonly seen with EHPVO. Among children, EHPVO is the commonest cause of upper GI bleeding in India (40–90 %), while in the West variceal bleeding is seen in only 10 % of upper GI bleeds.

(d) In an Indian study, it was shown that among children who have not bled, cirrhosis was the commonest cause of portal hypertension, but in those children who bled, EHPVO was the commonest cause of portal hypertension [35].

(e) In Western regions, approximately 58 % of idiopathic portal vein thromboses are associated with latent myeloproliferative disease in which the 1849G to T point mutation in the gene encoding the tyrosine protein kinase JAK2 is the most specifically detectable marker that is seen. Recent studies from the West [36, 37] have reported the presence of JAK2 mutation in about 17 to 35 % of patients with PVT, but such studies concentrating fully on silent thrombophilic genetic mutations are lacking in the Eastern population.

(f) There is no general consensus between the East and West regarding stepwise diagnosis, the utility of specific modalities in diagnosis of EHPVO and its complications and related management.

(g) Prevention of index variceal bleed in EHPVO is difficult as these patients invariably present with bleeding as the first presentation. Primary prevention with band ligation has been shown to be effective in preventing variceal bleed-

ing in children with high-risk varices during screening, but the utility of primary prophylaxis with beta blockers has not been studied well. In older studies, utility of propranolol has been shown to be effective in Japanese children with EHPVO; further large series are lacking from the West and the East. Even though beta blockers have been shown to decrease portal hypertension in presinusoidal cases in animal and human models, this has not been validated in randomized trials [38–40].

(h) Management of variceal bleeding in EHPVO has shown a major improvement. Earlier, sclerotherapy was considered a good modality for management of such bleeds in children. Nowadays, the use of band ligation, if feasible, is preferable. Some people have suggested the use of sclerotherapy after band ligation, but the data is limited [41–44].

(i) After resuscitation and endotherapy for first bleed, subsequent management to prevent future bleeds relies on two options – endotherapy continuation or shunt surgery. In the Indian population, the utility of distal or proximal shunts is questionable as most patients present with splenic vein thrombosis or a small splenic vein remnant and hence surgery is difficult. With the coming of Rex bypass, this problem has been tackled. It has also been shown that this bypass surgery improved growth retardation and metabolic profile in children. There are, however, no large series from Eastern countries that validate this fact. Hence, the precise role of shunt surgery vis-à-vis Rex bypass in EHPVO in the Eastern population remains unanswered, and the group of patients who could improve with the latter procedure has not been defined well. In the West, a recent study on Rex bypass has shown promising long-term effects. In this study, it was shown that meso-Rex bypass improves hypersplenism and metabolic derangements more than conventional portosystemic shunts, even though, as far as bleeding is concerned, both had similar outcomes [45, 46].

(j) The utility of repeated endotherapy for variceal eradication has been advocated among patients with EHPVO in India if it is used as the primary treatment modality, if the splenic vessels are too small for anastomosis, if there are no shuntable veins and there is extensive thrombosis and in those patients who cannot tolerate surgical procedures. The problem with this approach is that most patients develop gastric and ectopic varices in the long term on repeated endotherapy sessions and further management in the form of endotherapy does not address the underlying portal hypertension. Such data and implications do not apply in the West.

(k) Long-term follow-up of patients with EHPVO on endoscopic therapy leading to variceal eradication has been done in India. In a follow-up of 15 years, it was shown that recurrent bleeding after variceal eradication occurred at the 4th year and hence screening at 4 years after eradication was recommended. In the West, a very old study from the King's College, London, showed that in a mean follow-up of 8.7 years, re-bleeding occurred in 31 % of patients. Further large series and long-term studies are warranted from the West [43, 44].

(l) There is no general recommendation regarding the need for screening patients of EHPVO/PVT for other causes, such as thrombophilia, even if an evident

local or other systemic aetiology has been found. This is especially true for the East; because in studies from the West, a stepwise approach to aetiological diagnosis has been recommended to delineate multiple aetiologies and for holistic management.

(m) The management of portal biliopathy often poses challenges, especially if the strictures become permanent with repeated formation of bile duct stones. The role of self-expanding metal stents has not been established due to limited data.

(n) There is lack of data on the need and outcome of liver transplantation in patients with EHPVO who develop parenchymal extinction.

Idiopathic Portal Hypertension

Definition

Idiopathic portal hypertension (IPH) (also called as non-cirrhotic portal fibrosis (NCPF), hepatoportal sclerosis and idiopathic non-cirrhotic portal hypertension (INCPH) variably in different regions of the world) consists of liver disease associated with portal hypertension due to intrahepatic or pre-hepatic causes in the absence of cirrhosis. It is characterized by involvement of small and medium portal vein branches with periportal fibrosis and among other things has features of obliterative porto-venopathy [2]. This entity is defined classically as a heterogeneous group of diseases characterized by a rise in portal pressure (>10 mm of Hg) due to intra- or pre-hepatic lesions in the absence of cirrhosis and hepatic venous outflow tract obstruction. The HVPG in such patients is characteristically significantly lower than portal pressure identifying the presence of a pre-sinusoidal and perisinusoidal level of obstruction. The pathogenesis of IPH is not well understood but consists predominantly of vascular lesions which are pre- and/or perisinusoidal, leading to portal hypertension (Fig. 38.4).

Aetiology

In studies from India, as per the 'unifying hypothesis' proposed by Sarin and Kumar [47], it has been postulated that a major thrombotic event occurring during childhood involves the main portal vein and results in EHPVO, whereas repeated microthrombotic events occurring in the portal venous system (branches <300 μm in diameter) results in IPH. Western literature (the dual theory) has suggested that dual insults, in the form of intrahepatic venous obstruction (obliterative porto-venopathy) and increased splenic blood flow secondary to high levels of endothelial nitric oxide synthetase and inducible nitric oxide synthetase, lead to this disease. In Japanese studies (epithelial–mesenchymal transition theory), another pathogenetic mechanism was proposed in which vascular endothelial cells of portal venules transform into myofibroblasts leading to obliterative vascular pathology [47–50].

Clinical Features

Clinically, variceal bleed is well tolerated in IPH/NCPF/INCPH patients and ascites and encephalopathy are only a transient phenomenon in the presence of massive variceal bleeding or after shunt surgery. Jaundice and other signs of liver failure are rare. Gastric and ectopic varices are common and portal hypertensive gastropathy is less frequent than in cirrhotics [51].

Diagnosis and Imaging (Fig. 38.4)

Diagnosis of IPH depends on the presentation of portal hypertension without any evidence of liver dysfunction, and in establishing the diagnosis, it is necessary to demonstrate patency of the hepatic and portal venous system. Doppler ultrasonography is the first step in evaluation of a patient suspected to have IPH. The liver is essentially normal in size and echo texture, but the spleen is enlarged with a patent but dilated spleno-portal axis. The portal venous system could have the 'withered tree' appearance with thickened main portal vein (>3 mm) with echogenic walls and smooth, regular intrahepatic radicles with sudden cutoff at second- and third-degree branches of portal vein with high splenic index and portal vein flow. On contrast imaging using CT, intrahepatic portal venous abnormalities are more prominent and presence of spontaneous shunts can be appreciated (16 % of cases). The intrasplenic and intravariceal pressures are high in IPH in comparison with wedged hepatic and intrahepatic pressures (pre-sinusoidal portal hypertension). Even though the median HVPG is 7 mm of Hg in this group of patients, values of more than 10 mmHg can be seen in a proportion of patients. These patients require additional workup to

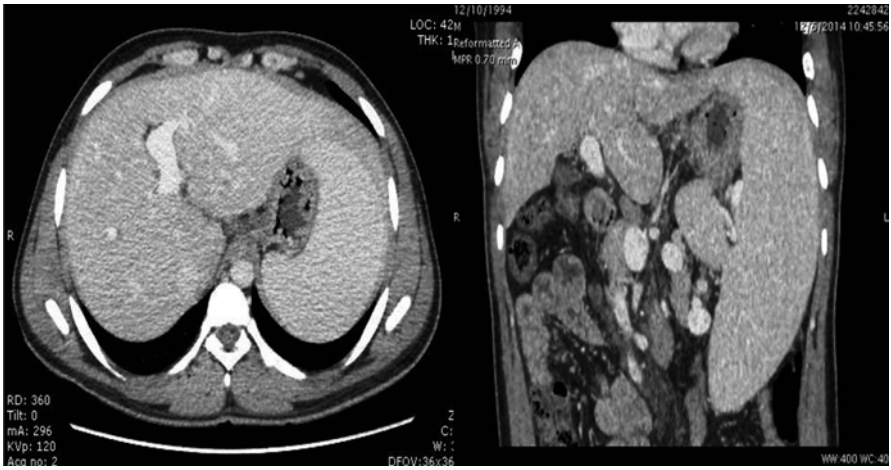

Fig. 38.4 Computed tomography of abdomen revealing presence of enlarged liver, massive splenomegaly, dilated portal system and multiple abdominal collaterals and shunts in a patient of idiopathic portal hypertension

exclude cirrhosis or advanced fibrosis of the liver. The diagnostic criteria for IPH as per prior studies are shown in Table 38.1. Fibroscan shows normal liver stiffness in patients with IPH. Nuclear scanning using sulphur colloids is useful in differentiating NCPF from cirrhosis. In cirrhosis, there is patchy uptake of nuclear tracer leading to colloid shift into the bone marrow [52]

