Hemostasis and Thrombosis in Cirrhotic Patients

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Nothing to disclose
Hemostasis and Thrombosis in Cirrhotic Patients

1. Cirrhosis could be a prothrombotic state
2. Coagulation activation is a fibrogenic factor
3. HVT & PVT associated with cirrhosis severity
4. PVT constitutes a limitation to LTx
5. A strengthening rationale for anticoagulation

HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis
Cirrhosis could be a prothrombotic state

- Coagulation imbalance in plasma
- Increased risk of venous thrombosis
- Bleeding related to mechanical factors or associated diseases
- Not reflected by usual screening tests
Tissue

Extracellular Matrix

Endothelium

Blood
Tissue

Cell

Tissue Factor

FVIIa

FVIII

FvW

FVIII

Platelets

Fibrin

Thrombin

FDP
Thrombocytopenia and Cirrhosis

- Splenic sequestration
- Decreased survival (platelet bound IgG)
- Inappropriate thrombopoiesis/thrombopoietin
- Altered platelet function

Lisman, Hepatology 2006
Thrombocytopenia and Cirrhosis

- Splenic sequestration
- Decreased survival (platelet bound IgG)
- Inappropriate thrombopoiesis/thrombopoietin
- Altered platelet function

Increased factor VIII and vW factor
No impairment in hemostasis when > 50,000/µL

Lisman, Hepatology 2006
Thrombocytopenia and Cirrhosis

When Platelets > 30,000/µL

- Not a risk factor for gastrointestinal bleeding
- In index of the severity of liver disease
- Increased risk of portal vein thrombosis with Eltrombopag (ELEVATE study)

Tissue

Cell

Tissue Factor

FVIIa

Fibrin

Platelets

FVIII

FvW

FDP

Thrombin
Coagulation in Cirrhosis

- Tissue factor increased
- Coagulation factor VIII increased
- Other coagulation factors decreased
- Clearance of activated factors decreased
- Coagulation inhibitors decreased
Coagulation Inhibitors in Cirrhosis

Child-Pugh

<table>
<thead>
<tr>
<th>Protein C</th>
<th>Protein S</th>
<th>Antithrombin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

Coagulation in Cirrhosis

- Tissue factor increased
- Coagulation factor VIII increased
- Other coagulation factors decreased
- Clearance of activated factors decreased
- Coagulation inhibitors decreased

Increased thrombin generation potential in plasma
Increased resistance to thrombomodulin in plasma

Cirrhosis could be prothrombotic state

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Coagulation in Cirrhosis

No benefit from recombinant activated Factor VII in patients with bleeding esophageal varices

Cirrhosis could be a prothrombotic state

- Coagulation imbalance in plasma
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The exception of hyperfibrinolysis!
Cirrhosis could be a prothrombotic state

• Coagulation imbalance in plasma
• Increased risk of venous thrombosis
• Bleeding related to mechanical factors or associated diseases
• Not reflected by usual screening tests

Tissue Factor
FVIIa
Thrombin
Fibrin
PL
From PT to INR

Pools of Plasma from VKA Patients

Producer

Lab

PT

INR

ISI
From PT to INR

Pools of Plasma from VKA Patients

Producer

Lab

PT

INR

ISI
From PT to INR

Pools of Plasma from Liver Patients

ISI LIVER

PT

INR LIVER

Producer

Lab
1. Cirrhosis is a prothrombotic state
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5. A strengthening rationale for anticoagulation

HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis
Liver Injury

Activated Coagulation

Thrombin

Fibrin

PAR1

Stellate Cell Activation

Neubauer. Gastroenterology 1995
Marsden JCI 2003

Gaca. J Hepatol 2002
Gillibert Duplantier. Gut 2004
Activated Coagulation

Liver Injury

Underlying Thrombophilia

Thrombin

Fibrin

Warfarin

PAR1

Stellate Cell Activation

Fibrosis

1

2

Warfarin

X
Hepatitis C → Cirrhosis → Decompensated Cirrhosis

Fibrogenesis

Prothrombotic factors

Factor V Leiden OR 3.5*

Hepatitis C → Cirrhosis → Decompensated Cirrhosis

Fibrogenesis

Prothrombotic factors

Factor V Leiden OR 3.5*

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HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis.
Hepatic vein thromboses

Explanted Cirrhotic Livers

- ~70% of veins involved
- Smallest first
- Parenchymal extinction

Explanted Cirrhotic Livers

Portal vein thromboses

- 30-50% of veins involved
- Largest first
- Focal atrophy/regeneration

## Association of PVT with a Small Liver

<table>
<thead>
<tr>
<th>At LTx</th>
<th>N</th>
<th>Liver weight</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVT</td>
<td>63</td>
<td>17 g/Kg</td>
<td>&lt; .02</td>
</tr>
<tr>
<td>No PVT</td>
<td>401</td>
<td>21 g/Kg</td>
<td></td>
</tr>
</tbody>
</table>

