Speciális helyzetek I. – Cirrhotikus beteg, urémiás beteg

Fazakas János, Smudla Anikó
Semmelweis Egyetem, Transzplantációs és Sebészeti Klinika
Hemostasis in Liver Disease

Hemostatic changes in patients with liver cirrhosis

Coagulopathy in liver disease is more of a myth than a reality.
Hemostasis in Liver Disease

Normal patient

Patient with liver disease

Bleeding

Thrombosis

Promoting bleeding

- thrombocytopenia + function defects
- enhanced NO + PGI₂ production
- low level of II, V, VII, IX, X, XI factors
- dysfibrinogenemia
- low levels of α₂-antiplasmin, XIII factor
- elevated tPA levels

Primary hemostasis

Secondary hemostasis

Fibrinolysis

Delicate rebalance

Promoting thrombosis

- elevated levels of VWF
- decreased levels of ADAMTS (VWF protease)
- elevated levels of VIII factor
- decreased levels of prot C, prot S, AT III
- decreased levels of heparin cofactors
- low levels of plasminogen

Current Opinion in Organ Transplantation 2008, 13: 298-303
Platelet Function in Liver Disease

Platelets and the coagulation balance of cirrhotic patients
Cirrhosis: a dynamic hemostatic balance = rebalance... rebalance... rebalance... rebalance...

THROMBOSIS

Clotting

Bleeding

HEMORRHAGE

Cirrhosis pts. or „...They...”

Normal pts. or „...We...”
Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests

PLT: $198 \times 10^9$ versus $80 \times 10^9$

P<.001

N.S.

Table 3. Endogenous Thrombin Potential Values for Patients and Controls in Platelet-Free Plasma

<table>
<thead>
<tr>
<th></th>
<th>Endogenous Thrombin Potential (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Thrombomodulin</td>
</tr>
<tr>
<td>Patients (n = 87)</td>
<td>1,398 (630-2,517)</td>
</tr>
<tr>
<td>Controls (n = 62)</td>
<td>1,872 (982-2,682)</td>
</tr>
<tr>
<td>P value (patients vs. controls)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE. All values other than P values are expressed as the median (range).

"severe thrombocytopenia may limit thrombin generation in patients with cirrhosis"

Coagulation Cascade and Liver Disease

Maximum amplitude of clot formation according to the number of SIRS

Inflammation and a dynamic hemostatic balance

Hyperfibrinolysis in Liver Disease

Figure 1. Schematic overview of the fibrinolytic system

http://www.mjhid.org/article/view/5283
Dynamics of coagulation – TEG; TAG

Thromboelastogram
whole blood hemostasis test

Coagulation factors
Anticoagulants
FDPs

Fibrinolytic enzymes
Fibrinolysis inhibitors
tPA, F XIII

Fibrinogen
Platelets
F XIII

Multiplate
platelet function
analysis on impedance
aggregometry

Fibrinogen
Platelets
F XIII
Coagulation in Liver Disease: A Guide for the Clinician

Primary Hemostasis
Activated platelets and thrombin burst. Measured by platelet count, WVF, platelet function analysis, and bleeding time.

Coagulation: Intrinsic and Extrinsic Pathways
Builds the fibrin mesh. Measured by PT/INR, aPTT and specific factor levels.

Fibrinolysis
Controls propagation of the fibrin mesh and dissolves clot when hemostasis is achieved. Measured by fibrinogen level, protein C and S levels, antithrombin III level, plasminogen activator inhibitor levels (PAI-1, TAFI).

Estimated Thrombin Potential
Measure of ability to generate fibrin mesh. Dependent on platelet levels, platelet function, procoagulant levels, and antithrombin/protein C activity.

