



A Summary of the 6th International Conference on Coagulation in Liver Disease: Discussion, Debate, Deliberations

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INTRODUCTION

Editor's Preface from Nahum Mendez Sanchez:

Below, the Editors of Annals of Hepatology provide a summary report from the 2015 multidisciplinary Coagulation in Liver Disease group meeting. This group which originated in 2005 is dedicated to issues of Coagulation, Hemostasis and Thrombosis in Liver Disease patients and includes members from diverse Specialties including representation from the fields of Hepatology, Hematology, Surgery, Anesthesiology, Pathology, Interventional Radiology, Laboratory Medicine, Transfusion Sciences and Blood Banking with a combined approach of basic and clinical Sciences. The aim of the symposium was to raise points of convergence of interest and research and to provide a forum to facilitate collaboration in order to advance the field.

SUMMARY

In October 2015, approximately 100 investigators and clinicians from around the world gathered in Charlottesville, Virginia (despite threatening weather from Hurricane Joaquin) to commemorate the 10th year of the Coagulation in Liver Disease group and to provide discussion, debate, and deliberations in this important aspect of liver disease. As a prelude to the upcoming October 6-7, 2017 meeting to be hosted by Francesco Violi at the University of Rome, the authors of this work aim to summarize some of the key aspects from the 2015 meeting of this multidisciplinary and

combined clinical and basic science group. The goal of the meeting was to consolidate information on recent advances in the field, provide a forum for the development of collaborative investigation, and to highlight key areas of debate such as hyperfibrinolysis in liver disease, controversies surrounding how to measure bleeding and thrombosis risk, how to define the role of thrombotic mechanisms in organ atrophy through parenchymal extinction, and the significance (or not) of portal vein thrombosis in cirrhosis were also discussed and debated.

The first of these meetings in 2005, also in Charlottesville, Virginia, was spurred by several key developments at that time including the seminal work by Italian investigators Armando Tripodi and Pier Mannucci from Milan, who demonstrated preserved thrombin generation in liver disease patients including even advanced cirrhosis,¹ the emergence of the cell based model of hemostasis mainly as a result of Uta Hedner's work in the development of recombinant activated factor VII (rFVIIa) at Novo Nordisk,² and an older but significant report regarding the potential role of thrombotic pathways in the development of organ atrophy in cirrhosis in a process that Ian Wanless termed 'parenchymal extinction'.³

These proceedings opened with a history of key developments in Hematology and the interactions between diseases of the liver and the hemostatic system which were recounted by Maureane Hoffman of Duke University and Adrian Reuben of the Medical University of South Carolina. Particularly notable points included recognition of the normal role of erythrocyte in clot integrity wherein

surface changes leads to formation of 'polyhedrocytes,' the packing of which, contribute to making the clot less permeable to water. Changes in erythrocyte phospholipid membrane composition could be especially relevant to this mechanism. From a more critical perspective, the almost immovable insinuation of the International Normalized Ratio (INR) into prophylactic therapy algorithms in cirrhosis despite overwhelming evidence of its irrelevance was also eloquently recounted in this section.

The first day of the meeting focused on aspects of bleeding in liver disease with discussion of the types and risk of bleeding in liver disease patients⁴ and centered around two debates: 1. 'Hyperfibrinolysis in Liver Disease' and 2. 'Measurement of Coagulopathy in Liver Disease.' In the first of these debates, Dick Rijken from Rotterdam in the Netherlands discussed the increased fibrinolytic capacity found in cirrhosis⁵ which can lead to premature clot dissolution, while Ton Lisman of Groningen in the Netherlands took a critical perspective of the ability to measure this process and cirrhosis-related changes in the fibrin molecule and questioned whether demonstrable hyperfibrinolysis was relevant to the potential efficacy of anti-fibrinolytics in cirrhosis.⁶ The authors conclude that the spectrum of changes seen in cirrhotic coagulopathy include clinical findings to suggest a hyperfibrinolytic process in some cases with diffuse, mucosal or delayed puncture wound bleeding, although the mechanisms and optimal measurement remain elusive (see below). We feel that this syndrome is identical to what was described many years ago by JH Joist as 'AICF' or accelerated intravascular coagulation and fibrinolysis.⁷

