Management of Critically Ill Patients with Liver Disease: A Conversation in Coagulation

A presentation for HealthTrust Members
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- The presenter nor her preceptor have any financial relationships with any commercial interests pertinent to this presentation

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Learning Objectives

- List proposed benefits of using prothrombin complex concentrate to reverse coagulopathy in critically ill patients with liver disease
- Identify the advantages of using TEG/ROTEM to assess bleeding and thrombosis risk in patients with liver disease
- Recommend appropriate blood products or pharmacologic agents based on a thromboelastography tracing

Abbreviations Glossary

- **ACLF** = acute on chronic liver failure
- **ALF** = acute liver failure
- **CCA** = conventional coagulation assays
- **FFP** = fresh frozen plasma
- **ITP =** idiopathic thrombocytopenic purpura
- **NALFD =** non-alcoholic fatty liver disease
- **NASH =** non-alcoholic steatohepatitis
- **PCC =** prothrombin complex concentrate
- **Plt** = platelet
- **ROTEM** =rotational thromboelastography
- **SCCM** = Society of Critical Care Medicine
- **TACO** = transfusion associated circulatory overload
- **TEG** = thromboelastography
- **TRALI** = transfusion related acute lung injury
- **vWF** = Von Willebrand factor

Introduction to Liver Failure & the Clotting Cascade

Defining Liver Failure

- **Chronic liver disease (CLD):** progressive deterioration of liver function for > 6 months
  - Cycle of inflammation, destruction, and regeneration leads to fibrosis and cirrhosis over time
  - Wide variety of etiologies:
    - Alcoholic liver disease
    - NAFLD/NASH
    - Chronic viral hepatitis
    - Genetic (e.g. α-1 antitrypsin deficiency, Wilson disease)
    - Autoimmune causes
    - Drugs – amiodarone, methotrexate, phenytoin
- **Acute liver failure (ALF):** liver insult plus development of encephalopathy within 8 weeks of insult in the absence of pre-existing liver disease
  - May or may not be reversible
  - Causes: acetaminophen toxicity, viral infection, ischemic hepatitis, etc.
- **Acute on chronic liver failure (ACLF)**
  - Associated with a high mortality rate
  - Can be precipitated by several causes: infection or viral reactivation, alcoholic hepatitis, acute variceal hemorrhage, etc.

Sources: Bernal et al. *N Engl J Med* 2013;369:2525-34.
Arroyo et al. *N Engl J Med* 2020;382:2137-45.

Grading Liver Failure

Child-Pugh Classification

Criteria	1 pt	2 pts	3 pts
Encephalopathy	None	Mild	Moderate
Ascites	None	Controlled	Uncontrolled
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	≤1.6	1.7-2.2	≥2.3

Class A: 5-6 pts / Class B: 7-9 pts / Class C: 10-15 pts

King's College Criteria (ALF)

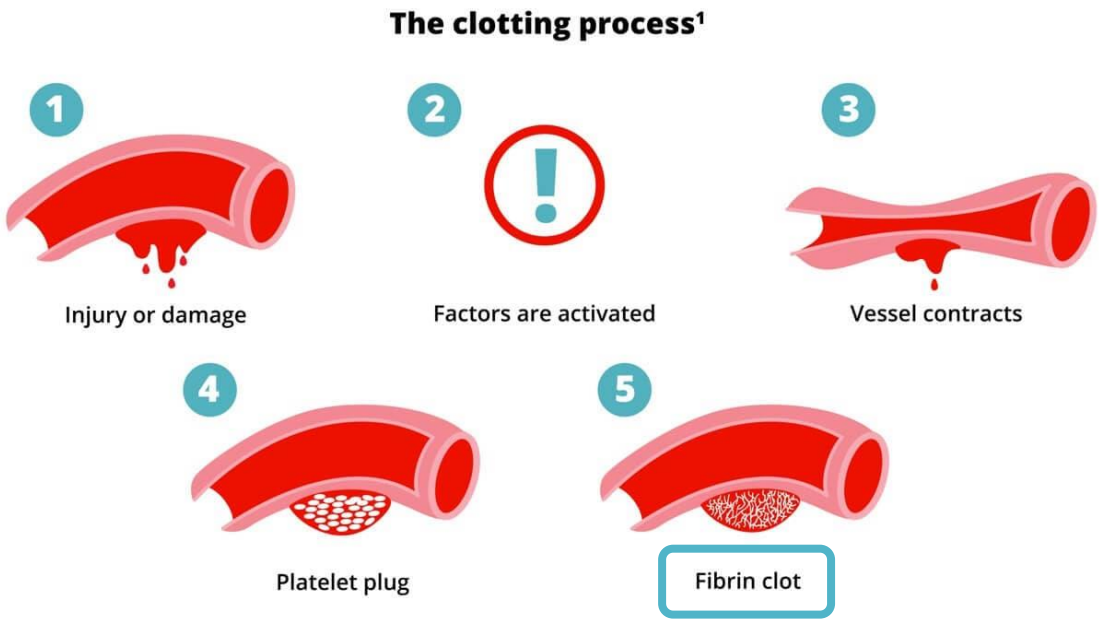
Acetaminophen	Non-Acetaminophen
pH <7.3 or lactate >3.0 or all of the following: • SCr >3.3 mg/dL • PT >100 s or INR >6.5 • Grade 3 or 4 encephalopathy	INR >6.5 (or PT>100s) or any 3: • Age <10 or >40 y • Not hepatitis A-E, not drug induced • INR >3.5 (or PT >50s) • Bilirubin >17 mg/dL • Duration of jaundice to encephalopathy >7 days