Treatment

The long-term survival in NCPF/IPH is good with 100 % at 5 years with endoscopic variceal eradication and 80 % with shunt surgery. Thirty-three percent of patients develop liver dysfunction in the long term leading to decompensation events requiring liver transplantation. About 9 % of these patients also develop portal vein thrombosis in 1 year, which leads to difficulty in differentiating these patients from EHPVO [52]. In an autopsy study done by Nayak and co-workers, 9 of 84 patients who were initially diagnosed to have cryptogenic cirrhosis in fact had NCPF on histological analysis proving that these patients could occasionally have extensive fibrosis and behave clinically like decompensated cirrhotics [53]. The chances of patients developing variceal bleed even on primary prophylaxis with beta blockers in the first year is 9 %. Transplant-free survival is 82 % at 10 years. Esophageal variceal bleeding is managed by band ligation and gastric variceal bleeding is managed with cyanoacrylate glue therapy [25]. An Indian study has shown that secondary prophylaxis with band ligation is as good as that with beta blockers [25]. Surgical shunts or transjugular intrahepatic portosystemic shunting are done when there is failure of endotherapy to control bleeding, presence of ectopic variceal bleeding and severe growth retardation with dysmetabolic profile. Symptomatic hypersplenism is best treated using shunt surgery with splenectomy or with splenectomy alone. In patients who develop progressive thrombotic events, anticoagulation can be considered, even though there is no universal recommendation for is policy [28, 54].

Salient Features of Idiopathic Portal Hypertension/NCPF/INCPH: East Versus West

1. Though the clinical entity is clear and its features are nearly the same across the globe, there is lack of agreement on the nomenclature. Different regions – Asia, Japan and the West – have termed this condition variably. In Asia, it is called as non-cirrhotic portal fibrosis (NCPF), in Japan as idiopathic portal hypertension (IPH) and in the West as idiopathic non-cirrhotic portal hypertension (INCPH).
2. In the East, NCPF and IPH are diagnosed as a syndrome with portal hypertension as primary event and not as a result of other diseases.
3. The second issue lies in diagnostic criteria for each of these diseases which does not have unity. The Asian Pacific Association for Study of Liver states that NCPF is diagnosed in the presence of moderate to massive splenomegaly, evidence of portal hypertension, patent spleno-portal axis, normal liver functions

Table 38.1 Criteria for diagnosis of idiopathic portal hypertension in various studies

Japanese criteria for IPH	APASL criteria for NCPF/IPH (2007)	Schouten et al., for INCPH (Hepatology 2009)
Clinical disorder of unknown aetiology Splenomegaly, anaemia and portal hypertension Absence of cirrhosis, blood disease, parasites in the hepatobiliary system and occlusion of the hepatic and portal veins *Additional points* 1. Normal to near-normal liver function tests 2. Varices demonstrable by endoscopy or radiography 3. Decrease of one or more of the formed blood elements 4. Liver scan not typical of cirrhosis 5. Patent hepatic veins with a normal to slightly elevated WHVP 6. Grossly non-cirrhotic liver surface 7. Hepatic histology not indicative of cirrhosis 8. Patent extrahepatic portal vein with frequent collateral vessels 9. Elevated portal pressure	Presence of moderate to massive splenomegaly Evidence of portal hypertension, varices and/or collaterals Patent spleno-portal axis and hepatic veins on ultrasound Doppler Test results indicating normal or near-normal liver functions Normal or near-normal HVPG Liver histology – no evidence of cirrhosis or parenchymal injury *Other features* 1. Absence of signs of chronic liver disease 2. No decompensation after variceal bleed except occasional transient ascites 3. Absence of causes of chronic liver disease 5. Imaging with ultrasound or other imaging techniques showing dilated and thickened portal vein with peripheral pruning and periportal hyperechoic areas	Clinical signs of portal hypertension (any one of the following): Splenomegaly/ hypersplenism Esophageal varices Ascites (non-malignant) Increased HVPG Porto-venous collaterals Exclusion of cirrhosis on liver biopsy Exclusion of known causes of chronic liver disease Exclusion of common conditions causing non-cirrhotic portal hypertension Patent portal and hepatic veins (on Doppler ultrasound or computed tomography scanning) *All 5 criteria* must be met to diagnose idiopathic non-cirrhotic portal hypertension

From Khanna and Sarin [48]

and no evidence of cirrhosis on liver biopsy. The Japanese group criteria for IPH consist of splenomegaly, anaemia and portal hypertension with absence of cirrhosis or parasites in hepatobiliary system and absence of occlusion of hepatic or portal veins. Even though there is no unified consensus from Western countries, Schouten and co-worker's criteria is followed for diagnosis of INCPH – which consists of five major points including presence of one sign of portal hypertension, absence of chronic liver disease, absence of cirrhosis on biopsy, exclusion of common conditions mimicking non-cirrhotic portal hypertension and patent spleno-portal and hepatic venous axes [2, 49, 55–57].

4. In the Indian continent, NCPF presents in young males between the third and fourth decade of life. In Japan, IPH presents in the fifth decade of life with female preponderance. The latter has also been shown to be similar in Western literature.

5. In the Indian subcontinent, NCPF occurs in young males who come from a low socio-economic status and is prevalent in the third and fourth decade of life. In Japan and the West, it occurs in the fifth and sixth decades and has a female preponderance.
6. The major presenting symptoms in Japanese population include splenomegaly, hepatomegaly, gastrointestinal bleeding and ascites. In Indian patients, NCPF usually presents with splenomegaly, variceal bleed and anaemia. In the West, INCPH presents less commonly with splenomegaly and variceal bleed but more often with ascites.
7. Anaemia and thrombocytopenia, signs and symptoms of hypersplenism, are more common in Asian patients than in the West.
8. Japanese patients with severe underlying diseases have poor prognosis. Likewise, in patients from Western studies, the presence of ascites at presentation predicts poor survival.
9. Endoscopic evaluation reveals oesophago-gastric varices more commonly in Indian and Japanese patients (80–90 %) than in Western patients (33–43 %).
10. While Japanese criteria do not include HVPG, the APASL criteria do mention that HVPG needs to be normal or near normal. In the series by Schouten et al., increased HVPG is one of the factors that confirms the presence of portal hypertension. However, high HVPG as a criterion is a bit controversial as it goes against the other two consensus criteria and because high HVPG (>10 mmHg) has been classically associated with sinusoidal and post-sinusoidal diseases such as cirrhosis of the liver and is not a feature of pre-or perisinusoidal diseases. Hence, the issue of HVPG in defining this disease required to be reanalysed [2, 49, 55–57]. This was done in Baveno VI and, after the discussion, it was agreed by consensus that, for the diagnosis of IPH/NCPH/INCPH, the measurement of HVPG is mandatory and it should be <10 mmHg.
11. The aetiologies of NCPF/IPH/INCPH are skewed in many studies conducted worldwide, and even now, there is no consensus as to the principal cause for this condition. The Western literature points to the presence of thrombotic states and also, in the long term, to portal vein thrombosis evolution in patients with INCPH. In the East, infections and poor living conditions are thought to be the pathogenetic basis of this disease entity.
12. In the West and in Japanese population, immunologic phenomena are thought to promote small-vessel thrombotic events and associated portal fibrosis. This also substantiates the female preponderance among these patients. This is not seen with patients of NCPF in India.
13. Familial clustering and genetic basis of disease have been seen in both West and East populations of NCPF, but there is no strong evidence for it to be the primary causal event [49, 58].
14. There is a staging system proposed by Nakanuma et al. for IPH. Such staging systems are lacking from India and also from the West. These are stages I–IV, stage I being the absence of peripheral parenchymal atrophy and stage IV showing the presence of obstructive thrombosis in intrahepatic large branches or trunk of PV. Based on staging, no prognostication has been made and prog-

nostic models are an unmet need in this condition in both West and East [59, 60].

