Management of Hemostasis in Acute Liver Failure: How much do we really need to manage?

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I have financial relationships to disclose within the past 12 months relevant to my presentation:  
*TEM Systems, Inc (research grant support)*

AND

My presentation includes discussion of off-label or investigational use:  
*Thromboelastography, thromboelastometry*
Features of Acute and Chronic Liver Disease
Fueling the Perception of a Bleeding Tendency

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cirrhosis</th>
<th>Acute Liver Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal Hypertension</td>
<td>+++</td>
<td>- / +</td>
</tr>
<tr>
<td>Synthetic Failure / ↑ INR</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>+ / ++</td>
</tr>
<tr>
<td>SIRS</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
Hemostasis in Acute Liver Failure: How much do we really need to manage?

- What are the clinical manifestations of abnormal hemostasis in patients with ALF?
- What is the state of global hemostasis?
- What mechanisms exist to rebalance hemostasis in patients with ALF?
- When/how does bleeding need treatment?
Bleeding in Acute Liver Failure: Study Patients

2,684 registry patients were assessed for eligibility

1,657 met study criteria

409 ALL patients
260 21-day outcome missing
28 no platelets on Day 1
280 non-monotonic missingness

N = 713
Spontaneous Survivors (43%)

N = 412
Liver Transplant (25%)

N = 532
Death (32%)

N = 48
Bleeders

N = 665
Non-Bleeders

N = 28
Bleeders

N = 384
Non-Bleeders

N = 97
Bleeders

N = 435
Non-Bleeders

INR and Platelet Counts by Day of Admission

**p<0.01  ***p<0.0001
Relationship Between Thrombocytopenia and the SIRS in Patients with Acute Liver Failure

N=1820
Platelet Count and INR According to Outcome of Acute Liver Failure

§ TFS vs. death
† OLT vs. death
*TFS vs. OLT
1 symbol, P<0.05
3 symbols, P<0.001
Sites of Spontaneous Bleeding in Patients with Acute Liver Failure

N = 173
(Incidence: 10.4%)

- GI
- Intracranial
- Skin/IV
- Oro/naso-pharyngeal
- Pulmonary
- Other

Stravitz, et al. AASLD. 2013
Spontaneous Bleeding Complications in ALF: Related to the Platelet Count, not the INR

**Platelet Count** (x10^9/L)

- **Non-Bleeder**
- **Bleeder**

**INR**

- **Non-Bleeder**
- **Bleeder**

***P < 0.001

*P < 0.05
Survival According to Spontaneous Bleeding Complications within Days 1-7 of Admission for ALF

Product-Limit Survival Estimates
With 95% Hall-Wellner Bands

Time after Admission (d)
Survival Probability

Bleeding Complications

+ Censored
Logrank p < .0001

BLEEDER
0
1
 Outcome of Acute Liver Failure According to Receipt of Transfusions

<table>
<thead>
<tr>
<th>Transfusion</th>
<th>Transplant/Death N = 846</th>
<th>Spontaneous Survivors N = 752</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percent</td>
<td>N</td>
</tr>
<tr>
<td>Red Blood Cells</td>
<td>403</td>
<td>47.64</td>
<td>205</td>
</tr>
<tr>
<td>Plasma</td>
<td>640</td>
<td>75.65</td>
<td>315</td>
</tr>
<tr>
<td>Platelets</td>
<td>257</td>
<td>30.38</td>
<td>105</td>
</tr>
</tbody>
</table>
Bleeding Complications in ALF: Summary of Clinical Findings

- Bleeding incidence is low (10.4%)  
- Primary site of bleeding: UGI (92%)  
- Many more receive RBC (37.4%) than bleed  
- Transfusion of any blood product portends a poor outcome  
- Bleeding complications within 7 d of admission are associated with increased mortality at 21 d, but increased mortality occurs after Day 7.
Hemostasis Assessed by Thromboelastography in Acute Liver Failure

<table>
<thead>
<tr>
<th>TEG Parameter</th>
<th>Normal Range</th>
<th>ALI/ALF (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-time (min)</td>
<td>2.5 - 7.5</td>
<td>4.7 ± 1.9</td>
</tr>
<tr>
<td>K-time (min)</td>
<td>0.8 - 2.8</td>
<td>1.7 [0.8-20.0]</td>
</tr>
<tr>
<td>( \alpha )-Angle (degrees)</td>
<td>55.2 - 78.4</td>
<td>63.7 ± 12.2</td>
</tr>
<tr>
<td>Maximum Amplitude (mm)</td>
<td>50.6 - 69.4</td>
<td>55.0 ± 10.9</td>
</tr>
<tr>
<td>Lysis 30 (%)</td>
<td>0.0 - 7.5</td>
<td>0.0 [0.0-2.1]</td>
</tr>
</tbody>
</table>

Relationship Between Maximal Clot Strength by Thromboelastography and the SIRS in Acute Liver Failure

Hypothesis:

SIRS ➔ Acute Phase Reaction ➔ vWF, Factor VIII ➔ Clot strength

P = 0.02
Thrombin Generation and Inhibition

Thrombin Generation

- FXI
- FIX
- FVIII
- FX
- Activated Platelets
- FVIIa TF
  - FXa
  - FVa
  - Prothrombin
  - Fibrinogen
  - Thrombin
  - Fibrin

Thrombin Inhibition

- Protein C/S
- Thrombomodulin
  - Endothelium
- Endogenous heparinoids
- Prothrombin
  - FXa
  - FVa
  - Thrombin
  - AT
  - INR
Thrombin Generation in Patients with Acute Liver Failure

Thrombomodulin (TM)

Endothelium

FXI

FIX  FVIIIa

FVIIa  TF

Prothrombin

Thrombin

Protein C

Fibrinogen  Fibrin

FXa  FVa

Rebalanced Hemostasis: Pro- and Anti-Coagulant Proteins Decrease in Parallel in Acute Liver Failure

Mean 25% of normal

$F_V$ vs. Protein C
$r = 0.42$
$P = 0.002$

Median 6% of normal

$F_V$ vs. Protein S
$r = 0.49$
$P = 0.0002$

Median 5% of normal

$F_{VII}$ vs. Protein C
$r = 0.62$
$P < 0.0001$

Mean 15% of normal

$F_{VII}$ vs. Protein S
$r = 0.37$
$P = 0.007$
Compensation for Thrombocytopenia in ALF: Increased Platelet-Endothelial Cell Adhesion

Platelet Adhesion and Aggregation in Patients with ALF and Normal Controls

A: Control

B: ALF

C: Surface coverage (%)

D: Platelet aggregate size (µm²)

p<0.01
Possible Role of Microparticles in Rebalancing Hemostasis in ALF

- Platelets → Platelet MP’s → SIRS → Thrombocytopenia → Tissue factor (TF) → Kupffer cells, hepatocytes, stellate cells → Necrotic hepatocytes
- Propagation of inflammatory response
- Thrombosis
- MOSF
- Liver Injury
- EC MP’s

Microparticles in Patients with Acute Liver Failure: Phenotyping by Flow Cytometry

Microparticle Sizing/Enumeration (ISADE®) on Admission for Acetaminophen Overdose


- INR 4.8
- FV < 5%
- Lactate 8.7
- Grade 4 Coma
- SIRS # 3
- pH 7.34
- Microparticles 0.28-0.64µm
- Larger platelet fragments
Concentration of Microparticles in Patients with Acute Liver Failure and Normal Healthy Controls


ALF N=50
Control N=13

\[ P < 0.0001 \]
Microparticles in Patients with Acute Liver Failure: Relationship to SIRS on Admission

Microparticles in Patients with Acute Liver Failure: Relationship to Outcome

Hospital Day 1

Hospital Day 3

\( P = 0.006 \)

\( P = 0.0002 \)

TFS, transplant-free survival

LT, liver transplantation

Microparticles in Patients with Acute Liver Failure: Tissue Factor-Dependent Procoagulant Activity

PS, phosphatidyl serine
TF, tissue factor (factor VII/VIIa receptor)

Procoagulant activity

0.1-1μm

MPTF, microparticle tissue factor

Key, NS. Thrombosis Res. 2010;125: S42-S45.
Defective Fibrinolysis in Patients with Acute Liver Failure

***P < 0.0001

Conclusion: Hemostasis Remains “Re-balanced” in Most Patients with Acute Liver Failure

Primary hemostasis

- Thrombocytopenia
- Microparticle Formation
  - High von Willebrand factor
  - Low ADAMTS-13

Coagulation

- Low Factors II, V, VII, IX, X, XI
- Low Protein C/S, AT
- High Factor VIII

Fibrinolysis

- Low antiplasmin, TAFI
- High t-PA
- Low plasminogen

Anti-hemostatic Drivers

Pro-hemostatic Drivers

Synthetic Failure + Cytokine Storm =

Hemostasis in Acute Liver Failure: Management Case

- 52 year old male with ALF of indeterminate etiology
- SIRS+, Grade 4 hepatic encephalopathy, NH$_3$ = 104, posturing
- INR 5.6, Factor VII 1%, Factor V 17%, Factor VIII 431%, platelets 126
- Central line and dialysis catheters *thrombosed*

- Thromboelastogram:

- Intracranial pressure monitor placed without factor repletion, without complication; Transplanted successfully.
Hemostasis in Acute Liver Failure: How much do we really need to manage?

- Global hemostasis in most patients with ALF remains rebalanced

- The administration of pro-coagulant factors may exacerbate a microcirculatory hypercoagulable state (and cause harm)

- Patients with ALF probably do not require correction of the INR prior to procedures

- Significant active bleeding might be best managed with an assay of global hemostasis.
## Blood Component Repletion in Patients with ALF: Recommendations made cautiously and with humility

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Level to Replete</th>
<th>Pre-procedure Prophylaxis</th>
<th>Treatment of Active Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>?</td>
<td>?</td>
<td>Just enough</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;60 x 10⁹/L</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&lt;100 mg/dl</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>RBC</td>
<td>Hb &lt;7 gm/dl</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Investigation of Hemostasis in Acute Liver Failure: Collaborators

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