Managing coagulopathies in liver disease

Sunny Dzik, MD
Co-Director, Blood Transfusion Service
Massachusetts General Hospital
In the Emergency Room....

• 54 yo man with known cirrhosis vomited blood at home.
• History of prior UGI bleeds;
• 150 lbs; 110/60, 110 reg, 37.5, 18, 98% (air)
  – Mild icterus, bruises on legs & arms, muscle wasting;
  – No murmur, flat JVP, round abdomen, 1+ edema bilat;
  – Confused; + asterixis; cranial nerves, motor, sensory OK.
  – NG tube placed in ER was pos for blood.
• Labs in ER @ 11 am:
  – CBC: Hgb 68 g/dL; WBC: 8.2; Plat: 47,000
  – INR: 2.4; aPTT: 34; fibrinogen 105
  – Bili: 3.6; AST: 350; BUN 41/Creat 2.0
4 Phases of Hemostasis

1. Vascular

2. Platelet plug
   Adhesion to damaged/activated endothelium
   Activation - release
   Aggregation

3. Fibrin formation on the platelet plug
   Tissue factor initiates
   Thrombin is main driver

4. Clot lysis
   Endothelial release of t-PA
Endoscopic treatment:
~60% reduction in risk of further bleeding

Laine L. NEJM 2016; 374: 2367-76
3:30 pm:
Has received 3 units of RBCs
Endoscopy shows bleeding beyond the stomach.
CVP is 3 cmH$_2$O; Lactate is 5.0;
Hb: 75 g/L; WBC 10.2; plate 31,000
INR = 2.7; aPTT = 42.

The nurse asks if you think he needs FFP and Platelets…
Pooling of platelets in the spleen
1. Recovery of platelets 2 hours after transfusion depends on the spleen size.
2. The transfused platelets go into the spleen.

Radioactivity counts over the spleen

Radioactivity in the circulation
2. The transfused platelets go into the spleen.

Radioactivity counts over the spleen

Radioactivity in the circulation
3. The lifespan of platelets is not diminished.
4. The platelets can come out of the spleen! … after infusion of epinephrine!

**Fig. 5.** Per cent change in platelet levels after infusion of epinephrine to asplenic and normal subjects and splenomegalic patients with thrombocytopenia (platelets 40,000 to 120,000 per mm³).
Think beyond the platelet count!

Each of these patients has a plt count of 30,000/uL. The hemostatic lesion is entirely different. The appropriateness of Platelet Tx is entirely different.
Normal hemostasis

Zone of therapeutic anticoagulation

Zone of anticoagulation
Toward Rational FFP Transfusion: Effect on Coagulation Test Results

- Retrospective cohorts at U of Oklahoma.

- Test group:
  140 adults receive 236 transfusions FFP
  39 pediatric patients receive 59 transfusions FFP

- Control group:
  Patients with INR < 1.6 who were not transfused

All patients get follow-up INR @ ~ 4-8 hrs

_Holland and Brooks, Am J Clin Path 2006; 126: 133._
INR Change per 2 units FFP

Decrease = 0.37 [pre-Tx INR] – 0.47

Holland and Brooks, Am J Clin Path 2006; 126: 133.
Normally, a stable balance...

Anti-coagulation

Protein C & S
activated by Thrombomodulin

Pro-coagulation

Clotting factors

...but Lab Tests (INR, aPTT)
only examine ‘pro-coagulants’
Thrombin generation

Endogenous thrombin potential (Units/min)

Without Thrombomodulin

normals

cirrhosis

Pier Mannucci  Hepatology 2005; 41: 553-558
Thrombin generation with TM is normal in cirrhosis

Endogenous thrombin potential
(Units/min)

Without Thrombomodulin

With Thrombomodulin

Pier Mannucci  Hepatology 2005; 41: 553-558
Defect in Liver Disease: *Unstable*, re-balanced hemostasis

Anti-coagulation
Protein C & S
activated *in vivo* by
Thrombomodulin

Pro-coagulation
Clotting factors

Normal = stable

Pier Mannucci  Hepatology 2005; 41: 553-558
Normal Thrombin Generation in Cirrhosis

Conclusion:

“These findings help clarify the pathophysiology of hemostasis in cirrhosis, …and that conventional coagulation tests are unlikely to reflect the coagulation status of these patients.”
INR Zones of response to bleeding risk

- INR 2.5:
  - Treat bleeding; Prophylaxis before procedure

- INR 2.2 to 2.0:
  - Treat bleeding; do not treat the lab test

- INR 1.7 to 1.5:
  - Zone of normal hemostasis; No treatment

- INR 1.5 to 1.2:

- INR 1.0 to 1.2:
  - Normal lab values

- Platelet number x % function:
  - 10,000 to 50,000
  - 50,000 to 100,000
  - 100,000 to 200,000
  - 200,000 to 300,000/uL
RCT: 12 trauma sites in N. Amer. Aug 2012 – Dec 2013

11,185 Eligible
10,505 Excluded (not severe)
n= 680 randomized

<table>
<thead>
<tr>
<th></th>
<th>1 RBC:1 FFP</th>
<th>2 RBC:1 FFP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hour mortality</td>
<td>12.7%</td>
<td>17%</td>
<td>0.12</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>22.4%</td>
<td>26.1%</td>
<td>0.26</td>
</tr>
<tr>
<td>RBC</td>
<td>9</td>
<td>9</td>
<td>n.s</td>
</tr>
<tr>
<td>FFP</td>
<td>7</td>
<td>5</td>
<td>n.s</td>
</tr>
<tr>
<td>Platelets</td>
<td>12</td>
<td>6</td>
<td>n.s</td>
</tr>
</tbody>
</table>

23 pre-specified secondary outcome measures were not different.