15. Histopathological studies have characterized the disease well in the Indian, Japanese and Western (mostly European) patients. The features of obliterative porto-venopathy are universally accepted to confirm the diagnosis of this entity, though it is seen in autopsy or explant specimens.
16. The importance of differentiating nodular regenerative hyperplasia, congenital hepatic fibrosis and hepatic schistosomiasis from classical INCPH has been underlined in the study from Belgium [49]. Efforts to differentiate these conditions have not been done among Japanese and Indian patients.
17. In patients with NCPF, the overall survival has been shown to be good after variceal eradication or a properly timed shunt surgery. This has been shown on long follow-up in the Indian and French patients.
18. In the French study, the poor prognostic factors in INCPH were found to be development of ascites, progressive liver failure and portal vein thrombosis. In Belgian patients, it was found that the presence of ascites itself was one of the most important poor predictors of survival. Poor predictors of survival among Eastern patients are still not fully delineated and warrant review. Japanese data have not shown the presence of portal thrombosis in autopsy studies to be adversely related to survival. Just as the aetiopathogenesis and clinical characteristics are different among different regions, the events that predict poor survival and outcomes could also be different among populations from the West and East [56, 57, 60, 61 ,62].

Baveno VI was able to evolve a consensus on the various contentious and emerging issues related to EHPVO and IPH/NCPF/INCPH. The consensus statements are placed together in the final recommendations. Several areas in the pathogenesis, natural history and management remain unanswered due to lack of sufficient data and these were listed as areas of future research.

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Budd-Chiari Syndrome/Hepatic Venous Outflow Tract Obstruction: East vs West

39

Dominique-Charles Valla

Introduction

Budd-Chiari syndrome [BCS] can be defined as the consequences from an obstructed hepatic venous outflow tract, excluding cardiac and pericardial diseases as well as sinusoidal obstruction syndrome/veno-occlusive disease [1, 2]. An equivalent to the denomination "BCS" is "hepatic venous outflow tract obstruction" [HVOTO] [1, 2]. BCS/HVOTO can be further classified into the following two categories according to the mechanism of the obstruction: secondary BCS/HVOTO when the obstructive process originates outside the venous tract [e.g., invasion by a malignant tumor or *Echinococcus multilocularis* or pressure from a benign or malignant tumor or a cyst] and primary BCS/HVOTO when the process originates from the lumen [thrombosis] or from the wall [phlebitis] of the veins [1, 2]. This chapter will deal only with primary BCS/HVOTO, thereafter referred to simply as BCS/HVOTO.

Stratifying risk and individualizing patient care is a crucial issue for BCS/HVOTO. Indeed, within the category of the primary disease, a marked heterogeneity is conspicuous, related to etiology, level of obstruction of the hepatic venous outflow tract, manifestations, and course of the disease [3]. In this respect the widely held distinction between a Western variant and an Eastern, Asian, variant requires particular consideration. Schematically, the Western variant would be characterized by a thrombotic obstruction of the hepatic veins sparing the inferior vena cava (IVC), related to underlying prothrombotic conditions, whereas the Asian variant would be characterized by a non-thrombotic, fibrous, obstruction of the IVC in the

D.-C. Valla, MD
Service d'hépatologie, DHU UNITY, APHP Hôpital Beaujon,
Clichy la Garenne, Clichy, France

Centre de recherche de l'inflammation, UMR 1149,
Université Paris Diderot and Inserm, Paris, France
e-mail: dominique.valla@bjn.aphp.fr; Dominique.valla@bjn.ap-hop-paris.fr

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absence of underlying prothrombotic conditions [4]. Although this view has been challenged, at least in part, since the turn of the millennium, it remains generally admitted that there are fundamental differences in the characteristics of the disease encountered in these two parts of the world [5].

This chapter will discuss recent data coming from the East and the West regarding epidemiology, the obstructive lesions of the hepatic venous outflow tract, the response to therapy, and hepatocellular carcinoma. For a review of the literature before 2004, the reader is referred to a previous article on the same topic [4]. Although this chapter will focus on primary BCS/HVOTO, it should be acknowledged that there may also be differences in the prevalence of secondary BCS/HVOTO between the East and the West according to the background prevalence of certain noncancerous diseases such as hydatid diseases, amoebiasis, or filariasis that are known to cause secondary BCS/HVOTO.

Epidemiology

Available epidemiological data do not allow a solid comparison between the East and the West. Incidence estimates presented in Table 39.1 have been derived using different methods for case retrieval as well as different case definitions. They have been performed at different periods between 1989 and 2010 and are based on a different number of cases. Despite this, it is remarkable that estimates for Europe yielded relatively consistent numbers (0.35–0.8 cases per million per year in adults) [7–9]. The most recently reported estimate was based on 185 incident cases retrieved in the year 2010 from an area covering 60 % of the French population, based on the results of a survey performed in the French network for vascular liver diseases and cross validated using a national registry of hospital discharge diagnosis; both estimates yielded highly consistent results [8]. Estimates in Denmark [7] and Sweden [9] were grounded on national registries for hospital discharge diagnoses, yielding 13 cases in the period 1981–1985 and 12 cases in the period 1990–2001, respectively.

By contrast, data from Asian countries are widely divergent. Japanese data were obtained through a questionnaire survey sent to specialized centers and cross validated by autopsy registry data [6]. The incidence estimate, 0.13 per million per year, was based on 160 cases collected in the year 1989. This estimate is 2–5 times lower than the European estimates. However, at the other end of the spectrum is the estimate derived from the data collected in the liver unit in Katmandu, Nepal [10]. Cases were identified on admission to the liver unit based on routine ultrasonography

Table 39.1 Estimates of incidence of Budd-Chiari syndrome HVOTO

	Japan [6]	Denmark [7]	France [8]	Sweden [9]	Nepal [10]
No. of cases	160	13	185	12	150
Incidence per 10 [7] per year	0.13	0.50	0.64	0.80	2.50
Period	1989	1981–1985	2010	1990–2001	1990–1992

findings. According to these data, assuming that all cases of BCS/HVOTO in Nepal were seen in this liver unit, the incidence of BCS would have been at least 2.50 per million per year, which is 20-fold higher that the Japanese estimate obtained at the same period in time by the same investigators. Intriguingly, IVC obstruction was reported to cause 100 and 93 % of Nepalese and Japanese cases, respectively.

Taken together, these estimates do not allow for a clear statement regarding differences in BCS epidemiology according to the area. Whereas there does not seem to be a marked heterogeneity in epidemiology across Europe, there might be wide geographical differences among Asian countries. It is noticeable that epidemiological data are lacking for the 2 Asian subcontinents, India and China. Within these countries further differences may be present according to area but also to socioeconomic status and urban or rural areas, as suggested by the few studies that have considered these aspects [10, 11]. Alternatively, or additionally, differences in case definitions and imaging methods used for documenting HVOTO, as well as procedures for case identification and retrieval, may explain part of the variations.

Type of Hepatic Vein and Inferior Vena Cava Obstruction

Findings in recent reports from various parts of the word on consecutive, unselected cases described with sufficient details are presented in Table 39.2. As to the obstruction of hepatic veins alone, the geographical pattern is relatively consistent. The lowest levels of prevalence were found in China and Korea (<35 %) [19, 21, 22], the highest levels in Southern Mediterranean countries (>70 %) [12, 14] and India/Pakistan (55–70 %) [11, 15, 16], with intermediate levels in Europe/Turkey (35–50 %) [17, 18]. A bias arising from difficult access to specialized care should not be ignored in view of the fact discussed below that low socioeconomic status appears

Table 39.2 Prevalence of the different types of hepatic venous outflow tract obstruction according to countries, as ranked by decreasing order of pure hepatic vein involvement

Country [ref]	First author	Year	*N*	% IVC alone	% IVC+HV	% HV alone
Egypt [12]	Sakr	2011	94	3	17	74
India [13]	Kathuria	2014	46	4	24	72
Algeria [14]	Faraoun	2015	176	0	29	71
India [11]	Shukla	2014	70	10	22	68
India [15]	Amarapurkar	2008	49	20	20	60
Pakistan [16]	Tasneem	2015	25	–	–	56
Europe [17]	Darwish Murad	2009	163	2	49	49
Turkey [18]	Uskudar	2008	75	23	30	47
China [19]	Cheng	2015	86	6	66	34
Iran [20]	Ebrahimi	2011	21	57	14	29
China [21]	Zhou	2014	338	2	85	13
Korea [22]	Park	2012	67	84	9	7

to be a risk factor for BCS/HVOTO in Asia. This factor will lead to an underestimation of pure hepatic vein involvement, misdiagnosed as chronic liver disease in the absence of experienced ultrasonography operators. By contrast, IVC obstruction will unlikely escape clinical diagnosis due to the marked development of the superficial collateral circulation on the trunk which makes diagnosis easy.