Whole Blood Clotting Assays
Thromboelastography, ROTEM, sonorheometry. Assessment of overall hemostasis activity including primary hemostasis, coagulation, and fibrinolysis.
Intenzív osztály: Májbeteg; Thr: 29 G/L

Thr: 29 G/L → DDAVP: 0,3 mg/kg vagy 5-10 ml/kg Thr
INR<sub>kva</sub> versus INR<sub>liver</sub>

"WHO standard" plasmas from patients on vitamin K antagonists

Calibration with plasma from patients with cirrhosis

INR<sub>kva</sub>
\[\Delta A-B = 0.3\]
\[\Delta C = 0.5\]
"healthy test"

INR<sub>liver</sub>
\[\Delta A-B = 0.01\]
\[\Delta C = 0.02\]

Assessment of validity of INR system for patients with liver disease associated with viral hepatitis

Fig. 2 Coagulant activities of factors II, V, VII, and X for 15 patients with liver disease and 15 patients on warfarin. *LD* liver disease, *OAC* oral anticoagulant.
# Management of Coagulopathy in Patients with Decompensated Liver Cirrhosis

Table 1: Therapeutic options in coagulopathy in decompensated liver cirrhosis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Utility in specific situations</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell transfusion</td>
<td>Bleeding patients</td>
<td>Transfusion should be minimum, not allowing Hb to exceed 8 to 9 mg%</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Every patient</td>
<td>May not be useful if patient has no deficiency</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Questionable in bleeding patients</td>
<td>May be used in bleeding patients when volume expansion is not a concern</td>
</tr>
<tr>
<td>Platelets</td>
<td>Count less than 50,000</td>
<td>Limited data</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>In bleeding patients</td>
<td>Limited data</td>
</tr>
<tr>
<td>Prothrombin complex concentrate</td>
<td>In bleeding patients</td>
<td>Limited data</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>In bleeding patients</td>
<td>Efficacy unproved</td>
</tr>
<tr>
<td>Aprotinin, tranexamine acid, and epsilon amino caprioric acid</td>
<td>Patients with hypofibrinogenemia Fibrinogen less than 100/dL</td>
<td>Can induce thrombosis</td>
</tr>
<tr>
<td>Recombinant factor VII</td>
<td>In placing ICP devices, bleeding after surgery, massive variceal bleed</td>
<td>Can induce thrombosis</td>
</tr>
<tr>
<td>Topical agents—cyanoacrylates, fibrin glue, and thrombin</td>
<td>Topical haemostasis and localized bleeding</td>
<td>Extremely expensive and limited data</td>
</tr>
<tr>
<td>Reduction in the portal pressure, maintaining low CVP by volume contraction (phlebotomy/diuresis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical techniques—vascular clamping, ultrasonic/hydrojet dissectors, and thermal techniques (aarten plasma coagulator, radio frequency ablators)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thrombosis and hemorrhage risk associated with extrahepatic surgery.
Prevention and Treatment Guidelines for Bleeding During Liver Surgery

Thrombosis and hemorrhage risk associated hepatic surgery

Adapted from Levy, Anesth Analg
Prevention and Treatment Guidelines for Bleeding During Liver Surgery

Thrombosis and hemorrhage risk associated hepatic surgery

A. Siniscalchi / Liver Transpl 10 (2004) 1144 -1149
Prevention and Treatment Guidelines for Bleeding During Liver Surgery

Thrombosis and hemorrhage risk associated hepatic surgery

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dissection:</strong></td>
<td><strong>Parenchyma transection:</strong></td>
<td><strong>Resection surface:</strong></td>
</tr>
<tr>
<td>- Correct anatomical ID</td>
<td>- Technique</td>
<td>- Hemostasis</td>
</tr>
<tr>
<td>- Blood products:</td>
<td>- vasc clamping</td>
<td>- Biliostasis</td>
</tr>
<tr>
<td>Platelets, FFP, etc.</td>
<td>- use of dissection devices</td>
<td>- Topical agents</td>
</tr>
<tr>
<td>- Minor blood loss</td>
<td>- Lower CVP</td>
<td>- Antifibrinolytics</td>
</tr>
<tr>
<td></td>
<td>- vol Contraction</td>
<td>- rFVIIa</td>
</tr>
<tr>
<td></td>
<td>- vasodilatation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- diuresis</td>
<td></td>
</tr>
</tbody>
</table>

