Editorial

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Emerging trends in hepatology: 30 years of the *Journal of Hepatology* and 50 years of EASL

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The availability of drugs that can cure hepatitis C virus infection provides a wonderful backdrop for the *Journal of Hepatology* to start its 31st year. It is clear to us all that the landscape of Hepatology will change within the next 10 years and therefore it is very exciting to introduce this supplement. Despite this progress, deaths from liver disease are occurring at a staggering rate (Table 1) [1] and the benefits of the hepatitis C drugs in reducing death rates will take many years. The main culprits of the increasing burden of disease, non-alcoholic fatty liver disease (NAFLD) and alcohol related liver disease, need to be tackled at a societal and political level. The immediate cause of death in these patients, liver failure and liver cancer require better biomarkers and new therapies for earlier diagnosis and treatment. This supplement is a collection of awe-inspiring, inspirational and must-read articles of exceptional quality written by the world leaders in their own fields, often collaborating across continents to bring together this celebratory issue. The articles not only provide the best current evidence and insights into what the future holds for hepatology but also highlight how we have got to this point.

Karlsen, Lammert, and Thompson combine their huge knowledge base into focusing on our current understanding of how genetics is helping us better understand the pathogenesis of liver disease. They extend their article to describe how genetics is being used to identify the cause of hereditary liver diseases and allowing predictions about susceptibility to complex diseases and their re-classification. They extend their paper to highlight that genetic studies suggests new modes of treatment of diseases. Finally, they look a little into the future to define how using genomics may help to customize the management of the individual patient.

Hepatic fibrosis underlies the occurrence of chronicity of liver disease. **Trautwein, Friedman, Schuppan, and Pinzani** combine their immense knowledge and huge scientific enterprise to provide an understanding of the current knowledge of the condition and provide insights into how close we may be in finding a 'true' anti-fibrotic. Given the relatively long timelines in the evolution of fibrosis, drug development is challenging. They highlight these potential difficulties and describe some of the many efforts that are being put into place to allow an adequate regulatory environment for drug development.

Those who are mad from bile are vociferous, malignant and will not be quiet. Hippocrates, 5th century BC. **Beuers, Trauner, Jansen, and Poupon** have dedicated their lives in trying to understand the underlying mechanisms of cholestasis. They masterfully turn an extremely complex area of Hepatology into an absolute delight to read. They highlight that the complex molecular mechanisms that are involved in the pathogenesis of cholestasis are now possible to target. There are real novel targets of therapy; the farsenoid X receptor pathway and the pregnane X receptor pathway. The clinical and pathophysiological effects of targeting these receptors are pleiotropic and have potential beneficial effects in many types of liver disease patients.

Alcohol, of course, is a huge and growing problem throughout the world and deaths from alcohol related liver disease is increasing worldwide at an alarming rate. Unfortunately, therapeutic advances in the management of alcoholic hepatitis have been limited to steroids since the 1980s. **Mathurin and Bataller**, combine their expertise in clinical, translational and basic research to describe the massive advance there has been in the field of alcohol related liver disease and point to how new models of care, standardization of management protocols and access to novel therapeutic agents will change the landscape. They also tackle the very thorny and widely debated issue of transplantation of patients with alcoholic hepatitis in a very balanced manner.

NAFLD is fast becoming the main cause of increase in the prevalence of liver disease not only in the Western countries but also in China, and urgent solutions for this condition are needed. **Byrne and Targher**, who are well known experts in the field highlight the rapidly expanding body of clinical evidence that supports the concept that NAFLD is a multisystem disease. They describe factors linking NAFLD with other extrahepatic chronic diseases, such as diabetes, coronary artery disease and chronic kidney disease, placing an urgent need to develop new drugs for its treatment. **Ratziu, Goodman, and Sanyal,** who are leading a large NAFLD consortia on either side of the Atlantic, indicate that the treatment of NAFLD is an unmet need. Their deep understanding of the issues of NAFLD treatment is reflected in their approach to analyzing why we do not have a drug to treat the condition yet and why we are now in an incredibly exciting phase where testing new interventions would be easier. They then provide an in-depth look at the different approaches that are being developed and predict what we may expect in the near future.

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Table 1. Global deaths related to liver disease in 2013 for all ages and both sexes, with change since 1990 expressed in absolute terms and as a percentage change in median estimate over the time period. (Data kindly provided by Benjamin Cowie).