The involvement of IVC is actually difficult to analyze as there are marked variations in the proportion of pure IVC that do not appear to correspond to a geographical pattern, e.g., 84 % in Korea [22] but less than 6 % in China [19, 21], 57 % in Iran [20], but less than 20 % in India [11, 13, 15]. However, compared with previous reports, the proportion of patients with pure IVC involvement has conspicuously decreased, in India as well as in China [4]. Several reasons suggest that these differences are in part spurious and related to a difficult analysis of the termination of inferior vena cava. The various types of IVC changes can now be described by using noninvasive means, including multidetector computed tomography angiography (MDCTA) [14, 21, 23], magnetic resonance angiography (MRA) [14, 21, 24], and Doppler ultrasound by experienced operators [14, 21, 25, 26]. In a recent study from North India using MDCTA, it was found that among 21 patients with an abnormal aspect of IVC at digital subtraction angiography, 7 had secondary IVC changes related to caudate lobe hypertrophy (4 with apparent stenosis of hepatic IVC on a front view but no stenosis on a lateral view and 3 with a significant stenosis of hepatic IVC); 12 had an obstruction of suprahepatic IVC (3 with a long-segment stenosis, 4 with a membranous obstruction and 5 with a hourglass stenosis) [23]. Similarly, the evaluation of the termination of hepatic veins and collateral circulation requires special attention [14, 27–29]. In this regard, it appears that specialized radiology units report the highest proportion of pure hepatic vein involvement as well as the lowest proportion of pure IVC involvement.

Taken together, these data suggest that pure hepatic vein involvement accounts for a lesser proportion of BCS/HVOTO in China and Korea than in other parts of the world including India; correlatively, combined IVC and hepatic vein involvement accounts for a higher proportion in China and Korea. The apparent decrease in the proportion of pure IVC involvement is likely due to an improved expertise and better access to accurate noninvasive imaging modalities for the terminal portion of the IVC, allowing for an increased recognition of associated hepatic venous obstruction and for a distinction of collaterals from native hepatic veins. It is also likely that a better access to on invasive imaging has allowed an increased proportion of hepatic vein obstruction to be recognized among patients with chronic liver disease. Distinguishing secondary stenosis of IVC by an enlarged caudate lobe from a primary stenosis, a crucial issue, will become easier using current noninvasive angiographic techniques.

The nature of the obstructive process is now better analyzed and consists in each patient, of short- and long-length stenosis, recent thrombi, and a combination of these, affecting IVC and hepatic veins, in a manner that is difficult to systematize [14, 30, 31]. There does not appear to be clear differences between the East and the West in this regard.

Etiology

A number of reports from non-European countries have appeared in the last two decades focusing on underlying prothrombotic conditions. Several systematic reviews with meta-analysis have been reported, allowing for a comparison with the findings in European countries.

In European countries, myeloproliferative neoplasms account for 35–50 % of BCS/HVOTO patients [32–34]. JAK2-V617F mutation is found in about 90 % of patients with myeloproliferative neoplasm [32]. Factor V Leiden ranks second as a prothrombotic factor being found in about 12–31 % of European patients with BCS/HVOTO [34, 35] and is associated with odds ratio of about 6.5 [36, 37] . The antiphospholipid syndrome appears to be the third most common prothrombotic factor [34, 38, 39] but its diagnosis is made difficult by the poor specificity of antiphospholipid antibodies in a context of chronic liver disease [40]. Compared to the general population, paroxysmal nocturnal hemoglobinuria is heavily overrepresented, but remains uncommon, among patients with BCS/HVOTO in Europe [41]. The role of G20210A mutation of the prothrombin gene appears to be negligible in patients with BCS/HVOTO [36, 37]. Unequivocal inherited deficiency in protein C, protein S, or antithrombin is difficult to establish in a context of liver disease without a familial documentation; such inherited defects have not been reported in European patients with BCS/HVOTO [42]. Other conditions such as Behçet's disease, sarcoidosis, inflammatory bowel disease, or celiac disease have been reported repeatedly but account only for a small proportion of patients. The role of hyperhomocysteinemia and C677T MTHFR polymorphism is not substantiated by the scarce data available [43]. Oral contraceptive use is found in over 35 % of female patients [34], a finding which is difficult to interpret in the absence of a control population.

In non-European countries, myeloproliferative diseases have become increasingly investigated using JAK2-V617F mutation testing. The results of recent studies in unselected consecutive patients are presented in Table 39.3. It can be seen that the prevalence varies according to the area. It can be seen also that, except for China where the numbers are similar across studies, the estimates have been quite different in two centers from Mumbai, India (8.8 % [47] and 47.8 % [15]), and in two cities from Turkey (Izmir, 20.5 % [48], and Istanbul, 50.0 % [49]). Given the relatively small numbers of patients included, these differences cannot be solidly interpreted. Still China appears to be a country of particularly low prevalence for JAK2-V617F mutation [45]. This finding is even more interesting as in a study where JAK2-V617F mutation was tested in patients with BCS/HVOTO, the number of positive results was low, but as high as expected in a European population in non-cirrhotic portal vein thrombosis (15 [27 %] out of 55 patients) and cirrhotic portal vein thrombosis (1 [6 %] of 64 patients) [44]. One of the possible explanations for these findings is that JAK2-V617F-positive patients were diluted into a large group of patients with BCS/HVOTO due to an alternative cause. This issue therefore is to identify this possible alternative cause.

Table 39.3 Proportion of patients with JACK2-V617F mutation in unselected patients with BCS/HVOTO in non-European countries or Turkey, as ranked by increasing order

Area	First author [ref]	Year	Number tested	Number positive	% positive
Xi'an, China	Qi [44]	2012	77	4	5.2
Xi'an, China	Qi [45]	2013	169	4	2.4
Jiangsu, China	Wang [46]	2014	295	7	2.4
Mumbai, India	Shetty [47]	2010	137	12	8.8
Cairo, Egypt	Sakr [12]	2013	94	18	19.1
Izmir, Turkey	Karakose [48]	2015	31	6	20.5
Mumbai, India	Amarapurkar [15]	2011	23	11	47.8
Istanbul, Turkey	Yonal [49]	2012	26	13	50.0

Table 39.4 Proportion of patients with factor V Leiden mutation in unselected patients with BCS/HVOTO in non-European countries or Turkey, as ranked by increasing order

Area	First author [ref]	Year	Number tested	Number positive	% positive
Xi'an, China	Qi [45]	2013	136	0	0
Jiangsu, China	Wang [46]	2014	95	0	0
Lucknow, India	Kumar [50]	2005	59	4	6.7
Mumbai, India	Shukla [11]	2014	70	8	11.7
Izmir, Turkey	Karakose [48]	2015	32	9	28.1
Cairo, Egypt	Sakr [12]	2013	64	34	53.1

Factor V Leiden is not the explanation, at least for China. Indeed, data presented in Table 39.4 show a decreasing gradient from the Mediterranean area to India and then to China, in parallel to the gradient of the mutation in the general population [36, 37]. It is noteworthy that in India, the prevalence may differ widely across close populations depending on inbreeding [51, 52].

Exposure to oral estro-progestative contraceptive does not play a role either as a factor diluting the etiology of BCS/HVOTO in the East. On the opposite, such an exposure has never been reported among patients with BCS/HVOTO from this area. Be it in India or in China, the use of such oral contraceptives is extremely low, below 2 %, compared to 30 % in Europe and above 40 % in France [53–55]. Pregnancy which was described as a significant cause for acute Budd-Chiari syndrome due to hepatic vein thrombosis in the past [56] has not been thereafter reported as a major contributor.

A recent meta-analysis has shown that, in Asia, homozygous C677T MTHFR polymorphism and hyperhomocysteinemia are significantly increased among patients with BCS/HVOTO as compared to healthy subjects. However, a nonspecific increase in homocysteinemia can be related to chronic liver disease itself, whatever its cause [57]. Similarly, data on protein C, protein S, and antithrombin show a minor contribution to the etiology of BCS/HVOTO in Asia. Behçet's disease is a significant cause for BCS in areas where the background prevalence is high [12, 18], which is not the case in India or in China.

Thus, it appears that, mostly in China, one or several, still unidentified, additional causal factors are explaining most cases of BCS/HVOTO. A factor related to low socioeconomic status, particularly among rural populations, is likely as indicated by a case-control study performed in Katmandu, Nepal, in the early 1990 [58]. However, the nature of this factor remains elusive. A recent study in Mumbai, India, found a similar prevalence of 85 % for low socioeconomic status among patients with BCS/HVOTO but no control population is available [11]. It is interesting to note that, despite a similar prevalence of low socioeconomic status, Nepalese cases were described as involving constantly the IVC, whereas the predominant site of involvement in the Indian survey was the hepatic veins alone. Future study on this topic is urgently needed.

It should also be clarified whether the putative additional factor(s) could be specifically associated with IVC involvement. Indeed, based on findings in European patients, it appears that the causal factors determine in part the site of thrombosis and obstruction. In this regard, given the association of oral contraceptives and pregnancy with hepatic vein involvement [3, 4, 56], the predominance of IVC obstruction in non-European countries could be in part related to the lower exposure to estro-progestatives. In this line, it should be also investigated whether the different fecundity rate between Indian and Chinese women [http://data.worldbank.org/indicator/SP.DYN.TFRT.IN] could explain in part the different distributions of the predominant site of involvement.