Amount of blood loss
Map of hemostasis
during liver transplantation

Endogeneous heparinoids

Prepare for anhepatic phase
Optimize all function
ESDL etiology and coagulation profile

**PLT, INR, APTI, coagulation factors**
- Plasminogen, $t\,PA$, PAI 1, PAI 2

**ATIII, protein S, protein C**
- $\alpha_2$-antiplasmin, $\alpha_2$-macroglobulin

**Risk of thrombosis**
- Budd Chiari syndr., POPH, glycogen storage disease, AIH, PSC, PBC

**Risk of bleeding**
- Wilson’s d., HCV, HBV, ALD, hemochromatosis

**Multiplate TAG**

**Reperfusion**
- $R, K$ time ↓
- $MA / MCF$ ↑

**Normothermia**
- fibrinogen, PCC, platelets, FFP

**Hypothermia**
- fibrinogen, PCC, platelets, FFP

**More AT III (±Na Heparin) than fibrinogen, PCC, platelets, FFP**

**Yes**
Fibrinogen < 1 g/l  V < 20%  VII < 20%  PLT < 50,000

„initiation – amplification - propagation”

- $G_{2a/3b}$ receptor function
- fibrin polymerization trouble

- vonW syndr.
- factor dilution
- VIII ↓,

adapted from Görlinger

G2a/3b receptor function

Anti-coagulation

Factors

surgical hemostasis = factor XIV

TEG, fibrinolysis, TXA?

pH > 7.2  SeCa > 1  HGB > 100 g/l  T > 35
Systemic Manifestations of Acute Liver Failure

- Hepatic encephalopathy
- Brain edema
- Intracranial Hypertension
- Acute lung injury
- Adult Respiratory Distress Syndrome
- Cardiovascular collapse
- Endothelial dysfunction
- Immunoparesis
- Neutrophil dysfunction
- Systemic Inflammatory Response
- Muscle catabolism
- Renal Dysfunction
- Adrenal insufficiency
- Portal Hypertension
- Pancreatitis
- Ileus
Paradoxical and balanced coagulation state in patients with ALF

Acute liver failure

Prothrombotic

Prohemorrhagic

↑ Levels of VW F
↑ Levels of FVIII
↓↓ Levels of natural anticoagulants
↓ Levels of plasminogen

↓↓ Levels of coagulation factors
↑↑ Production of NO, prostacyclin
↓ Platelet count
Dysfibrinogenemia
Hemostasis in acute liver and kidney failure: nothing is as it seems

- Levels of FVIII
- Levels of natural anticoagulants
- Levels of plasminogen
- Levels of VWF
- Levels of tissue factor
- Level of microparticle activity
- Thrombin generation

- Levels of coagulation factors
- Production of NO, prostacyclin
- Platelet count
- Dysfibrinogenemia
- Platelet dysfunction

Reduced procoagulants and anticoagulants at admission to ICU with ALF
### Relative changes in thrombin generation parameters of ALF patients compared to healthy controls at admission

<table>
<thead>
<tr>
<th>TG parameters</th>
<th>Median + IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETP (nM.min)</td>
<td>Healthy controls: 1602 (1289-1891)</td>
</tr>
<tr>
<td>ETP + P (nM.min)</td>
<td>488 (300-572)</td>
</tr>
<tr>
<td>ETP%</td>
<td>29 (22-36)</td>
</tr>
<tr>
<td>Lag-time (sec)</td>
<td>2.5 (2.3-2.8)</td>
</tr>
<tr>
<td>Time-to-peak (min)</td>
<td>5.8 (5.2-6.1)</td>
</tr>
<tr>
<td>Peak height (nM)</td>
<td>278 (221-319)</td>
</tr>
<tr>
<td>Slope (velocity index) nM.min</td>
<td>91 (69-110)</td>
</tr>
<tr>
<td>Microparticles (PPL assay) sec</td>
<td>68 (55-73)</td>
</tr>
<tr>
<td>Microparticles (activity assay) nM</td>
<td>4.0 (3.2-5.3)</td>
</tr>
</tbody>
</table>

