# LIVER DISEASE & PLASMA TRANSFUSION

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A patient with liver failure secondary to EtOH presents with sepsis and needs a central line placed. His INR is 2.9. Do you order 4 units of plasma before you put in the line?

**A. YES**

**B. NO**

A patient with acute liver failure needs a liver biopsy. His INR is 2.9. Do you order 4 units of plasma before you send him to IR?

**A. YES**

**B. NO**

A patient with cirrhosis needs a large volume paracentesis. His INR is 2.9. Do you order 4 units of plasma before you tap him?

**A. YES**
**B. NO**

# Objectives

1. **Review the hemostatic impairment in liver disease**

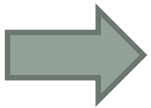
2. **Understand how to interpret laboratory tests in liver disease**

3. **Review the evidence for plasma transfusion in the setting of bleeding and periprocedure**

# Hemostatic Derangement - Liver Disease

- Vascular: chronically dilated varices and nutritional deficiencies leading to more friable tissues and bleeding
- Coagulation: “rebalanced”
- Thrombocytopenia: better than the number
- Fibrinolysis: likely hyperfibrinolysis in severe liver disease

High INR
Must be a bleeder



4 units of FFP

# Rebalanced hemostasis

| Factors | Procoagulant | Anticoagulant |
|---|---|---|
| **Platelet** | High vWF<br>High Factor VIII<br>Low ADAMTS13 | Thrombocytopenia<br>Platelet dysfunction |
| **Coagulation factors** | High Factor VIII<br>Low Protein C<br>Low Protein S<br>Low antithrombin III | Low coagulation factors<br>(except Factor VIII) |
| **Fibrinogen** | High fibrinogen (early) | Dysfibrinogenemia |
| **Fibrinolytic pathway** | Low plasminogen<br>High plasminogen-activator inhibitor | Low antiplasmin<br>Low tissue factor pathway inhibitor<br>High tPA |
| **Heparinoids** | | High natural heparinoids |

Callum J, et al. Hematologic Challenges in ICU Patients with Liver Disease, in Hematologic Challenges in the ICU (ed. Corwin, Shander)

# Coagulation: Rebalanced hemostasis

- Numerous alterations in the both procoagulant and anticoagulant pathways = preserved hemostasis
  - Hence you can't use the INR/PTT (only assesses procoagulant)
  - Liver disease patients have high VTE rates (not autoanticoagulated)
- Coagulation factors drop with increasing Child-Pugh class except: F8, vWF, and fibrinogen that all go up
  - Reduced clearance (decreased LDL receptor-related protein), increased release due to gut derived LPS, decreased degradation due to reduced ADAMTS13
- Natural anticoagulant proteins (antithrombin III, Protein C, Protein S) progressively fall with increasing liver failure
- Highly variable patient to patient (but we use a one size fits all approach when transfusing)

# Thrombocytopenia

- Common - <50x$10^9$/L in 13% of patients
- Multifactorial: portal HTN, reduced TPO production, bone marrow suppression (alcohol, viral and drugs)
  - 50-90% of the platelets are sequestered in the spleen – but can be mobilized
  - A platelet count of 30 in liver disease is not the same as 30 in a hematology patient
- Largely offset by marked increase in vWF

Hermos JA, et al. Dig Dis Sci. 2013;58(2):562-73

# Fibrinolysis

- Liver = primary site of synthesis of both pro-fibrinolytic and anti-fibrinolytic proteins
  - balance believed to be slightly tipped in favor of hyperfibrinolysis
  - plasminogen, α2-antiplasmin, thrombin-activatable fibrinolysis inhibitor (TAFI) and Factor XIII are reduced (decreased synthesis)
  - tPA and PAI-1 (synthesized by endothelial cells) normal or increased due to reduced clearance by the liver
  - **Key impact**: tPA is released from endothelial cells in response to injury and hemodynamic stress - liver disease clearance is impaired and accumulation of tPA is thought to trigger hyperfibrinolysis
- Wide variability patient to patient

