THE COAGULOPATHY OF CHRONIC LIVER DISEASE

P.M. Mannucci

IRCCS Ca’ Granda Foundation Maggiore Hospital and University of Milan, Italy
AGENDA

• The past as prologue
• Progress of knowledge on hemostasis in chronic liver disease (CLD)
  • Coagulation
  • Platelet function
  • Fibrinolysis
• The role of hemostatic drugs in bleeding patients with CLD
Severe liver disease not uncommonly terminates with a severe bleeding state due to the gross deficiency of many coagulation factors... In general bleeding is treated with replacement therapy...
Acquired coagulation disorders

Peter W Collins¹, Jecko Thachil² and Cheng-Hock Toh²

¹Cardiff University School of Medicine, University Hospital of Wales, Cardiff, UK
²School of Clinical Sciences, University of Liverpool, Liverpool, UK

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Recent progress of knowledge on hemostasis and chronic liver disease
COAGULATION
Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests* and low plasma levels of coagulation factors

Tripodi et al, Hepatology 2005;41:553–558

* Prothrombin time and activated partial thromboplastin time (PT, APTT)
Thrombin generation with thrombomodulin treatment.
PLATELET NUMBER AND FUNCTION
Elevated levels of von Willebrand factor in cirrhosis support normal platelet adhesion

Lisman et al, Hepatology 2006; 44: 53-61
A GLOBAL PLATELET FUNCTION TEST

Platelet adhesion, %

Control plt/control plasma  cirrhosis plt/cirrhosis plasma
FIBRINOLYSIS
Thrombin-activatable fibrinolysis inhibitor (TAFI) deficiency in cirrhosis is not associated with increased plasma fibrinolysis

Lisman et al, Gastroenterology 2001; 121: 131
A GLOBAL FIBRINOLYSIS ASSAY

Clot lysis time (min)

Control A B C

Child
Hemostasis (coagulation, platelet function, fibrinolysis) is not abnormal in stable chronic liver disease when measured with global tests (reflecting the function of both activators and inhibitors of hemostasis)

Tripodi and Mannucci. NEJM 2011; 365:147-56
Normal situation-Hemostatic balance

Thrombophilia-Hypercoagulability

Hemophilia-Hypocoagulability

Liver disease-Hemostatic rebalance

Normal liver

pro-hemostatic factors

anti-hemostatic factors

Cirrhotic liver

pro-hemostatic factors

anti-hemostatic factors
The Coagulopathy of Chronic Liver Disease

Armando Tripodi, Ph.D., and Pier Mannuccio Mannucci, M.D.
Abnormal hemostasis, reflected by abnormal laboratory tests, causes a bleeding tendency in patients with chronic liver disease.

The demise of this paradigm questions the usefulness of hemostatic agents in the prevention and treatment of bleeding in patients with chronic liver disease.

Tripodi and Mannucci. NEJM 2011; 365:147-56
A role for hemostatic agents in chronic liver disease?
No agent acting on hemostasis is ever mentioned in this comprehensive narrative review written by established authorities in the field.
No agent acting on hemostasis is ever mentioned in this comprehensive narrative review written by established authorities in the field.
YET, A RECENT QUESTION TO ME FROM A PRACTICING ANESTHESIOLOGIST…

…One question crucially important to my specialty but not addressed is how liver disease patients with exsanguinating hemorrhage (variceal bleeding) should be reversed, or if reversal is even indicated….
MAIN HEMOSTATIC AGENTS AND THEIR ACTION SITES IN LIVER DISEASE

- Vitamin K
- Fresh Frozen Plasma or PCC
- Platelet concentrates
- Thrombopoietin mimetics
- Fibrinogen concentrates
- Anti-fibrinolytics

Coagulation Cascade:
- Fibrinogen → Fibrin
- Coagulation Factors
- Liver

Platelets
- rFVIIa
- Plasmin
- Fibrin Degradation Products
HEMOSTATIC AGENTS

Vitamin K

- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates
- Red cell concentrates
- Antifibrinolytic agents (aprotinin tranexamic acid)
HEMOSTATIC AGENTS

- Vitamin K
- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates
- Red cell concentrates
- Antifibrinolytic agents (aprotinin tranexamic acid)
CORRECTION OF ABNORMAL COAGULATION IN CHRONIC LIVER DISEASE BY COMBINED USE OF FRESH-FROZEN PLASMA AND PROTHROMBIN COMPLEX CONCENTRATES

P.M. Mannucci, Franca Franchi, N Dioguardi

3rd Department of Clinical Medicine, University of Milan and Haemophilia and Thrombosis Centre Angelo Bianchi Bonomi, Milan, Italy.
HEMOSTATIC AGENTS

- Vitamin K
- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates
- Red cell concentrates
- Antifibrinolytic agents (aprotinin tranexamic acid)
PROTON TRIAL
Background and aim

To investigate the hemostatic efficacy and safety of Cofact (4 factor PCC) in reduction of blood requirements and blood loss in patients with cirrhosis undergoing liver transplantation

Cofact has theoretical important advantages:

- Low volume: no aggravation of portal hypertension.
- Balanced supply of both pro- and anticoagulants
HEMOSTATIC AGENTS