**ALF:** no correlation between PT/PTR and thrombin generation

1. Endogenous thrombin potential lower (total amount and peak as well)
2. Relative protein C deficiency in ALF patients, in the presence of Protac ETP
3. ALF pts generated thrombin faster

Journal of Hepatology 2012 vol. 57 j 780–786
Correlation between fibrinogen and TEG native versus functional fibrinogen

Journal of Hepatology 2012 vol. 57 j 780–786
Urémiás beteg

- HD, CAPD, urémia (preHD vagy 2 HD között)
- Na-heparin, LMWH, citrát, kumarin
## Hemostasis in chronic renal failure

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>CAPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>F II activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>F VII activity</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>FVIII activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>F IX activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>F X activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>F XII activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Protein C activity</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Protein S activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>antithrombin</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>vWF</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>thrombomodulin</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TF</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TFPI</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>F1+2</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TAT</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PAP</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>t-PA</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>PAI-1</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>TAFI</td>
<td>↔</td>
<td>↑</td>
</tr>
</tbody>
</table>
Urémiás beteg

- HD, CAPD, urémia (preHD vagy 2 HD között)
- Na-heparin, LMWH, citrát, kumarin
Venous Thromboembolism in Patients with Renal Insufficiency: Findings from the RIETE Registry

**Table 3**  Multivariate Analysis on the Risk of Developing Fatal Pulmonary Embolism

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic PE</td>
<td>17 (8.8-34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CrCl &gt; 60 mL/min</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>CrCl 30-60 mL/min</td>
<td>2.0 (1.2-3.4)</td>
<td>.008</td>
</tr>
<tr>
<td><strong>CrCl &lt; 30 mL/min</strong></td>
<td>5.2 (3.4-7.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Table 5**  Multivariate Analysis on the Risk of Developing Fatal Bleeding

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobility ≥ 4 d</td>
<td>3.3 (1.5-7.3)</td>
<td>.003</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.7 (1.2-6.0)</td>
<td>.015</td>
</tr>
<tr>
<td>Renal function</td>
<td>-</td>
<td>.002</td>
</tr>
<tr>
<td>CrCL &gt; 60 mL/min</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>CrCl 30-60 mL/min</td>
<td>1.4 (0.3-5.9)</td>
<td>.677</td>
</tr>
<tr>
<td><strong>CrCl &lt; 30 mL/min</strong></td>
<td>5.0 (2.0-12)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CrCl = creatinine clearance; CI = confidence interval.

**CONCLUSIONS:** Patients with VTE who have renal insufficiency had an increased incidence of both fatal PE and fatal bleeding, but the risk of fatal PE far exceeded that of fatal bleeding. Our data support the use of full-dose anticoagulant therapy, even in patients with a CrCl less than 30 mL/min. © 2006 Elsevier Inc. All rights reserved.
Hypercoagulability in chronic kidney disease is associated with coagulation activation but not endothelial function