Leebeek FW, Rijken DC. Semin Thromb Hemost. 2015;41(5):474-80

# Objectives

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# INR, PTT, fibrinogen, and platelet count

1. INR does not correlate with bleeding at time of surgery or procedure
2. INR's ISI is for vitamin K antagonists
3. INR does not reflect the concomittent drop in natural anticoagulants
4. PTT shortened by high F8
5. PLT count does not adjust for increase in "function" due to increase in vWF

# Random distribution

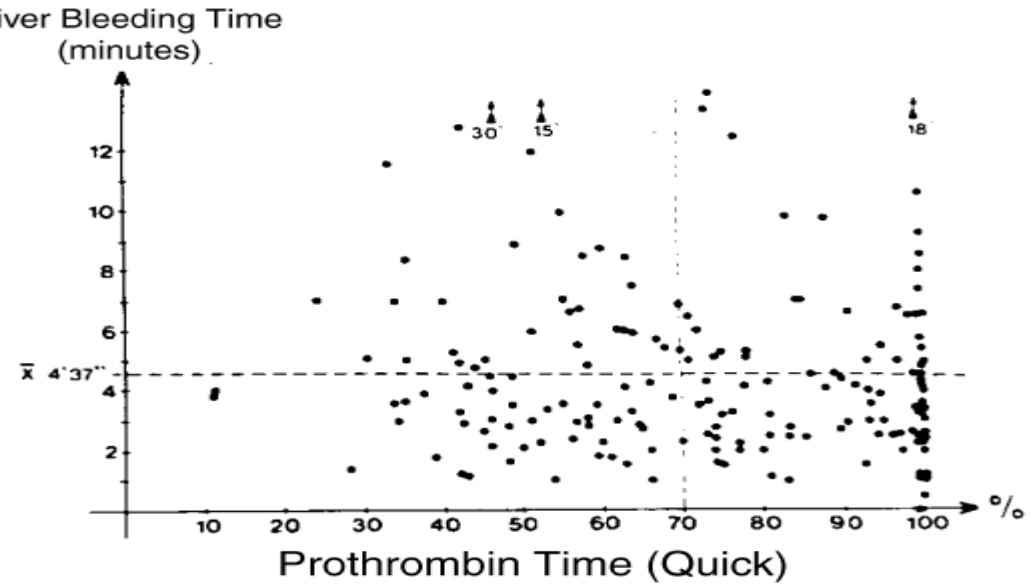



Figure 1-5. Lack of relationship between the liver bleeding time and the preprocedure PT. The time that the liver was directly observed to bleed after biopsy is plotted as a function of the percentage of activity of the PT. Use with permission from Ewe et al.[70]