Aside from use in warfarin therapy or as a marker of vitamin K deficiency, the INR as a measure of bleeding risk in cirrhosis has repeatedly been shown to lack a physiological basis in cirrhosis, to correlate poorly with bleeding, and to have poor inter-laboratory reproducibility (based on its derivation as a test for vitamin K antagonists therapy).⁸⁻¹⁰ With these limitations in mind the second debate of day one between Susan Mallet of the Royal Free in the United Kingdom and Neeral Shah of University of Virginia focused on alternatives for bleeding risk stratification, including the possibility that no *ex vivo* test will accurately capture procedural bleeding risk, making it necessary to approach patients with a sound rescue plan rather than ineffective or potentially hazardous prophylactic measures. While fibrinogen levels and the platelet count are emerging as potentially useful measures of bleeding risk in cirrhosis^{11,12} and may therefore provide reasonable prophylactic targets, whole blood viscoelastic testing (TEG, ROTEM and sonorheometry) also appear to be useful in providing reassurance to proceduralists and thus decrease the use of potentially risky and unnecessary blood product use.¹³

The first day also included a section on newer concepts in coagulation from the basic science field including work from Nigel Key of the University of North Carolina discussing the pro- and anti-coagulant effects of microparticles ('extra-cellular vesicles'),¹⁴ Craig Jenne of the University of Calgary, Canada reviewing immune-mediated pathways of thrombosis in the liver¹⁵ and James Luyendyk from Michigan State University discussing the relationship between liver injury and intrahepatic coagulation.¹⁶ In addition, Cynthia Leveille-Webster from Tufts University in Boston presented an important perspective on liver disease related thrombotic complications from a veterinary medicine perspective.¹⁷ These discussions offered new insights into the basic mechanisms of thrombotic problems in liver disease and potentially important new therapeutic pathways. The first day concluded with lectures on the potential role of anti-coagulation therapy in patients cured of hepatitis C with the new agents, but left with residual cirrhosis from Zachary Henry of University of Virginia, a still unresolved field. The key note lecture for this meeting was delivered by Dominique Valla of Hôpital Beaujon, Clichy, France on the diagnosis and management of non-cirrhotic portal vein thrombosis – a related but distinct aspect of vascular liver disease.¹⁸

The focus of the second day of the conference was on liver-related thrombotic disease including Budd-Chiari syndrome¹⁹ and mechanisms of hypercoagulability in cirrhosis mediated by diminished anti-coagulant protein C to an extent which mimics congenital protein C deficiency and elevated procoagulant (endothelial-derived) factors VIII and von Willebrand factor.^{20,21} As a notable departure from past concepts, it was noted that current work indicates that these hypercoagulable conditions are actually accentuated in acute liver failure²² and metabolic syndrome associated fatty liver diseases, such as NASH.²³

The first debate of Day 2 was between two liver pathologists, Ian Wanless of Dalhousie University in Halifax, Nova Scotia and David Kleiner of the National Institutes of Health in Bethesda, Maryland who debated the evidence and significance of intrahepatic activation of hemostatic pathways and the histological grounds of 'parenchymal extinction'. The session was moderated by two other liver pathologists: Karolin Lackner of Graz, Austria and Yoshihiro Ikura of Osaka, Japan. Combined with the Basic Science evidence presented at the end of the first day, the authors conclude that the histological evidence is convincing that intrahepatic activation of thrombotic pathways at the small vessel level is a key event in the progression of cirrhosis to a decompensated state. We feel that it is a compelling mechanism underlying organ atrophy in cirrhosis and offers a potential sound basis for further study of anti-coagulant therapy in stable cirrhosis.²⁴

The final debate session of the meeting presented by Michael Englesbee of the University of Michigan and Patrick Northup of University of Virginia focused on cirrhosis-related PVT and whether this common occurrence is clinically relevant or represents only a marker of disease progression. The debate was preceded by perspectives on cirrhosis related PVT including the natural history and radiological diagnosis from Marco Senzolo of the University of Padua, Italy. There was a general consensus that PVT complicates technical aspects of liver transplantation and transplant listed patients who develop PVT warrant consideration for anti-coagulant therapy. The authors conclude that outside of this situation, the relative risk-benefit of anti-coagulant therapy remains unresolved and that prophylactic therapy based on a promising study several years ago which demonstrated a remarkably reduced rate of clinical progression warrants much more additional work.²⁴

The field of coagulation in liver disease has seen remarkable growth over the last 10 years. Through advances in basic science and clinical research our understanding of the mechanisms of bleeding and thrombosis has dramatically improved. The notion of a re-balanced coagulation system in cirrhosis is now firmly supported by *in vitro* studies and clinical data. With growing interest in this field, the need for collaborative studies and cooperation is now paramount. Past conferences on Coagulation in Liver Disease (www.coagulationinliverdisease.org) have produced invaluable relationships and collaborations. With this in mind, we greatly anticipate the next conference October 6 and 7, 2017 hosted by Francesco Violi at the University of Rome, Italy. The theme of this conference will be to refine concepts in the field and build bridges over gaps in our current knowledge. The future of this field is exciting as we explore a promising frontier with potential discoveries in important disease mechanisms and therapies that could offer significant advances in the care of liver disease patients.