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Markers of the Tissue Factor Pathway, Natural Inhibitors and Thrombin Generation in Healthy Controls and Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF (pg/mL)</td>
<td>HC 101 ± 114</td>
</tr>
<tr>
<td>TFPI (U/mL)</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>FX (%)</td>
<td>148 ± 42</td>
</tr>
<tr>
<td>FVIIc (%)</td>
<td>113 ± 11</td>
</tr>
<tr>
<td>F₁₋₂ (nmol/L)</td>
<td>1.3 (1.0–1.5)</td>
</tr>
<tr>
<td>TAT (µg/L)</td>
<td>3.0 (2.1–4.2)</td>
</tr>
<tr>
<td>PC (%)</td>
<td>93 ± 12</td>
</tr>
<tr>
<td>PSt (%)</td>
<td>98 ± 19</td>
</tr>
<tr>
<td>PSf (%)</td>
<td>100 ± 29</td>
</tr>
<tr>
<td>PSf/PSt</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>ATIII (%)</td>
<td>110 ± 31</td>
</tr>
</tbody>
</table>
Urémiás beteg

- HD, CAPD, urémia (preHD vagy 2 HD között)
- Na-heparin, LMWH, citrát, kumarin
# Uremic Bleeding: Pathophysiology, Diagnosis, and Management

## Table 1. Clinical Presentations of Uremic Bleeding

- Petechiae, purpura, ecchymoses
- Epistaxis
- **Bleeding after invasive procedures** (e.g., surgery, catheter placement, biopsy)
- Hemorrhagic pericarditis (e.g., pericardial tamponade)
- Hemorrhagic pleural effusion
- **Gastrointestinal hemorrhage**
- Intracranial bleeding (e.g., from a subdural hematoma or subarachnoid hemorrhage)
- **Retroperitoneal bleeding** (spontaneous or occurring after invasive radiology)
- Spontaneous subcapsular hematoma of the liver
- Ocular hemorrhage
- Uterine hemorrhage

*Arranged in approximate order of frequency.

## Table 2. Factors Involved in the Uremic Bleeding Tendency

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors related to the vessel wall</strong></td>
<td>Decreased production of the largest multimers of von Willebrand's factor</td>
</tr>
<tr>
<td></td>
<td>Enhanced nitric oxide production</td>
</tr>
<tr>
<td></td>
<td>Enhanced prostacyclin production</td>
</tr>
<tr>
<td><strong>Factors related to platelets</strong></td>
<td>Abnormal mobilization of calcium ions in platelets</td>
</tr>
<tr>
<td></td>
<td>Defective activation of glycoprotein Iib-Illa receptors</td>
</tr>
<tr>
<td></td>
<td>Defective cyclooxygenase activity (reduced ability to generate thromboxane A2)</td>
</tr>
<tr>
<td></td>
<td>High levels of cyclic adenosine monophosphate</td>
</tr>
<tr>
<td><strong>Factors related to the blood</strong></td>
<td>Low levels of serotonin and adenosine diphosphate</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Altered blood rheology (i.e., deranged radial transport of platelets)</td>
</tr>
<tr>
<td></td>
<td>Altered transfer of adenosine diphosphate from erythrocytes to platelets</td>
</tr>
<tr>
<td></td>
<td>Uremic toxins (e.g., guanidinosuccinic acid, phenol, phenolic acid, urea)</td>
</tr>
</tbody>
</table>
Therapies for uremic bleeding

- **HD-CAPD**
  - Toxin removal $\rightarrow$ Platelet function improve

- **Anemia correction: RBC or rhEPO**
  - Static plasma and Platelets

- **DDAVP**
  - $0.3 \, \mu g/kg \rightarrow vWF$ release↑ for 4-8 hours

- **Conjugated estrogen**
  - GI bleeding, Intracranial bleeding
  - $25 \, mg$ per oral $\rightarrow$ normal BT 3-10 days

- **Platelet transfusion**

- **TXA only in acute setting**
Management of severe perioperative bleeding
Guidelines from the European Society of Anaesthesiology

Coagulopathy and renal disease

Point-of-care prothrombin time measurement is recommended for the treatment of bleeding in uremic patients with chronic kidney disease. We suggest that desmopressin should be used in uraemia. 2C

We suggest that desmopressin should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. 2C

There is no evidence to support use of rFVIIa in this setting.

Amikor POC eszköz nélkül nem megy...
„ne csak a számokat kezeljük”