- Vitamin K
- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates
- Red cell concentrates
- Antifibrinolytic agents (aprotinin tranexamic acid)
# Poor Clinical Efficacy of Recombinant Activated FVII to Stop Bleeding in Cirrhosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Clinical Setting</th>
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<tbody>
<tr>
<td>Bosch J, et al.</td>
<td>GI bleeding</td>
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<td>Gastroenterology 2004;127:1123</td>
<td></td>
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<tr>
<td>Lodge JP, et al.</td>
<td>Liver transplantation</td>
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<tr>
<td>Liver Transplantation 2005;11:973</td>
<td></td>
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<tr>
<td>Shao YG, et al.</td>
<td>Partial hepatectomy</td>
</tr>
<tr>
<td>Lodge JP, et al.</td>
<td>Major liver resection</td>
</tr>
<tr>
<td>Anesthesiology 2005;102:269</td>
<td></td>
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<tr>
<td>Bosch J, et al.</td>
<td>GI bleeding</td>
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<tr>
<td>Hepatology 2008; 47:1604</td>
<td></td>
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</tbody>
</table>
HEMOSTATIC AGENTS

- Vitamin K
- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates
- Red cell concentrates
- Antifibrinolytic agents (aprotinin tranexamic acid)
HEMOSTATIC AGENTS

- Vitamin K
- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates/thrombopoiesis enhancers
- Red cell concentrates
- Antifibrinolytic agents (aprotinin tranexamic acid)
20. Platelet transfusion should be considered when levels are less than 50,000-60,000/mL (this applies whether one is attempting biopsy transcutaneously or transvenously) (Class I, Level C).

21. The use of prophylactic or rescue strategies such as plasma, fibrinolysis inhibitors, or recombinant factors should be considered in specific situations, although their effectiveness remains to be established (Class IIa, Level C).
Eltrombopag before Procedures in Patients with Cirrhosis and Thrombocytopenia

Nezam H. Afdhal, M.D., Edoardo G. Giannini, M.D., Ph.D., Ghias Tayyab, M.D., Aftab Mohsin, M.D., Jin-Woo Lee, M.D., Ph.D., Angelo Andriulli, M.D., Lennox Jeffers, M.D., John McHutchison, M.D., Pei-Jer Chen, M.D., Ph.D., Kwang-Hyub Han, M.D., Fiona Campbell, B.Sc., Denise Hyde, Ph.D., Andres Brainsky, M.D., and Dickens Theodore, M.D., M.P.H., for the ELEVATE Study Group*
HEMOSTATIC AGENTS

- Vitamin K
- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates
- Red cell concentrates
- Antifibrinolytic agents (aprotinin tranexamic acid)
CONCLUSIONS: the probability of survival was significantly higher in the subgroups of patients with cirrhosis and Child-Puget class A and B disease who chose a restrictive transfusion approach (hazard ratio 0.30, 95%, CI 0.11-0.85) but not in those in class C.
HEMOSTATIC AGENTS

- Vitamin K
- Fresh frozen plasma
- Prothrombin complex concentrates (PCC)
- Recombinant factor VIIa (rFVIIa)
- Fibrinogen concentrates
- Platelet concentrates
- Red cell concentrates

Antifibrinolytic agents (aprotinin, tranexamic acid)
Liver transplantation and fibrinolysis

Hyperfibrinolysis by tPA release in some, but not all patients


<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>Confidence Interval</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Aprotinin use</td>
<td>0.40</td>
<td>0.23-0.71</td>
<td>0.002</td>
</tr>
<tr>
<td>Recipient age</td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female recipient</td>
<td>2.11</td>
<td>1.21-3.66</td>
<td>0.008</td>
</tr>
<tr>
<td>MELD score</td>
<td>1.10</td>
<td>1.06-1.14</td>
<td>&lt;0.001</td>
</tr>
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</table>
Effect of removal of aprotinin from the market

Increase in blood loss after 2007?
A Cochrane meta-analysis found that TA reduced mortality vs placebo (RR 0.61, 0.42 to 0.89) in upper GI bleeding.

However, there was no clear effect of TA in studies using modern endoscopic therapies and/or proton pump inhibitors.

Gluud LL, et al 2012; Cochrane Database of Systematic Reviews (issue 1)
RECOMMENDATIONS FOR BLEEDING CONTROL IN CLD .1

• Limited concern for abnormal PT and APTT in the setting of CLD

• Control any infection that disrupts the unstable hemostasis rebalance

• Control uremia to prevent further platelet dysfunction

• Replacement with red cell transfusion: prefer a restrictive strategy (7 g Hb), to avoid deterioration of portal hypertension
RECOMMENDATIONS FOR BLEEDING CONTROL IN CLD .2

• Consider fibrinolysis inhibitors such as aprotinin and tranexamic acid to reduce blood loss and transfusion requirement in liver transplantation

• Consider the same fibrinolysis inhibitors in the setting of active bleeding or as pre-procedural therapy
A. Tripodi

M. Colombo, M Primignani, F. Salerno, A. Dell’Era, F. Fabris M. Cazzaniga, R. de Franchis
(Patient care)

M. Clerici, D. Asti
(Laboratory Testing)

V. Chantarangkul
(Supervisor & Data manager)
Thank you for listening