2013	Estimate	Change 1990-2013	% Change 1990-2013
Acute hepatitis infection	136,657	-25,327	-15.6%
Acute HAV	14,912	-7724	-34.1%
Acute HBV	68,642	-16,349	-19.2%
Acute HCV	3451	+1154	+50.2%
Acute HEV	49,652	-2409	-4.6%
Liver cancer	817,969	+307,911	+60.4%
Liver cancer due to HBV	300,003	+101,649	+51.2%
Liver cancer due to HCV	342,530	+255,083	+291.7%
Liver cancer due to alcohol	92,159	-30,638	-25.0%
Liver cancer due to other causes	83,278	-18,183	-17.9%
Cirrhosis	1,221,129	+383,133	+45.7%
Cirrhosis due to HBV	317,384	+83,487	+35.7%
Cirrhosis due to HCV	357,807	+144,738	+67.9%
Cirrhosis due to alcohol	383,797	+91,551	+31.3%
Cirrhosis due to other causes	162,142	+63,357	+64.1%
Total HBV related	**686,029**	**+168,787**	**+32.6%**
Total HCV related	**703,788**	**+400,975**	**+132.4%**
Total viral hepatitis related	***1,454,381***	***+559,630***	***+62.5%***
Total alcohol related	***475,956***	***+60,913***	***+14.7%***
Total other liver disease related	***245,420***	***+45,174***	***+22.6%***
Total liver disease	**2,175,755**	**+665,717**	**+44.1%**

The story of hepatitis C by **Pawlotsky, Feld, Zeuzem, and Hoofnagle**, is probably the most inspirational I have read for a long time; a story that every liver trainee should read and all liver disease experts would like to be able to write about regarding their own areas some time in their life. They start at the beginning and highlight how we have arrived at a cure for this nasty disease. They then discuss the challenges that face us in implementing the treatment of hepatitis C. To quote the authors ***'It is the story of this adventure, from discovery to cure, that we are telling here'***. A part of the challenge that faces hepatitis C is already being faced by hepatitis B, that has been battling the challenge for over a decade. **Locarnini, Hatzakis, Chen, and Lok,** provide a worldwide perspective of the challenges that faces hepatitis B virus (HBV) infection; which, unlike hepatitis C, has been a controllable disease with effective drugs and vaccine for a long time. They explore the potential impact of migration from countries with high prevalence rates to those countries with low rates of HBV infection. They then suggest that in order to eradicate HBV, a world-view is necessary and the recent establishment of the World Health Organisation Global Hepatitis Program provides a framework for global action. Lessons learnt from HBV programmes are providing guidance to the treatment of hepatitis C.

Manns, Lohse, and Vergani, who have helped change the landscape of autoimmune hepatitis (AIH) pathogenesis and treatments, make an extremely reasoned and potentially achievable target of avoiding the need for liver transplantation for this indication. They analyze the key developments in the understanding and treatment of AIH over the past 50 years and also provide an insight into how the understanding of the molecular and cellular pathogenesis of AIH will lead to newer therapies allowing us to achieve the stated aim.

Acute liver failure (ALF) is probably the most devastating and dramatic liver disease that a Hepatologist can be called upon to manage. The team led by **Williams, Wendon, Bernal, Lee, and Larsen,** all innovators who have led the area over the past 30 years, explore the notion that ALF will indeed be a curable disease in the next 10 years. They argue that mortality rates for ALF are declining rapidly and that with simple, non-specific measures, deaths from intracranial hypertension has become rare. They think that the availability of liver support devices will help in attaining this aim but also point to a focus on meticulous and early management of this condition in partnership with expert units. Better understanding of liver injury will allow the use of novel interventions, which will prevent the occurrence of ALF.

Cirrhosis is by far the biggest immediate cause of mortality from liver disease. **Bosch, Groszmann, and Shah**, all individuals who made seminal observations and contributed enormously to the successes in the field of portal hypertension, focus on how paradigm changes in disease pathogenesis are leading to further changes in the management of portal hypertension. Mortality rates from variceal bleeding have reduced by more than 5 times in the past 30 years. They suggest that the next horizons are to focus attention to intrahepatic resistance and angiogenesis as potential therapeutic targets. The article by **Arroyo, Moreau, Jalan, and Ginès,** all individuals who have helped define the syndrome, make a huge statement that '***the discovery that acute on chronic liver failure (ACLF) is a distinct syndrome will re-classify cirrhosis'***. They argue that ACLF is a complex syndrome, prevalent, affecting up to 30% of cirrhotic patients admitted to the hospital, is distinct from decompensated cirrhosis, has a distinct diagnostic and prognostic criteria and is associated with high rates of mortality. Pathophysiologically, the syndrome is characterized by systemic inflammation pointing to potentially new targets of therapy. The authors suggest that knowledge in ACLF is at a point where it is possible to perform informed clinical trials. European, American and Asian consortia have been formed to study this syndrome.