# Thrombin potential in liver disease

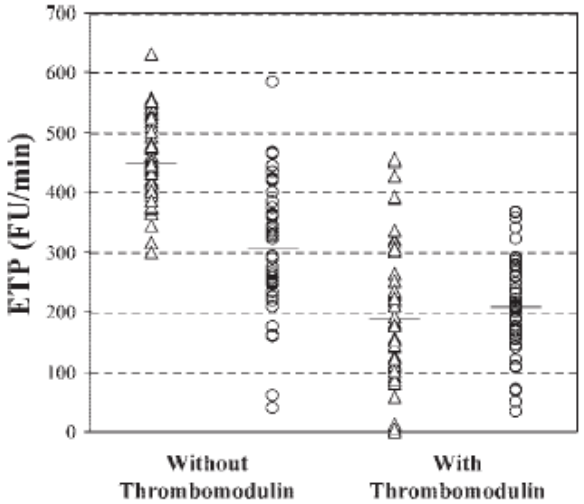
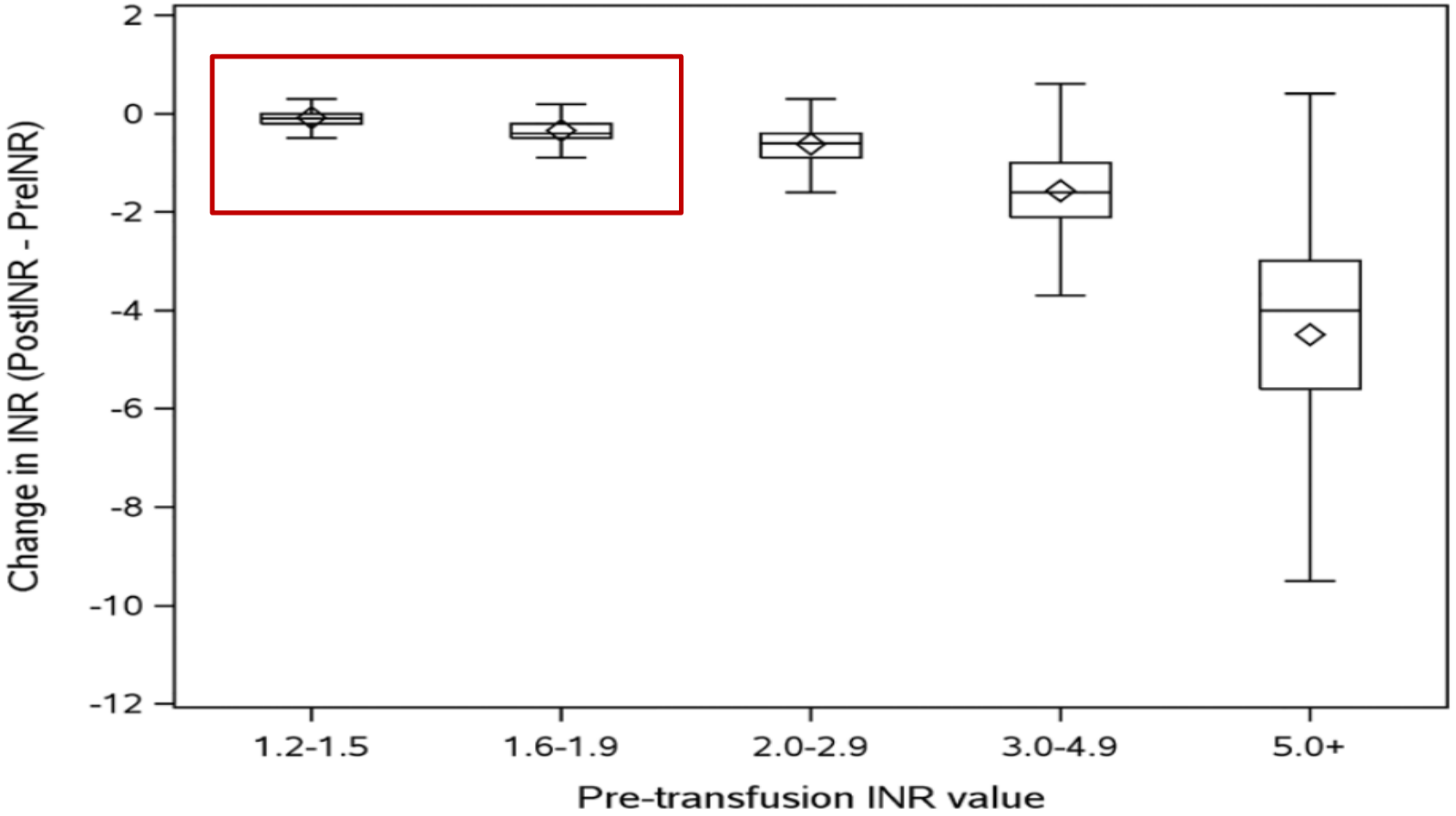



Fig. 2. ETP values for controls **(triangles)** and patients **(circles)** measured without and with thrombomodulin. **Horizontal bars** represent median values. Abbreviations: ETP, endogenous thrombin potential; FU, fluorogenic unit.

Tripoli et al. Hepatology 2005 Mar;41(3):553-8.