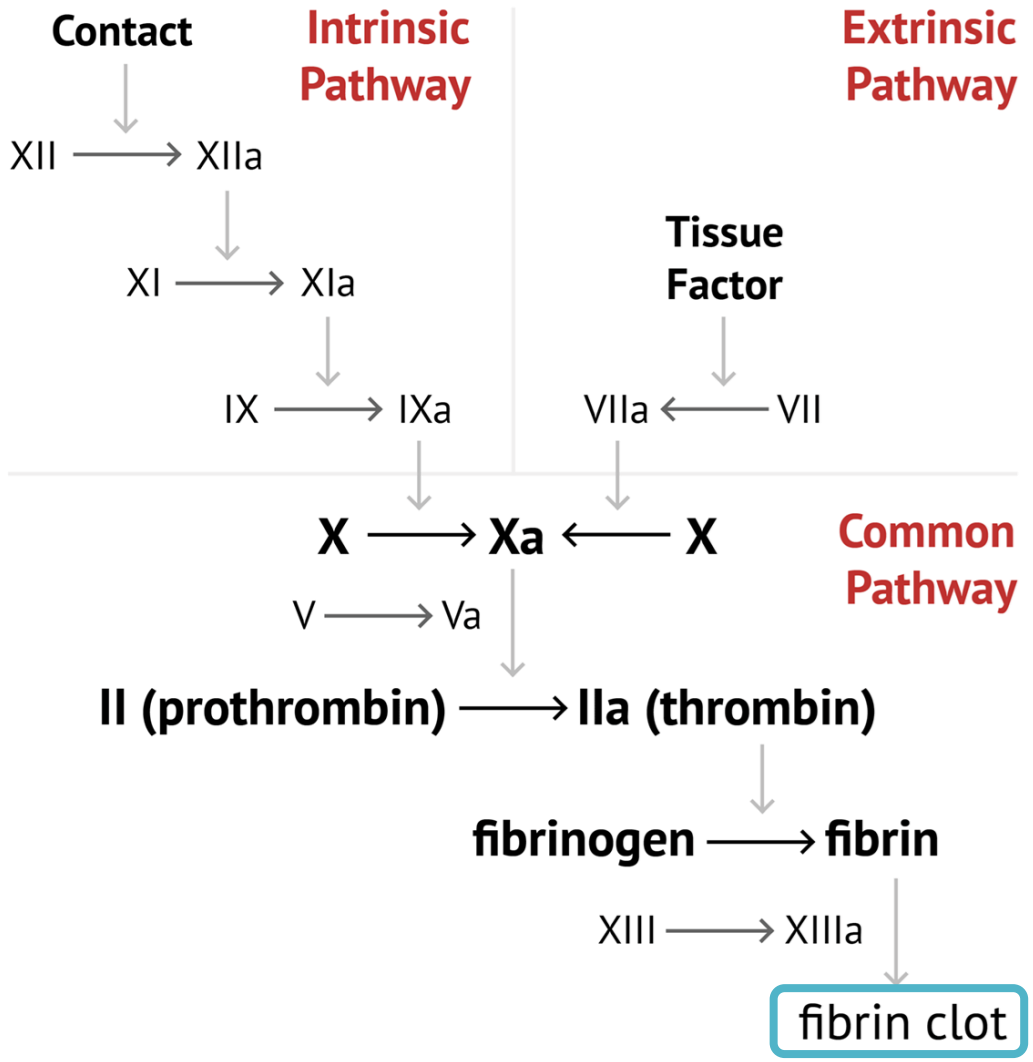
MELD Score

Score	Mortality Risk
0-9	1.9%
10-19	6.0%
20-29	19.6%
30-39	52.6%
≥40	71.3%

Source: Bernal et al. *N Engl J Med* 2013;369:2525-2534.