PVT and Complications of Cirrhosis

- Portal hypertensive bleeding
- Failure to control bleeding
- Ascites
- Hepatic encephalopathy
### Extrahepatic PVT in Cirrhosis

<table>
<thead>
<tr>
<th>Event</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for HCC</td>
<td>0.6 %</td>
</tr>
<tr>
<td>In-Hospital</td>
<td>7.0 %</td>
</tr>
<tr>
<td>Necropsy</td>
<td>8.0 %</td>
</tr>
<tr>
<td>Before LTx or PSS</td>
<td>15.0 %</td>
</tr>
</tbody>
</table>

Thrombosis

Advanced Liver Disease

Blood stasis

Wall changes (PHT)

Thrombosis

Decreased Portal Blood Inflow

Thrombosis

Advanced Liver Disease
Advanced Cirrhosis

Decreased Portal Flow

Portal Vein Thrombosis

Gene Mutation

Independent predictor
Portal flow velocity

Independent predictor
*MTHFR, FII*

Advanced Cirrhosis

Decreased Portal Flow

Portal Vein Thrombosis

Gene Mutations
Hemostasis and Thrombosis in Cirrhotic Patients

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HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis
Pre and post LTx impact of PVT

Hazard Ratio (95% CI)

Englesbe. Liver Transplant 2010. SRTR 22,291 recipients. PVT 4.02%
Hemostasis and Thrombosis in Cirrhotic Patients

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Anticoagulation in Patients with Cirrhosis

Anticoagulation therapy targeting PVT

- Recanalization
- Prophylaxis
Anticoagulation for PVT and Cirrhosis

- <150 patients reported
- Various anticoagulation protocols
- Partial occlusion in 80-88% of patients
- Recanalization 60-80% (3-12 months). More likely when occlusion is partial and anticoagulation therapy is prolonged
- Bleeding apparently not a problem
Patients on the Waiting List for LTx

PVT before transplantation (n = 29)

No anticoagulation (n = 10)
- Recanalization (n = 0)

Anticoagulation (n = 19)
- Recanalization (n = 8)

Francoz, Gut 2005
Anticoagulation on the Waiting List for LTx

PVT before transplantation 24

Partial 21
Recanalization* 15

Complete 3
Recanalization 0

* No PVT post-OLT

Francoz, ILTS 2008
Treatment of PVT in Patients with Cirrhosis

Anticoagulation or TIPS for recanalization?
TIPS in Cirrhosis with PVT

• Several case series. N = 13 - 100 patients
• Only retrospective uncontrolled studies
• Anticoagulation frequently added after TIPS
• Cavernoma, Total/Partial obstruction merged

TIPS in Cirrhosis with PVT

- Feasible when intrahepatic veins are visible.
- Effective for recanalization of partial occlusion.
- TIPS dysfunction, encephalopathy, & mortality were similar to TIPS patients without PVT.
- Impact on complications and mortality unclear.

Anticoagulation in Patients with Cirrhosis

Anticoagulation for PVT

• Recanalization
• Prophylaxis
## Prophylaxis of PVT in Cirrhosis

### Child B7-C10 patients

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Pt</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Partial PVT</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Complete PVT</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Zechini. EASL ILC 2010. Enoxaparin 4 000 UI/day 24 months

2. Cirrhosis certainly a prothrombotic state for splanchnic veins due to reduced flow velocity.

3. Hepatic or portal venous thromboses common in advanced cirrhosis.


5. PT/current INR not satisfactory tests for investigating the coagulopathy of cirrhosis.
Mainly studied in a context of extrahepatic PVT

• The risk of bleeding appears to be acceptable.
• Recanalization of a partial thrombus is usual.
• Recanalization of complete occlusion less clear.
• The benefit of recanalization is to be established.
• The places of TIPS and AC are to be clarified.
Treatment for PVT in Patients with Cirrhosis

• Complication refractory to medical/endoscopic therapy and visible intrahepatic portal veins: → TIPS feasible, PVT not a contraindication

• In candidates to liver transplantation and partial occlusion due to PVT: → Anticoagulation feasible & usually effective
Anticoagulation in Cirrhosis

In the absence of overt PVT, there might be a role for anticoagulation to prevent aggravation.
Anticoagulation in Cirrhosis

A practical issue: How to monitor anticoagulation

• Vitamine K antagonists: which INR? $\text{INR}_{\text{VKA}}$ or $\text{INR}_{\text{LIVER}}$?

• LMWH: antithrombin deficiency renal dysfunction antiXa level?
INR in Patients with Cirrhosis

- Not related to prothrombin levels along the same regression line as for Vitamin K antagonists.
- Due to uncarboxylated metabolites of coagulation factors
- Interlaboratory variability.