JAMA 2015; 313: 471-482.
Is a 1:1:1 ratio harmful?

Retrospective review of 865 patients with massive transfusion

Finding #1: Most MT patients (89%) are non-trauma.
Finding #2: FFP:RBC ratio same in survivors vs non-survivors.
Finding #3: 30 d survival worse with high ratios in some groups.
Is a 1:1:1 ratio harmful?

Retrospective review of 865 patients with massive transfusion

Finding #1: Most MT patients (89%) are non-trauma.
Finding #2: FFP:RBC ratio same in survivors vs non-survivors.
Finding #3: 30 d survival worse with high ratios in some groups.

5 pm: In the ICU now.

Has received 6 RBCs, 3 FFP, 1 dose (6 units) of platelets
CVP is 3 cm H₂O; Lactate is 3.5;
Hb 69 g/L; WBC 10.2; plate 50,000
INR =2.2; aPTT =35; fibrinogen= 110; D-dimer >5,000.
Patient just passed a melanotic stool

*Is there anything else to help him stop bleeding?*
The enormous endothelium....

Skin 1.5-2 m²

Alveoli 100 m²
(< 1 tennis court)

Gut 250 m²
(> 1 tennis court)

Endothelium: 1,000 m²
1 Trillion cells; (Football field)
Fibrinolysis is the vascular response to injury and shock
t-PA mediated fibrin(ogen)-olysis during liver transplantation

Thromboelastography (TEG / ROTEM)

Fibrinolysis

Lysine

Fibrin / Fibrinogen
PLASMIN

Fibrin / Fibrinogen

Lysine binding sites

Lysine

Enzymatic site

Anti-Fibrinolytics

Amicar or Tranexamic Acid
Clot Lysis is *the central defect in cirrhosis*

**Fibrin-olysis**

- Bad
- Previously clotted surfaces are oozing;
- Lab tests may be normal;
- D-dimer always elevated;
- Be pre-emptive

**Fibrinogen-olysis**

- Worse!
- Not making clot
- +++ D-dimer
- Low fibrinogen
- Increased INR and aPTT
- TEG → fibrinolysis

Anti-fibrinolytics are effective!

Anti-fibrinolytics are essential to catch up...
At 6 pm, he was given a 5 gram loading dose of EACA (epsilon caproic acid, Amicar) and started on a 1 gram/hour infusion.

During the night, he received 2 more RBCs.

In the morning, he was stable:
Hgb: 80; WBC 11.2; Plts 44,000.
INR 2.4; Fibrinogen 140 mg/dL.

The exact source of the bleed was not found.
4 Phases of Hemostasis

1. Vascular

2. Platelet plug
   Adhesion to damaged/activated endothelium
   Activation - release
   Aggregation

3. Fibrin formation on the platelet plug
   Tissue factor initiates
   Thrombin is main driver

4. Clot lysis
   Endothelial release of t-PA
#1 Vascular Phase: Local bleeding ~ local measures

Angiography and direct embolization
#2 Platelet plug formation

- Platelets are re-distributed to the spleen.
- Thrombopoietin levels may be low.
- Platelet transfusions add *volume* but limited value.

![Image of platelet plug formation](image1)

*Maslak, P. ASH Image Bank 2004;2004:101115*

*Lazarchick, J. ASH Image Bank 2001;2001:100177*
#3 Fibrin Formation

- Rebalanced hemostasis; unstable; low reserves.
- Don’t chase the INR;
- Dose FFP by…
  - by “time” for ICU patients;
  - by “ratio” for OR bleeding (2 RBCs –to- 1 FFP)
- More is NOT better…
  - Drowning the patient
  - Increasing venous volume → worse bleeding
  - FFP infuses more plasminogen
Cirrhosis teaches the 4 phases of Hemostasis

**Physiology**

- Vascular
- Platelet plug
- Fibrin formation
  - Re-balanced; unstable; without good reserves
- Fibrinolysis
  - Dominant defect in cirrhosis
Cirrhosis teaches the 4 phases of Hemostasis

**Physiology**
- Vascular
- Platelet plug
- Fibrin formation
  - Re-balanced; unstable; without good reserves
- Fibrinolysis
  - Dominant defect in cirrhosis

**Therapy**
- Conservative RBCs better than liberal use;
- Endoscopic control of bleeding;
- Platelet transfusions add volume with little value;
- FFP has a role, but not guided by the INR!
- Anti-fibrinolytic therapy is essential.