**N=6779 patients**

Warner MA, et al. A & A 2018 Epub ahead of print

CSTM SCMT
Canadian Society for Transfusion Medicine
Société canadienne de médecine transfusionnelle

Choosing Wisely Canada™

**Don’t transfuse plasma to correct mildly elevated INRs (<1.8) or PTT before a procedure**

# What about “research” tests?

- Thrombin Generation Test
  - Important test - it shows us there is no value in the INR (repeated studies show normal TGT despite high INR)
  - Not available in most places, very complex, not standardized
- ROTEM
  - Studies to date have failed to confirm a correlation between the TGT and ROTEM, suggesting ROTEM may not reflect the true coagulation balance in liver disease (or maybe TGT wrong)
- TEG
  - 2 studies suggesting TEG normal despite abnormal INR
- Both TEG and ROTEM: lack activation of Protein C in the test system and lacks sensitivity to vWF levels

# TEG guided vs. “standard of care”

- All liver disease, n=60, PLT<50, INR>1.8
- Undergoing any procedure (paracentesis to liver resection)
- Randomized to:
  - SOC: PLT if <50, plasma if INR>1.8
  - TEG guided: PLT if MA<30, plasma if R time >40 min
- Patients in SOC arm were more likely to be transfused (100% vs. 17%)
- 1 hemorrhagic complication in the standard of care group and none in the TEG arm

De Pietri L, et al. Hepatology. 2016;63(2):566-73

# Okay…so you are telling me…

All aspects of the coagulation cascade are messed up…

Most patients in “balance”

INR and PTT aren’t helpful

Platelet count ≠ platelet function or reserve

New fancy tests not validated (or available)…

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# Plasma – Retrospective studies

- 24% of plasma is transfused to patients with liver disease
- 1313 consecutive patients admitted with cirrhosis from 85 hospitals in the UK:
  - 11% of plasma was transfused to patients with an INR <1.5
- Delays procedures for the infusion, TACO risk, and increases in venous pressures increasing the risk of hemorrhage
  - Plasma transfusion is not risk free

Desborough MJ et al. Liver Int. 2016;36(4):522-9

# Plasma – Retrospective studies

**Table 3.** Transfusion thresholds for patients who received FFP or platelet transfusion

| | Bleeding patients *n* (%) | Non-bleeding patients *n* (%) | All patients *n* (%) |
|---|---|---|---|
| Pre-transfusion INR | Fresh frozen plasma transfusions | | |
| ≤1.5 | 11/81 (14) | 3/45 (7) | 14/126 (11) |
| 1.6–2.0 | 31/81 (38) | 10/45 (22) | 41/126 (33) |
| >2.0 | 18/81 (22) | 14/45 (31) | 32/126 (25) |
| Not checked | 21/81 (26) | 18/45 (40) | 39/126 (31) |
| Total | 81 | 45 | 126 |
| Pre-transfusion platelet count ($\times 10^9$/L) | Platelet transfusions | | |
| <50 | 20/37 (54) | 21/30 (70) | 41/67 (61) |
| ≥50 | 14/37 (38) | 9/30 (30) | 23/67 (34) |
| Not checked | 3/37 (8) | 0/30 | 3/67 (4) |
| Total | 37 | 30 | 67 |

Desborough MJ et al. Liver Int. 2016;36(4):522-9

# Bleeding in chronic liver failure

- 1,493 ICU patients - 211(12%) had cirrhosis with 17% of patients developing new major bleeding during their ICU stay
- Patients that experienced new major bleeding - platelet count, fibrinogen level, and PTT were more deranged
- Patients who experienced major bleeding: history of varices, large varices, and half were bleeding on admission
- Unclear in a retrospective review if the bleeding was triggered by the coagulopathy, the coagulopathy was a marker of more severe portal hypertension, or the bleeding resulted in derangement of laboratory test results (consumption)