→ Adjustment based on Factor II level 25-35%?

Bechmann. Liver Int 2010. 75 patients with prophylactic doses
LMWH in Cirrhosis

84 patients with prophylactic (75) or therapeutic (9) doses
Risk Factors for Portal Vein Thrombosis. Cirrhosis without HCC

Univariate: Age, Child-Pugh class, Surgery for portal hypertension, Endoscopic sclerotherapy, Prothrombotic features

Multivariate*: G20210A FII (OR 5.94)

Risk Factors for Portal Vein Thrombosis: Cirrhosis without HCC

Univariate: MELD > 13
Platelets
Antithrombin
Protein C
Protein S
Portal flow velocity < 15 cm/sec

Multivariate: Portal flow velocity < 15 cm/sec

Zocco. J Hepatol 2009
Anticoagulation in Patients with Cirrhosis

Rationale

• Cirrhosis as a prothrombotic state
• Coagulation as a fibrogenic factor
• Anticoagulation in BCS and PVT
• PVT and cirrhosis severity
• PVT as a limitation to LTx
## Occult PVT in Explanted Cirrhotic Livers

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Small mural thrombus (all veins)</td>
<td>64 %</td>
</tr>
<tr>
<td>Intimal fibrosis (large veins)</td>
<td>25 %</td>
</tr>
<tr>
<td>Intimal fibrosis (small veins)</td>
<td>36 %</td>
</tr>
</tbody>
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PVT and Survival in Patients with Cirrhosis

Englesbe Liver Transplant 2010a. 3295 patients with cirrhosis, 148 with occlusive PVT
PVT and LTx: Survival Benefit from LTx

Englesbe. Liver Transplant 2010. 22,291 recipients. PVT 4.02%
HVT – Improvement in Survival

Valla, D-C Gut 2008;57:1469-1478
HVT: Improvement in Survival

Valla, D-C Gut 2008;57:1469-1478
Portomesenteric venous thrombosis

Portal vein thrombosis – Anticoagulation

Condat et al. Gastroenterology 2001; 120:490

Thrombosis

- Anticoagulation: 6.0
  + Anticoagulation: 1.2
  p = 0.015

Bleeding

- Anticoagulation: 17
  + Anticoagulation: 7
  p = 0.212
Feasibility of TIPS in Cirrhosis with PVT

• Related to the type of obstruction
  - Thrombus, partial obstruction ~ 100%
  - Thrombus, complete obstruction ~ 90%
  - Cavernoma ~ 65%

• Predictive factors for successful insertion: Visible intrahepatic portal veins

Results of TIPS in Cirrhosis with PVT

• Dysfunction ~ 25-30% at 1 yr
  Similar to patients without PVT

• Encephalopathy ~ 20-25% at 1 yr

• Impact on complications of cirrhosis
  Limited data.
  Mortality similar to patients without PVT

Perarnaud, Eur J Gastro Hepato 2010. Han, J Hepatol 2010
PVT and Survival in Patients with Cirrhosis

Englesbe Liver Transplant 2010. 3295 patients with cirrhosis, 148 with occlusive PVT
Impact of PVT on pre and post LTx survival

Englesbe. Liver Transplant 2010. 22,291 recipients. PVT 4.02%
Maladies du Foie

<table>
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<th>Variabilité due à la thromboplastine</th>
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<tr>
<td>• Temps de Quick</td>
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<td>• Ratio de Temps de Quick M/T</td>
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<tr>
<td>• % activité M/T (Taux de Quick)</td>
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<td>INR</td>
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| Child-Pugh ou MELD                 | +++     |

*Trotter Liver Transpl 2004*
De l’INR à l’INR$_{AVK}$ et à l’INR$_{FOIE}$

Plasma de Patients

AVK → ISI$_{AVK}$ → INR$_{AVK}$

Plasma de Patients

FOIE → ISI$_{FOIE}$ → INR$_{FOIE}$

<table>
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<tr>
<th>Influence de la Thromboplastine</th>
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<tr>
<td>Temps de Quick</td>
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<tr>
<td>Ratio de Temps de Quick M/T</td>
</tr>
<tr>
<td>% activité M/T (Taux de Quick)</td>
</tr>
<tr>
<td>INR$_{AVK}$</td>
</tr>
<tr>
<td>INR$_{FOIE}$</td>
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</table>

De l’INR$_{AVK}$ à l’INR$_{FOIE}$
## Extrahepatic PVT in Cirrhosis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotherapy</td>
<td>12 per 100 pt-yr</td>
</tr>
<tr>
<td>Listed for LTx</td>
<td>18 per 100 pt-yr</td>
</tr>
</tbody>
</table>