Response to Therapy

Current recommendations for the treatment of BCS/HVOTO are to proceed in a stepwise manner, giving early anticoagulant therapy to all patients and treating the underlying disease(s) as appropriate. Prevention and treatment of complications of liver disease should be given according to the recommendations for cirrhosis. Lesions of the hepatic venous outflow tract amenable to percutaneous angioplasty, stenting, and local thrombolysis should be actively investigated. When these measures fail to achieve improvement, or are not applicable, TIPS insertion should be considered. Failure to insert a TIPS or poor response to TIPS should lead to consider liver transplantation. Recent follow-up data on the European multicenter cohort EN-Vie indeed show that this strategy is associated with a good long-term outcome. Sixty-month mortality remains relatively high [26 %], but the rest of the patient appears to be well controlled, either only on medical therapy (about 27 %), or after percutaneous angioplasty alone (about 5 %), or TIPS (about 39 %). Only 13 % of surviving patients had received liver transplantation.

Until recently, data from Asian countries have been missing for comparison. A number of cross-sectional series have been reported on large samples of patients. They have, however, been difficult to interpret due to a lack of extensive characterization at baseline, a lack of follow-up data, and a selection by therapeutic procedures applied (interventional radiology or surgery). Still, recent data indicate that the strategy tested in the West might well be applied to the East with similar results.

Anticoagulation was given to 43 patients in whom TIPS insertion was not technically possible or could not be afforded by the patient [59]. After a follow-up of 21 months (range 15–33 months), 61 % of patients had a response defined by no ascites, no encephalopathy, no portal hypertension related bleeding, normal AST and ALT, and bilirubin <1.5 g/dL. Six patients [16 %] died, five from liver failure and one from gastrointestinal bleeding. This report indicates that a proportion of Asian patients, at least similar to European patients, can benefit from anticoagulation. A couple of other reports show that prolonged anticoagulation prior to [60] or following [61] angioplasty for short-length obstruction is associated to resolution of clots in the IVC.

Angioplasty appears to have been extensively used in China, although the proportion of patients treated with this procedure remain unknown [62, 63]. A study with a median follow-up of 30 months in 167 patients was recently reported [64]. These patients were referred for percutaneous angioplasty based on unreported criteria. Various approaches were used according to the type of obstruction (IVC, hepatic veins, or both); technical success was 86 % for hepatic vein obstruction alone and over 96 % for IVC with or without hepatic veins. Five-year cumulative primary and secondary patency rate were about 80 % and 90 %, respectively. Cumulative survival in patients with successful recanalization was 80 % at 5 years. Last, TIPS insertion as an initial therapy or after failed angioplasty or stenting was used.

The experience with TIPS in Eastern countries, thus far limited, appears to be growing. In a recent report on 51 patients treated with TIPS, 39 patients had previously been treated with percutaneous angioplasty and the rest underwent initial TIPS insertion. Again, the selection of the patients set to this experienced center for international radiology is not known. Technical success rate was 100 %. Bare stents were used in 33 patients and covered stents in 18. Major procedure-related complications consisted in nonfatal intraperitoneal bleeding in 3 patients (6 %). Mean follow-up was relatively short (2 years). Encephalopathy developed in 22 % of patients. Cumulative 5-year incidence of shunt dysfunction was 77 %. Cumulative 5-year survival rate was 56 %. It is noteworthy that previous treatment with angioplasty and stenting did not prevent insertion of TIPS and did not affect survival.

These data need to be expanded and externally validated in other Eastern centers. They indicate that a strategy where anticoagulation and angioplasty are used in a first step and TIPS in a second one could be also applied in Asia and particularly in areas where IVC obstruction is very common. It remains to be further analyzed (1) whether IVC angioplasty with or without stenting could be sufficient to achieve hepatic decompression in some patients with combined IVC and hepatic vein obstruction, or combined angioplasty at both sites is needed [30]; and (2) whether IVC angioplasty with or without stenting followed by TIPS insertion should be a preferred alternative to secondary hepatic vein angioplasty and stenting [65]. Last, studies where unselected patients are analyzed are needed to evaluate the place anticoagulation alone may have.

Hepatocellular Carcinoma

Development of hepatocellular carcinoma (HCC) has long been reported in patients with BCS/HVOTO from South Africa [66] and Japan [67]. HCC is still reported as one of the major causes of death in series of patients with appropriate follow-up [68]. HCC has been reported in European and North-American patients with BCS/HVOTO as well [69, 70]. In these Western patients, the occlusion of inferior vena cava was found to be a major risk factor for the development of HCC [69, 70]. A recent systematic review showed a pooled prevalence of HCC of 15.4 % in BCS/HVOTO patients (95 % confidence interval 6.8–26.7 %), after excluding coinfection with hepatitis viruses [68]. Such an estimate is dependent on the duration of follow-up. Due to a generally short follow-up, prevalence estimates in studies from China were lower than in other areas [71]. However, in a cohort study from Korea based on 67 patients where median follow-up was not specified, HCC was diagnosed in 17 patients, corresponding to a cumulative prevalence of 42.6 % after 15 years and an annual incidence rate of 2.8 % [22]. By contrast, Indian and Nepalese surveys disclosed much lower prevalence and incidences of HCC than in other parts of the world [56, 72–75]. Due to the high prevalence of IVC obstruction in Asia, it has not been possible to evaluate whether HCC would be specifically associated with IVC obstruction as was found in Western and Indian studies [56, 69, 70, 74].

The difficult differentiation between benign large regenerative nodules commonly encountered in patients with BSC/HVOTO and HCC has been addressed with similar conclusions in Western and Eastern studies [69, 76–79]. HCC, as compared to benign nodules, is characterized by a larger size (> 3 or 4 cm in diameter), a heterogeneous aspect before and after vascular enhancement, hyper-enhancement at the arterial phase, and washout at the portal and/or late phase. Furthermore, as stated above, HCC appears to be particularly associated with IVC obstruction. Increased alpha-fetoprotein level is suggested to be a specific marker with a high (75 %) sensitivity, insufficient however to be used to rule out HCC. Data on natural history are scarce. HCC developed in patients with BCS/HVOTO appears to differ from HCC developed in patients with chronic HBV infection by a uni- or paucinodular pattern, a peripheral location, being well differentiated and associated less commonly with portal venous invasion and, overall, a less aggressive behavior [76, 77, 80–82].

Specific data on treatment for HCC in patients with BCS/HVOTO are still scarce, both in the Western and Eastern literature. It seems however that selective transarterial chemoembolization is well tolerated and can be associated with prolonged survival [76, 77]. Much more data are needed however before an opinion can be made on the optimal therapy. It appears that surveillance should be maintained long term after adequate decompression of the liver has been achieved. Further studies are needed particularly on the relationship, if any, between the risk of HCC and the underlying causal factors for BCS/HVOTO.

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Antithrombotic Treatment in Cirrhosis

40

Frank W.G. Leebeek

Introduction

In patients with cirrhosis, various changes in the hemostatic system occur. The liver is the main site of synthesis of many proteins involved in coagulation, both pro- and anticoagulant proteins, and a reduced synthesis function of the liver will lead to reduced levels of these proteins in the circulation, resulting in abnormal prothrombin time and INR [1]. Also, primary hemostasis is frequently altered in cirrhosis caused by thrombocytopenia and platelet dysfunction. In addition, the liver is involved in the synthesis of fibrinolysis proteins and clearance of many protein-inhibitor complexes from the circulation [2]. These changes will lead to a shift in the balance of the hemostatic potential [3]. In clinical practice, cirrhosis patients frequently present with bleeding episodes, especially variceal bleeding. For long, it has been thought that patients with liver disease are at a high risk of bleeding caused by these hemostatic changes. However, in recent years, new, more sophisticated coagulation assays have become available showing that thrombin generation is normal or even increased in patients with cirrhosis [4]. This led to the concept of a rebalanced delicate hemostatic system in these patients [3, 5]. This has been further exemplified by the fact that thrombosis occurs in patients with cirrhosis, for which anticoagulant treatment should be installed or used as prophylaxis to prevent thrombosis.

F.W.G. Leebeek, MD, PhD
Department of Hematology, Erasmus University Medical Center,
'S Gravendijkwal 230, Rotterdam 3015 CA, The Netherlands
e-mail: f.leebeek@erasmusmc.nl

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The Liver and the Regulation of the Hemostatic Mechanism

The liver plays a central role in the hemostatic system. Liver parenchymal cells are the site of synthesis of most coagulation factors like factor II, V, VII, IX, X, and XI, but also the naturally occurring anticoagulant proteins such as protein C, protein S, and antithrombin and fibrinolysis proteins [6]. In addition, the liver regulates primary hemostasis mediated by platelets, von Willebrand factor (VWF), and ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 repeats). Most patients with moderate-to-severe cirrhosis have mildly decreased platelet counts, and some even have platelet counts below 50,000/μl [7]. Thrombocytopenia may be due to hypersplenism, reduced synthesis of thrombopoietin, and/or low-grade disseminated intravascular coagulation [8–10]. In addition, primary hemostasis may also be defective by a reduced platelet function. Von Willebrand factor (VWF) levels are strongly increased in patients with cirrhosis. The high levels of VWF counterbalance the hemostatic defect caused by thrombocytopenia and platelet function defects [11]. In vitro studies using a flow-based model of thrombocytopenia revealed that platelet adhesion to collagen was normalized by high levels of VWF in cirrhotic plasma [11]. Decreased levels of procoagulant factors are commonly observed in cirrhosis. On the other hand, the natural anticoagulant protein C, protein S, and antithrombin are decreased to the same extent in patients with liver disease. Factor VIII levels are strongly increased, because factor VIII is synthesized primarily in hepatic sinusoidal endothelial cells, whose function is relatively preserved in liver disease, and because high levels of VWF protect the breakdown of FVIII [12, 13]. In many patients with cirrhosis, the fibrinolytic activity in plasma is increased. This has now been well established using newly developed and optimized fibrinolysis tests. This is especially encountered in patients with Child-Pugh C cirrhosis [14]. The various changes, both pro- and anticoagulant, lead to a rebalanced hemostatic system in cirrhosis [3].