Drolz A, et al. Hepatology. 2016;64(2):556-68

# Bleeding in acute liver failure

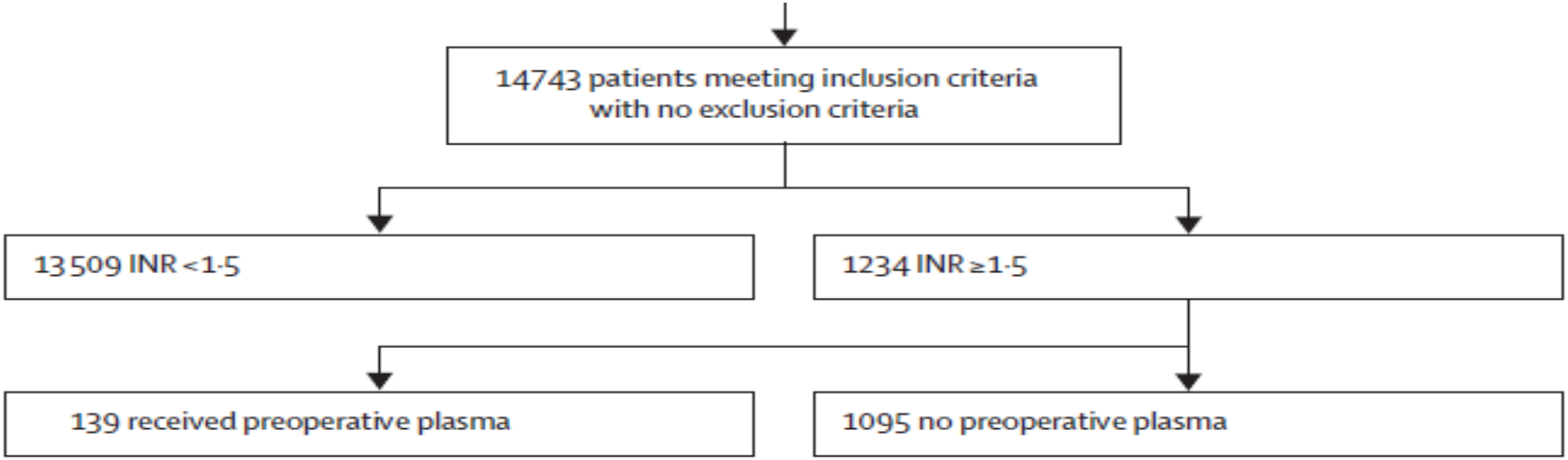
- 1770 patients
- 11% bled, 94% UGIB
- Bleeders more likely:
  - Male
  - Administered plasma!
  - Higher creatinine
  - No difference in INR and PTT
- 641 central lines placed – bleeding in 0.8%
- All serious procedure related bleeds = ICP monitor placement

Stravitz et al. Hepatology 2018; 67: 1931-42

# Pre-operative retrospective study

- In a study of 1234 non-cardiac surgery patients with INR>1.5
  - 11% were prophylactically transfused plasma before the procedure
  - No reduction in bleeding
  - Perioperative outcomes, including mortality, were inferior in the plasma-treated group.

# Plasma transfusion may be over-rated




Median INR 1.7 in both groups

*Lancet Haematol* 2016; 3: e139–48

# Just unnecessary or harmful?

| | No therapy (n=1095) | Preoperative plasma (n=139) | p value |
|---|---|---|---|
| Perioperative WHO grade 3 bleeding | 350 (32%) | 73 (53%) | <0·0001 |
| Intraoperative red blood cell transfusion | 268 (24%) | 56 (40%) | <0·0001 |
| Estimated blood loss, mL (n=564) | 200 (50–500) | 300 (85–930) | 0·0844 |
| Reoperation | 49 (4%) | 16 (12%) | 0·0008 |
| Postoperative haemoglobin, mg/dL (n=961)* | 10·1 (9·1–11·3) | 10·2 (9·1–11·5) | 0·44 |
| ICU admission | 389 (36%) | 88 (63%) | <0·0001 |
| ICU length of stay, days (n=477)† | 2·0 (1·1–5·1) | 5·1 (1·8–8·0) | <0·0001 |
| Postoperative mechanical ventilation | 251 (23%) | 66 (47%) | <0·0001 |
| Duration of mechanical ventilation, days (n=317)† | 1·1 (0·4–5·9) | 2·5 (1·2–7·0) | 0·0016 |
| Hospital length of stay, days | 6·0 (2·2–13·1) | 12·8 (6·7–20·5) | <0·0001 |
| Discharge haemoglobin, mg/dL (n=977) | 9·8 (9·0–10·9) | 9·8 (9·0–11·1) | 0·97 |
| Death | 83 (8%) | 24 (17%) | 0·0002 |