REFERENCES

1. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology* 2005; 41: 553-8.
2. Hedner U. Recombinant activated factor VII: 30 years of research and innovation. *Blood Reviews* 2015; 29: S4-S8.
3. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. *Hepatology* 1995; 21: 1238-47.
4. Giannini EG, Greco A, Marengo S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. *Clin Gastroenterol Hepatol* 2010; 8: 899-902; quiz e109.
5. Rijken DC, Kock EL, Guimaraes AH, Talens S, Darwish Murad S, Janssen HL, Leebeek FW. Evidence for an enhanced fibrinolytic capacity in cirrhosis as measured with two different global fibrinolysis tests. *Journal of Thrombosis and Haemostasis. JTH* 2012; 10: 2116-22.
6. Hugenholtz GC, Macrae F, Adelmeijer J, Dulfer S, Porte RJ, Lisman T, Ariens RA. Procoagulant changes in fibrin clot structure in patients with cirrhosis are associated with oxidative modifications of fibrinogen. *Journal of thrombosis and haemostasis. JTH* 2016; 14: 1054-66.
7. Joist JH. AICF and DIC in liver cirrhosis: expressions of a hypercoagulable state. *Am J Gastroenterol* 1999; 94: 2801-3.
8. Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for endstage liver disease (MELD) based on selection of clinical laboratory. *American Journal of Transplantation. Official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2007; 7: 1624-28.
9. Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. *Clin Gastroenterol Hepatol* 2013; 11: 1064-74.
10. Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, Ariens RA, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. *Hepatology* 2006; 44: 1039-46.
11. Drolz A, Horvath T, Roedel K, Rutter K, Stauffer K, Kneidinger N, et al. Coagulation Parameters and Major Bleeding in Critically Ill Patients With Cirrhosis. *Hepatology* 2016; 64: 556-68.
12. Tripodi A, Caldwell SH, Hoffman M, Trotter JF, Sanyal AJ. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. *Alimentary pharmacology & therapeutics* 2007; 26: 141-8.
13. De Pietri L, Bianchini M, Montalti R, De Maria N, Di Maira T, Begliomini B, Gerunda GE, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. *Hepatology* 2016; 63: 566-73.
14. Lemoinne S, Thabut D, Housset C, Moreau R, Valla D, Boulanger CM, Rautou PE. The emerging roles of microvesicles in liver diseases. *Nature Reviews Gastroenterology & Hepatology* 2014; 11: 350-61.
15. Jenne CN, Kuberski P. Immune surveillance by the liver. *Nature Immunology* 2013; 14: 996-1006.
16. Kopec AK, Joshi N, Luyendyk JP. Role of hemostatic factors in hepatic injury and disease: animal models de-liver. *Journal of Thrombosis and Haemostasis. JTH* 2016; 14: 1337-49.
17. Kavanagh C, Shaw S, Webster CR. Coagulation in hepatobiliary disease. *Journal of Veterinary Emergency and Critical Care* 2011; 21: 589-604.
18. Valla D. Splanchnic Vein Thrombosis. *Seminars in thrombosis and hemostasis* 2015; 41: 494-502.
19. Rautou PE, Douarin L, Denninger MH, Escolano S, Lebec D, Moreau R, Vidaud M, et al. Bleeding in patients with Budd-Chiari syndrome. *J Hepatol* 2011; 54: 56-63.
20. Lisman T, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, de Groot PG, Leebeek FW. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology* 2006; 44: 53-61.
21. Tripodi A, Primignani M, Lemma L, Chantarangkul V, Dell'Era A, Iannuzzi F, Aghemo A, et al. Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. *Hepatology* 2010; 52: 249-55.
22. Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, Ibrahim A, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *J Hepatol* 2012; 56: 129-36.

23. Northup PG, Argo CK, Shah N, Caldwell SH. Hypercoagulation and thrombophilia in nonalcoholic fatty liver disease: mechanisms, human evidence, therapeutic implications, and preventive implications. *Semin Liver Dis* 2012; 32: 39-48.
24. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012; 143: 1253-60 e1251-4.

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