Coagulation Tests in Cirrhosis

Screening tests of coagulation, including the prothrombin time (PT), international normalized ratio (INR), or activated partial thromboplastin time (aPTT), are frequently prolonged in patients with cirrhosis. The PT and aPTT are sensitive to levels of procoagulant proteins in plasma, but not of protein C, protein S, and antithrombin. More recent studies using the thrombin generation test, which measures the total amount of thrombin generated, revealed decreased total thrombin generation in patients with cirrhosis compared to controls [15–17]. However, if thrombomodulin was added, thereby taking into account the contribution of protein C, thrombin generation was similar to controls, despite abnormal conventional coagulation tests (e.g., INR). Others even found increased thrombin generation with addition of thrombomodulin [18–20]. These results suggest that thrombin generation in vivo can be normal or even increased in patients with cirrhosis even in case of an increased INR. These findings indicate that a concomitant decrease of pro- and

anticoagulant factors results in a rebalanced hemostatic system [3]. Despite the limitations of the use of the PT in patients with liver disease, the INR, which is derived from the PT, is still widely used in clinical practice, whereas the thrombin generation tests are not. This is due to the fact that thrombin generation tests have only been used in research settings and have not yet been validated in clinical practice. It remains unclear whether thrombin generation tests can predict bleeding or thrombotic events in cirrhosis patients. The INR was originally developed and validated only to monitor anticoagulant therapy with vitamin K antagonists (VKA). The interlaboratory variation of the INR in patients with liver disease is substantial using various PT reagents [21, 22]. The use of alternative ISI values obtained by calibration against plasma samples from patients with liver disease (INR Liver), which was suggested by Tripodi et al., was shown to decrease this variability, but has not yet been generally implemented [23, 24]. In a more recent study, Magnusson et al. found that the variation in INR could be limited by using Owren-based INR reagents in patients with liver disease [25].

Clinical Evidence for a Prothrombotic State in Cirrhosis

Recent studies suggest that patients with cirrhosis may have an increased risk of venous thromboembolism, not only liver-specific thrombosis but also deep vein thrombosis [26–28]. The hemostatic balance in patients with liver disease remains delicate and both bleeding and thrombosis may occur. It is difficult to identify patients who are prone to bleeding or to thrombosis based on current laboratory assays. In addition, the delicate hemostatic balance in patients with cirrhosis may be changed by comorbidities, such as bacterial infections and renal failure, which are frequently observed in these patients [29].

Thrombosis in Cirrhosis Patients

Deep Vein Thrombosis and Pulmonary Embolism

Recent studies revealed that deep vein thrombosis and pulmonary embolism occur in patients with cirrhosis [26, 30]. A large nationwide population-based case-control study in Denmark indicated that patients with liver disease have a substantially increased risk of for venous thromboembolism, with an odds ratio of 1.7 for patients with cirrhosis compared to controls [26]. Between 0.5 and 1.8 % of all hospitalized patients with cirrhosis developed venous thrombosis. Therefore, it has been questioned whether thromboprophylaxis should be used in these patients, as is done in other patients with an increased risk of thrombosis. In the past, liver cirrhosis was considered a contraindication for thromboprophylaxis with low molecular weight heparin (LMWH) based on the presumed increased risk of bleeding. In most hospitals, prophylactic LMWH is therefore not routinely given to patients with cirrhosis due to the fear of bleeding complications and not advised in guidelines because only

a limited number of studies have been performed [31]. A recent meta-analysis of retrospective studies did not suggest a benefit of thromboprophylaxis with regard to prevention of venous thrombosis; however, this included only a very small number of patients [32]. Based on the laboratory findings of enhanced thrombin generation and the accumulating clinical evidence of increased risk of venous thrombosis, thromboprophylaxis is recommended in patients with cirrhosis that are immobilized or undergo surgery or with active cancer (hepatocellular carcinoma) [33, 34]. More recent data have shown that this is safe and effective and not associated with high rates of gastrointestinal bleeding or death [35, 36]. If venous thrombosis, deep vein thrombosis, or pulmonary embolism occurs in patients with cirrhosis, it is recommended to treat the thrombotic event as it is treated in patients without cirrhosis, i.e., a short course of LMWH followed by VKA for 3–6 months. Of course anticoagulant therapy and prophylaxis have to be applied with caution in patients hospitalized with recent bleeding episodes.

Portal Vein Thrombosis

Patients with cirrhosis are at an increased risk of developing thrombosis in the portal and mesenteric veins. These complications may be related to decreased levels of the natural inhibitors of coagulation, antithrombin, protein C, and protein S and the concomitant increased thrombin generation potential. Also, decreased blood flow in the portal venous circulation has been indicated as a risk factor for portal vein thrombosis [37]. In addition, several studies have shown that systemic prothrombotic factors including factor V Leiden mutation and especially prothrombin G20210A variant are frequently found in these individuals, and they increase the risk even further [37–39]. The prevalence of portal vein thrombosis (PVT) in patients with cirrhosis increases with the progression of the disease, from less than 1 % in Child A patients to 8–25 % percent in liver transplant candidates [5, 40–42]. Because of this high incidence, Villa et al. investigated in a randomized clinical trial whether prophylactic treatment with LMWH [enoxaparin 4000 IU (40 mg) once daily] was feasible and beneficial in patients with cirrhosis. They found that LMWH prophylaxis reduced the risk of PVT without significant bleeding complications [43]. Despite this interesting finding, the use of prophylactic LMWH is still questioned and not adopted in clinical practice [44]. Prophylaxis should be reserved for patients at highest risk of thrombosis, such as patient eligible for liver transplant or those undergoing hepatic resection for liver cancer [41, 45].

For cirrhosis patients in whom a portal vein thrombosis is diagnosed, the optimal treatment remains to be established. It is of utmost importance to balance the benefit of anticoagulant treatment (e.g., recanalization, prevention of progression of thrombus) versus the risk of complications (e.g., bleeding), especially in this vulnerable patient group already at a higher risk of gastrointestinal bleeding [46]. Treatment with LMWH of vitamin K antagonists (VKA) may prevent progression of thrombosis and can achieve recanalization in patients with PVT with or without cirrhosis [45, 47, 48]. The duration of treatment has also not yet been established. Delgado

et al. showed that nearly 40 % of cirrhosis patients with PVT recanalization had a recurrent thrombosis after stopping anticoagulant treatment [48]. Therefore, it has been suggested to continue treatment in cirrhosis patients with PVT who are candidates for liver transplant till the procedure has been performed. Others have suggested to give 6 months of treatment and extend this in those individuals with additional prothrombotic disorders [39, 41]. However, not all patients with cirrhosis and portal vein thrombosis will benefit, and an individualized approach seems warranted [46]. Some patients, especially those with partial thrombosis may not be in need of anticoagulant treatment, whereas patients with thrombosis in the main portal trunk or progressive PVT may benefit from anticoagulant treatment [46]. Anticoagulant treatment should be given with caution in individuals with low platelet counts [<50 × 10e9/l]. The complexity of treating patients with PVT was shown by the recent analysis of 120 patients in our institution with non-cirrhotic PVT in whom rethrombosis and bleeding occurred in a large proportion. In these patients, 27 % had a recurrent thrombosis after 10 years, and bleeding occurred in 37 patients (31 %) for a total of 83 gastrointestinal bleedings. The use of anticoagulant treatment was associated with a significantly increased risk of bleeding (OR 2.0) [49].

Thrombolytic therapy has been used in individuals with progression of PVT, for instance, to the splenic and superior mesenteric veins, despite anticoagulant treatment. Thrombolysis is however frequently associated with severe bleeding complications, sometimes even fatal [50]. Therefore, thrombolysis is not recommended in these patients.