Why? – More liberal with plasma more liberal with RBCs, hemodilution, transfusion of natural anticoagulants, aggravating heparin effect, increasing vascular pressures

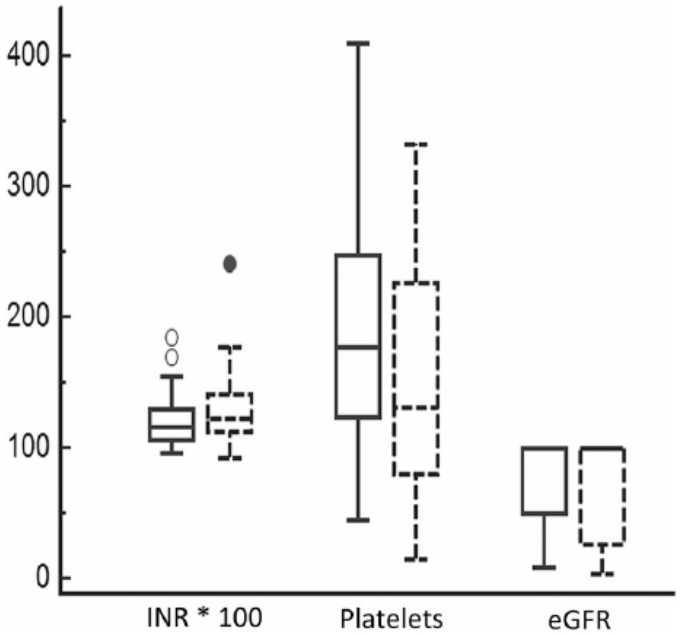
# Liver biopsy

- 68,276 percutaneous biopsies published in 1986 found that major bleeding occurred in only 42 patients
  - 1 in 1626 patients!

Piccinino F, et al.  J of Hepatology 1986; 2: 165-73.

# Liver biopsy

- 847 liver biopsies
- 25 bleeds
- Bleeding = hemoperitoneum, 20 g/l drop (plus inotropes or transfusion or embolization)
- Legend:
  - Solid = no bleeding
  - Dotted = bleeding




Abdom Radiol (2016) 41:643–649
DOI: 10.1007/s00261-016-0655-5

# Local plasma?!?

Haaga et al. Acad Radiol 2018 Dec;25(12):1617-1623.

**TABLE 4. Bleeding Rates**

| | Local FFP | Gelfoam | Systemic FFP | Local Coils |
|---|---|---|---|---|
| All type bleeding rate | 0% | 17.5% | 16.5% | 37.5% |
| Clinical significant bleeding rate | 0% | 12.5% | 7.1% | 37.5% |
| Total number of clinically insignificant bleeds | 0 | 2 | 8 | 0 |
| Total number of clinically significant bleeds | 0 | 5 | 6 | 6 |
| Total number of nonbleeding complications | 0 | 0 | 6 | 0 |
| Total complication rate related to procedure | 0% | 17.5% | 23.5% | 37.5% |

Retrospective
238 patients
Local vs. systemic plasma
INR>2
Mostly liver biopsies

**TABLE 5. Additional Complications**

| | Local FFP | Gelfoam | Systemic FFP | Local Coils |
|---|---|---|---|---|
| Shortness of breath | 0 | 0 | 1 | 0 |
| Shortness of breath requiring intubation or other treatment | 0 | 0 | 1 | 0 |
| Infection | 0 | 0 | 1 | 0 |
| Death related to volume overload or transfusion reaction | 0 | 0 | 3 | 0 |

# Paracentesis and Thoracentesis

- A review of outcomes in 608 consecutive procedures (391 paracenteses, 207 thoracenteses, and 10 both)
- None of the patients was given prophylactic components
- Bleeding complications occurred in 0.2%
- No difference between normal PT/PTT compared with those with a prolonged PT/PTT

McVay PA, et al. Transfusion. 1991;31:164-71.