Hepatocellular carcinoma (HCC) is increasing at an astonishing rate and is one of the major causes of mortality in liver disease patients. The article by **Bruix, Han, Gores, Llovet, and Mazzaferro,** brings together the leaders in HCC from all over the world to address current issues, pointing to the fact that this is an heterogeneous disease that requires a personalized approach. They explore the huge advances that have been made to the lives of patients with HCC, with distinct options for cure of patients with resection, transplantation and radiological approaches. They point to the massive expansion of the knowledge in the field, the increasing interest from industry and a favorable regulatory environment as the key elements that will drive even more effective and focused approaches to treatment.

Liver transplantation has revolutionized the management of patients with liver failure but is limited by the availability of organs and the associated costs. As the liver has an amazing capacity to regenerate, temporary support with cells rather than a whole organ would suffice. Also, patients who are often transplanted for metabolic diseases can survive with cell

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Table 2. The top 10 cited original papers in the *Journal of Hepatology*; 1984–2014. Source of citations: Scopus. Courtesy, Joël Walicki; ***Journal of Hepatology*** Editorial office.

Authors	Title	Year of publication	No. of citations
Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, …, Thaler H	Histological grading and staging of chronic hepatitis	1995	2672
Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP	The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide	2006	713
Piccinino F, Sagnelli E, Pasquale G, Giusti G, Battocchia A, Bernardi M, …, Zivelonghi P	Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies	1986	629
Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, Rayón M, …, Wright TL	HCV-related fibrosis progression following liver transplantation: Increase in recent years	2000	567
Soto B, Sánchez-Quijano A, Rodrigo L, Olmo JAD, García-Bengoechea M, Hernández-Quero J, …, Lissen E	Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis	1997	539
Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J	Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C	2001	489
Colloredo G, Guido M, Sonzogni A, Leandro G	Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease	2003	459
Rubbia-Brandt L, Quadri R, Abid K, Giostra E, Malé P-J, Mentha G, …, Negro F	Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3	2000	423
Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, …, Makuuchi M	Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy	2003	420
Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, …, Tanikawa K	Therapeutic effects of restricted diet and exercise in obese patients with fatty liver	1997	410

transplantation rather than the whole organ. It is with this in mind that cell transplantation as an alternative to liver transplantation is being developed. **Forbes, Gupta, and Dhawan,** who have led the field of translational research in liver cell therapies provide an excellent update and explore the current evidence for various types of cell transplantation. They suggest that utilization of stem cells offers significant hope for producing suitable liver cells of clinical interest for transplantation. **Adams, Sanchez-Fueyo, and Samuel,** combine their very different expertise in clinical and experimental liver transplantation to explore the issues around inducing tolerance, which would reduce the need to immunosuppression with calcineurins. They provide an excellent overview of where we are and develop a roadmap to clinical translation of immune tolerance in liver transplantation.

The idea for this supplement was conceived and developed by the current and previous Editors or their representatives. I am therefore very grateful to **Prof. Roger Williams, Prof. Gustav Paumgartner, Prof. Vicente Arroyo, Prof. Pere Ginès, Prof. Massimo Colombo, and Prof. Didier Samuel** for their fantastic ideas and help in putting this supplement together. I would like to thank the EASL Governing Board and the Senior Editors of the current Editorial team for refining the ideas and supporting this endeavor. Of course, a huge vote of thanks is due to the many authors of the excellent articles in this supplement. We thought a lot about putting the leaders in individual fields to co-author articles understanding full well that this was going to be difficult given their individual lines of thought and their incredibly busy schedules. Therefore, I admire and acknowledge the enormous contribution of the Editorial team led by **Joël Walicki**, in producing this supplement. I invite you, the reader to celebrate 30 years of the *Journal of Hepatology* and enjoy this supplement. The *Journal of Hepatology* has come a long way from its humble beginnings in 1984, reaching its highest impact factor, 10.4, which is a fantastic achievement of the past Editors, Associate Editors, reviewers, authors and readers. In order to celebrate our most highly cited-authors, we have enumerated the highest cited 'original' papers published in the *Journal of Hepatology* in Table 2.

Finally, let us not forget the patients with liver disease. All the research we perform and publish are inspired by them, involves them and ultimately is for them!

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reference

[1] GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national levels of age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–171.