Problems Encountered with Anticoagulant Treatment in Cirrhosis

Treatment of venous thromboembolism in patients with liver disease is difficult, because of a higher risk of bleeding associated with anticoagulant treatment than in healthy individuals, because of the aforementioned delicate hemostatic balance [3]. Recently, some studies have shown that applying a therapeutic dose of LMWH in cirrhosis patients with thrombosis is safe; however, randomized controlled trials have not been performed and are urgently needed [36]. In order to reduce the risk of bleeding during anticoagulant treatment, it is of importance to treat portal hypertension and varices, by beta blockers and/or endoscopic treatment. Furthermore, the optimal type of anticoagulant has not yet been established. Both VKA and LMWH are used in patients with cirrhosis and both anticoagulants have their pitfalls. Several studies have shown that the monitoring of these anticoagulants is different in individuals with cirrhosis compared to individuals with a normal liver function [19]. LMWH or unfractionated heparin may be difficult to monitor due to low levels of antithrombin [36]. Anti-factor Xa measurement seems to be unreliable in patients with liver disease due to analytical problems [36, 51]. Also, monitoring of treatment with vitamin K antagonists is difficult and may not be reliable based on the preexistent prolongation of the PT due to the underlying disease [5]. It is advised however to maintain the INR in the normal target range of 2.0–3.0 considering the lack of

studies specifically in cirrhosis patients [4]. Future studies should focus on developing new methods to optimize monitoring of anticoagulant drugs in patients with liver disease.

Direct Oral Anticoagulants (DOAC)

Direct oral anticoagulants (DOACs, formerly called novel oral anticoagulants, NOACs) are direct-acting oral anticoagulant drugs, which target factor IIa (thrombin) (e.g., dabigatran) or factor Xa (e.g., rivaroxaban, apixaban, and edoxaban). DOACs have several potential advantages over LMWH and VKA treatment [52]. The advantages of DOACs are a fixed orally administered dose without monitoring of INR, a fast action within 2–3 h, short half-life, no interaction with food ingestion, and only limited drug interactions. Possible disadvantages are the lack of an antidote in case of bleeding, the inability to monitor these drugs with standard/routinely used assays, lack of compliance, and the high costs [52]. DOACs have been extensively studied and are currently in use in a prophylactic dose to prevent venous thrombosis in elective orthopedic surgery and in a therapeutic dose in the prevention of ischemic stroke in patients with atrial fibrillation and in case of venous thromboembolism, including deep vein thrombosis and pulmonary embolism [53–55]. For all these indications, the efficacy end points of the studies were similar for DOACs compared to LMWH and/or warfarin. Bleeding complications, including major bleeding and fatal bleeding, seem to occur less frequent with DOACs. A meta-analysis of all atrial fibrillation studies, including over 58,000 patients, revealed that the risk of intracranial hemorrhage is reduced by 50 % [53]. This was also observed in VTE patients treated with DOACs compared to warfarin [54, 56]. Direct comparison between the various DOACs for atrial fibrillation and VTE treatment have not been performed, but is seems that of the four registered DAOCS, apixaban has the lowest bleeding risk compared to VKA [55]. Despite the reduced bleeding rate in DOACs versus VKA, the incidence of gastrointestinal bleeding was increased in atrial fibrillation patients by around 25 %, with an absolute risk in the studies of 2.6 % versus 2.0 % in VKA-treated patients [57]. This is of importance in cirrhosis patients that are already at a higher risk of gastrointestinal bleeding. It is still unclear whether DOACs can be safely used in patients with liver disease, including cirrhosis. In all DOAC studies, patients with liver function abnormalities were excluded, because the use of the first developed direct oral thrombin inhibitor ximelagatran resulted in abnormal liver function test in a considerable number of patients, and therefore this drug was not FDA approved [58, 59]. In all atrial fibrillation and VTE studies with the more recently introduced DOACs, liver function was closely monitored, and no severe liver toxicity was observed. Pharmacokinetic studies in patients with mild liver impairment showed a PK profile of dabigatran comparable to healthy individuals [60]. The label advice for using DOACs in patients with hepatic dysfunction suggests not to use NOACs in moderate-to-severe (CHILD B/C) cirrhosis [61]. In a recent article by the Swissmedic on pharmacovigilance with DOACs, two patients on rivaroxaban were reported with elevated liver function tests in whom no

other cause could be detected. Liver function tests normalized immediately after stopping the drug [62]. Despite the fact that the use of DOACs is not yet recommended in patients with liver disease, recently, some case reports have been published in patients with PVT or other splanchnic vein thrombosis with and without cirrhosis [63, 64]. Monitoring of these drugs may be necessary in patients with cirrhosis; however, preliminary studies have shown that this may be difficult in these patients [65]. The VALDIG study group recently sent out a questionnaire on the use of DOACs in patients with cirrhosis or with vascular liver disease, including PVT and Budd-Chiari syndrome and presented results of around 60 patients with cirrhosis treated with DOACs (mainly rivaroxaban) (oral presentation at the 2015 EASL meeting, Vienna). Despite the limitations of this questionnaire, the results were encouraging, with major bleeding and recurrent thrombosis occurring in a limited number of patients. However, there is a need for prospective randomized clinical trials to investigate the efficacy and safety of DOACs in comparison to current treatment in patients with cirrhosis and in patients with vascular liver disease, before DOACs can be advised in these clinical settings.

Conclusions

In patients with cirrhosis, a delicate hemostatic balance is encountered, and based on new laboratory-based and clinical insights, these patients may have a prothrombotic phenotype. Prophylactic anticoagulant therapy with LMWH may be useful to prevent venous thrombosis in high-risk situations. Treatment of thrombosis remains a challenge in cirrhosis patients, because of several pitfalls with monitoring of anticoagulant treatment. Because hardly any data are available on the use of the direct-acting oral anticoagulants (DOACs), these should not yet be prescribed in cirrhosis patients. There is a need for well-designed large randomized studies with DOACs versus standard therapy in this vulnerable patient group at high risk of bleeding.

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Session 6: Consensus Statements – Vascular Diseases of the Liver in Cirrhotic and Noncirrhotic Portal Hypertension

41

Jonel Trebicka, Andrea De Gottardi, Alessandra Dell'Era, Frank Leebeek, Shiv Sarin, Susana Seijo, Dominique Valla, and Massimo Primignani

Etiological Workup in Primary Thrombosis of the Portal Venous System or Hepatic Venous Outflow Tract

- Close collaboration with hematologists is suggested for complete workup for prothrombotic factors including inherited and acquired thrombophilic factors, PNH, and autoimmune disorders (5;D).
- Myeloproliferative neoplasia (MPN) should be investigated in all adult patients, first by testing for V617F JAK2 mutation in peripheral blood (2b; B).

J. Trebicka (✉)
Department of Internal Medicine I, University of Bonn, Bonn, Germany
e-mail: jonel.trebicka@ukb.uni-bonn.de

A. De Gottardi
Department of Hepatology, Clinic of Visceral Surgery and Medicine, Inselspital, Berne, Switzerland

A. Dell'Era
Department of Biomedical and Clinical Sciences, University of Milan, Gastroenterology Unit, Luigi Sacco University Hospital, Milan, Italy

F. Leebeek
Department of Hematology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

S. Sarin
Department of Hepatology, Institute of Liver and Biliary Sciences (ILBS), New Delhi, India

S. Seijo
Liver Unit, Hospital Clínic, Barcelona, Spain

D. Valla
Hépatologie, Hôpital Beaujon, Clichy, France

M. Primignani
First Division of Gastroenterology, Università degli Studi di Milano, Milan, Italy

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- When V617F JAK2 is undetectable, further tests for MPN (including somatic calreticulin) may detect additional cases of JAK2-negative MPN (2b;B).
- Irrespective of peripheral blood cell counts, bone marrow biopsy is recommended for the diagnosis of MPN in patients without any biomarker of MPN. Bone marrow biopsy may be useful for the characterization of the subtype of MPN in patients with any positive biomarker (2b; B).

Use of Anticoagulants and Antiplatelet Drugs in Vascular Liver Diseases

- Low molecular weight heparin (LMWH) and vitamin K antagonists (VKA) are widely accepted and used in primary thrombosis of the portal venous system or hepatic venous outflow tract [1b; A].
- No current recommendation can be made on direct oral anticoagulants (DOACs) and antiplatelet drugs due to limited data [5;D].

Anticoagulation and Portal Vein Thrombosis (PVT) in Cirrhosis

- Screening for PVT is indicated in patients on the waiting list for liver transplant (LT) every 6 months (5;D).
- Occurrence of PVT in the presence of HCC does not imply vascular malignant invasion, but further imaging is recommended (5;D).
- Anticoagulation should be considered in potential candidates with thrombosis of the main portal vein trunk or progressive PVT (3a;B).
- In this setting, the goal is to permit/facilitate LT and reduce posttransplant mortality/morbidity, and anticoagulation should be maintained until transplantation to prevent re-thrombosis (4;C).
- In untreated potential LT candidates with PVT, an imaging follow-up every 3 months is recommended. Anticoagulation is recommended in case of progression (5;D).
- In noncandidates to LT, no recommendation regarding anticoagulation treatment can be made at present. Anticoagulation could be considered in selected cases (extension to superior mesenteric vein, known "strong" prothrombotic conditions) (5;D).
- Patients with low platelet count (e.g., $<50 \times 10^9$/L) are at higher risk of both PVT and bleeding complications under anticoagulation and require more caution (5;D).
- The benefit/risk ratio of anticoagulation for preventing or treating PVT in cirrhotic patients requires further randomized controlled trials (RCTs) (5;D).
- LMWH and VKA appear to be equally effective in cirrhotic individuals with PVT (5;D). Data on DOACs are scarce. There is an urgent need for improved tools for monitoring anticoagulation in cirrhotic patients. Measurement of thrombin generation might be an option (5; D).