# Paracentesis

- 1,100 paracenteses at a center where no pre-procedure coagulation test result was deemed unsafe
- All procedures were performed without ultrasound guidance and without the transfusion of platelets or plasma
- The lowest platelet count was 19 (IQR 42-56) and the highest INR was 8.7 (IQR 1.4-2.2)
- There was no significant bleeding in any patient

Grabau CM, et al. Hepatology. 2004;40:484-8.

# Thoracentesis

**TABLE 1: International Normalized Ratio (INR) Values Before Thoracentesis In 822 Patients**

| Group | No. of Patients | INR | | % Complication Rate (95% CI) |
|---|---|---|---|---|
| | | Mean ± SD | Range | |
| All procedures | 822 | 1.53 ± 0.63 | 0.91–6.19 | 0 (0–0.45%) |
| INR ≤ 1.5 | 555 | 1.21 ± 0.14 | 0.91–1.5 | 0 (0–0.66%) |
| INR > 1.5 | 267 | 2.20 ± 0.70 | 1.51–6.19 | 0 (0–1.37%) |
| INR > 2.0 | 139 | 2.65 ± 0.71 | 2.01–6.19 | 0 (0–2.62%) |
| INR > 2.5 | 59 | 3.26 ± 0.71 | 2.51–6.19 | 0 (0–6.06%) |
| INR > 3.0 | 32 | 3.71 ± 0.70 | 3.01–6.19 | 0 (0–10.89%) |

Note—NA = not applicable.

Patel MD, et al. AJR 2011 Jul;197(1):W164-8.

# Plasma - prophylactic

- Plasma should never be transfused for an asymptomatic elevation of the coagulation tests – only lasts 6 hours!
- For minor bedside procedures with bleeding rates below 1% (paracentesis, thoracentesis, central line placement), plasma should only be transfused after the procedure for the exceptional patient who has bleeding
- For patients undergoing more major procedures, the current standard of care is not to transfuse plasma prophylactically (only 11% transfused)

# PCCs = Experimental

- Low volume product (40-80 mL) vs.1000 mL for plasma
- Smaller volume is appealing in liver disease - concerns regarding transfusion causing increases in portal pressures plus TACO risk
- Ongoing study (PROTON) involving 70 patients scheduled for liver transplantation with “severe coagulopathy” (INR>1.5) will randomize patients to PCCs or placebo before surgery
  - Remembering that INR does not tell us anything!
- The primary endpoint is the volume of red cell transfusion during and up to 24 hours after surgery
- Three small studies (45, 30, and 25 patients) = garbage

# Plasma for liver disease – bottom line

- Most liver disease patients are in balance despite elevations in INR and PTT
- Given the complete lack of clinical studies and the lack of correlation between the INR and the coagulation status of the patient with liver disease, one cannot make a recommendation for when to give plasma based on the INR
- One can make a recommendation, of when **not** to give plasma:
  - INR <1.8 and the patient is bleeding or going for a procedure, plasma transfusion is very unlikely to change the INR or mitigate the rate of hemorrhage
  - INR >1.8 and no bleeding or planned procedure

# Plasma for liver disease – bottom line

- Plasma transfusion decisions should be individualized, consider:
  - rate and location of hemorrhage, whether local hemostatic measures or prompt surgical intervention would be sufficient, evidence of coagulopathy due to bleeding at multiple sites
- Vitamin K 10 mg iv should only be considered with risk factors (poor intake, alcoholism, antibiotic therapy)
- Don’t withhold thromboprophylaxis (ie. not auto-anticoagulated)
- The following are unproven/experimental for the management of hemostatic derangements: tranexamic acid, DDAVP, thrombopoietin agonists, rF7a, and PCCs


Thank you!