Budd-Chiari Syndrome (BCS)/Hepatic Venous Outflow Tract Obstruction (HVOTO)

Definition

- Hepatic venous outflow tract obstruction (HVOTO) also known as Budd-Chiari syndrome (BCS) is the consequence of obstruction to hepatic venous outflow.
- BCS/HVOTO can be located from the level of the small hepatic veins to the level of the termination of inferior vena cava into the right atrium.
- BCS/HVOTO is a heterogeneous condition with regard to causes and pathogenesis.
- BCS/HVOTO is considered secondary when the mechanism for HVOTO is compression/invasion by a benign or malignant tumors, abscess, or cyst.
- BCS/HVOTO is considered primary otherwise.

Diagnosis

- BCS/HVOTO is diagnosed by the demonstration of an obstruction of the venous lumen or by the presence of hepatic vein collaterals (2b;B).
- Liver biopsy is not necessary to make a diagnosis of BCS/HVOTO when vascular imaging has demonstrated obstruction of the hepatic venous outflow tract (4;C).
- Liver biopsy is the only means to make a diagnosis of BCS/HVOTO of the small intrahepatic veins (4;C).
- Hepatic nodules are frequent and most often are benign. However, HCC may occur, and therefore patients should be monitored with periodic imaging and alpha-fetoprotein measurements and referred to centers experienced in managing BCS/HVOTO (2a;B).

Management

- Management of BCS/HVOTO should be undertaken using a stepwise approach including anticoagulation, angioplasty/thrombolysis, TIPS, and OLT at experienced centers (3b;B).
- Long-term anticoagulation should be given to all patients, although there is no definitive evidence for patients without identified risk factors (5;D).
- Portal hypertension should be treated since it is the major risk factor for bleeding, while excess anticoagulation plays a secondary role (4;C).
- Complications of portal hypertension should be treated as recommended for the other types of liver diseases (4;C).
- Previous bleeding related to portal hypertension is not considered a major contraindication for anticoagulation, provided that appropriate prophylaxis for recurrent bleeding is initiated (4;C).

- Stenoses that are amenable to percutaneous angioplasty/stenting (short-length stenoses) should be actively looked for and treated accordingly (5;D).
- TIPS insertion should be attempted by experts when angioplasty/stenting is not feasible and when the patient does not improve on medical therapy (4;C).
- BCS-TIPS Prognostic Index score may predict outcome in patients with TIPS (3b;B).
- Patients with high BCS-TIPS Prognostic Index score (≥7) are likely to have poor outcome following TIPS, and OLT should be considered (3b;B).
- Liver transplantation should be considered in patients with manifestations refractory to the above procedures (5;D).

Extrahepatic Portal Vein Obstruction (EHPVO)

Definition

- EHPVO is the obstruction of the extrahepatic portal vein, with or without involvement of the intrahepatic portal veins or other segments of the splanchnic venous axis. It does not include isolated thrombosis of splenic vein or superior mesenteric vein (SMV).
- EHPVO is characterized by features of recent thrombosis or of portal hypertension with portal cavernoma as a sequel of portal vein obstruction.
- Presence of cirrhosis, other underlying liver diseases (i.e., noncirrhotic portal hypertension), and/or malignancy should be ruled out. EHPVO in those situations should be considered as different entities.

Diagnosis

- EHPVO is diagnosed by Doppler US, CT, or MRI angiography, which demonstrate portal vein obstruction, presence of solid intraluminal material, or portal vein cavernoma (2a;B).
- Doppler US should be considered as first-line investigation, and CT or MRI angiography should be performed subsequently for the assessment of thrombosis extension and of potential local factors.
- EHPVO in adults is frequently associated with one or more risk factors for thrombosis, which may be occult at presentation and should be investigated (3a;B).
- Liver biopsy and HVPG are recommended, if the liver is dysmorphic on imaging or liver tests are persistently abnormal, to rule out cirrhosis or idiopathic noncirrhotic portal hypertension (1b;B). Liver stiffness by TE may be useful to exclude cirrhosis (5;D).

Anticoagulation in recent EHPVO

- Recent EHPVO rarely resolves spontaneously (3a,A).
- Low molecular weight heparin should be started immediately followed by oral anticoagulant therapy (2b;B). Most patients treated with early anticoagulation have a good clinical outcome. Therefore, even failure of recanalization do not warrant further interventions (e.g., local thrombolysis) in most cases (2b;B).
- Anticoagulation should be given for at least 6 months. When an underlying persistent prothrombotic state has been documented, long-term anticoagulation is recommended (1b;A).
- Antibiotic therapy should be given if there is any evidence of SIRS/infection (5;D).
- In patients with persistent abdominal pain, bloody diarrhea, and lactic acidosis, the risk of intestinal infarction and organ failure is increased, and recanalization and surgical intervention should be considered (3b;B).

Anticoagulation in Chronic EHPVO

- In patients without underlying prothrombotic disease, there is scarce information to recommend anticoagulant therapy (5;D).
- In patients with a persistent documented prothrombotic state, recurrent thrombosis or intestinal infarction long-term anticoagulant therapy is recommended (3b;B).
- Anticoagulation should be started after adequate portal hypertensive bleeding prophylaxis has been initiated (5;D).

Treatment of Portal Hypertension in EHPVO

- All patients in whom thrombosis has not been recanalized should be screened for gastroesophageal varices within 6 months of the acute episode. In the absence of varices, endoscopy should be repeated at 12 months and 2 years thereafter (5;D).
- There is insufficient data on whether beta-blockers or endoscopic therapy should be preferred for primary prophylaxis. Thus, guidelines for cirrhosis should be applied (5;D).
- For the control of acute variceal bleeding, endoscopic therapy is effective (1a;A).
- Evidence suggest that beta-blockers are as effective as endoscopic ligation therapy for secondary prophylaxis (2b;B).
- Mesenteric-left portal vein bypass (Meso-Rex operation) should be considered in all children with complications of chronic EHPVO, who should be referred to centers with experience in treating this condition (5;D).

Idiopathic Portal Hypertension/Noncirrhotic Portal Fibrosis/ Idiopathic Noncirrhotic Portal Hypertension (IPH, NCPF, INCPH)

- Idiopathic portal hypertension, noncirrhotic portal fibrosis, and idiopathic noncirrhotic portal hypertension indicate the same clinical entity (5;D). This includes the histological diagnosis of obliterative portal venopathy.

Diagnosis of IPH/NCPF/INCPH

- Diagnosis requires the exclusion of cirrhosis and other causes of noncirrhotic portal hypertension (2b;B).
- A liver biopsy is mandatory and HVPG is recommended for the diagnosis (2b;B).
- Immunological diseases and prothrombotic disorders should be screened (5;D).

Management of IPH/NCPF/INCPH

- There is insufficient data on which therapy should be preferred for portal hypertension prophylaxis. Management according to cirrhosis guidelines is recommended (5;D).
- Screening for the development of portal vein thrombosis. There is no data on the best screening method and interval. Doppler ultrasound at least every 6 months is suggested (5;D).
- In those patients that develop portal vein thrombosis, anticoagulant therapy should be started (5;D).

Research Agenda

- Further etiological investigations using whole genome sequencing in primary thrombosis of the portal venous system or hepatic venous outflow tract.
- Role of PVT in the course of liver cirrhosis.
- Identify risk factors for PVT in cirrhosis.
- The benefit/risk ratio of anticoagulation for preventing or treating PVT in cirrhotic patients requires further RCTs.
- Improved tools for monitoring anticoagulation in cirrhotic patients.
- Efficacy and safety of the new oral anticoagulants in patients with vascular disorders of the liver, either with cirrhosis or not.
- Role of antiplatelet drugs as add-on antithrombotic treatment.
- Role of anticoagulation and other treatments in chronic EHPVO.
- Further characterization and treatment of IPH/NCPF/INCPH.

Erratum to: Chapter 9 in Consensus Statements: Session 1—Screening and Surveillance

Annalisa Berzigotti, Thomas D. Boyer, Laurent Castera, Massimo Pinzani, Roberto de Franchis, and Joan Genescà

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Dr. Joan Genescà was not listed among the contributing authors of chapter 9.

J. Genescà, MD
Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain
e-mail: jgenesca@vhebron.net

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