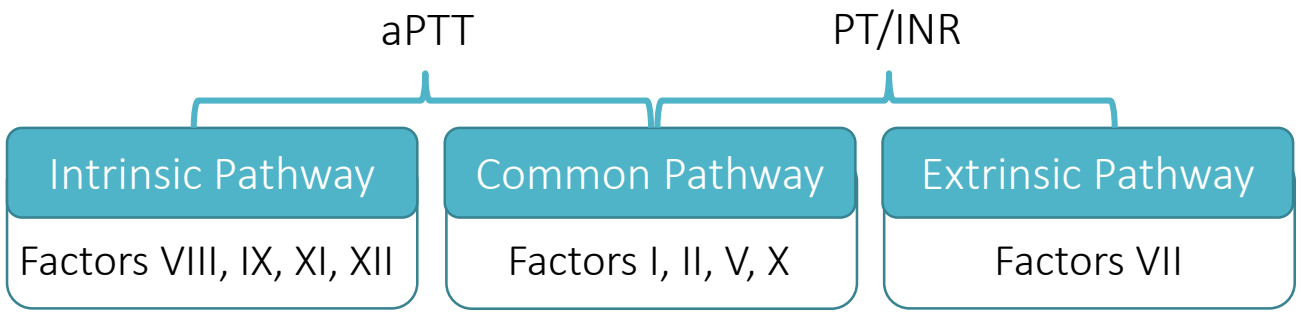
Coagulation Cascade



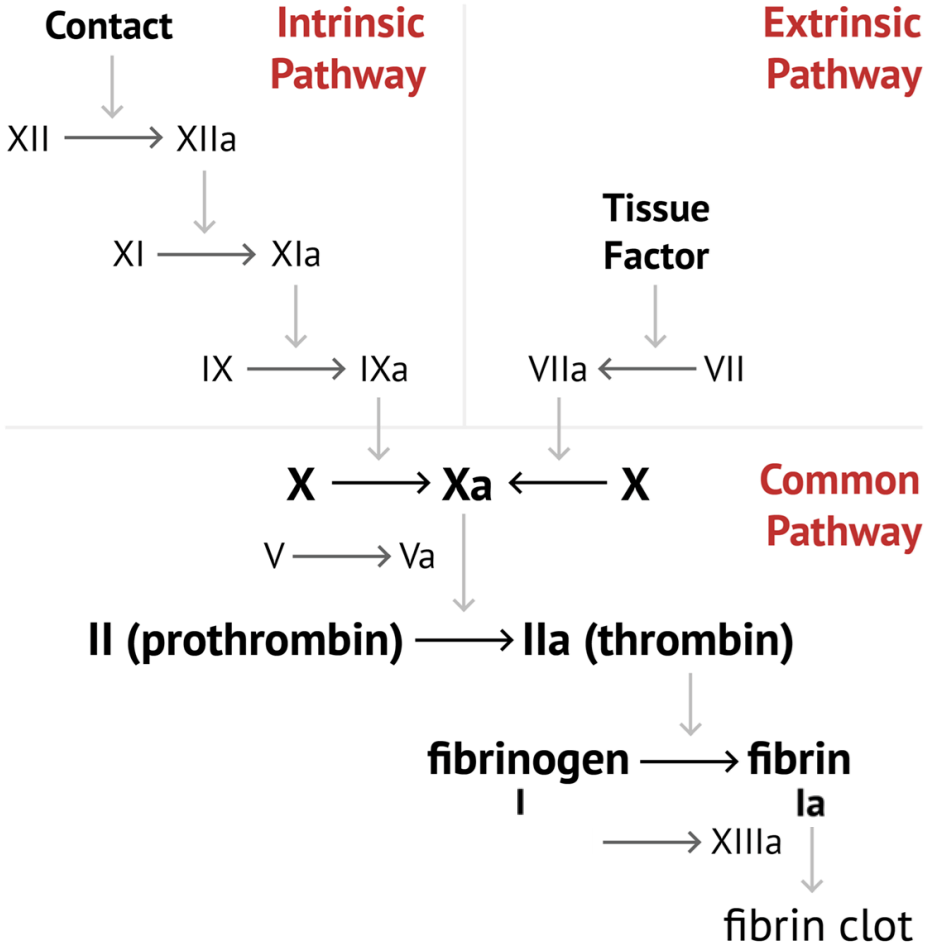


Sources: Blood clots and coagulation. https://www.bleedingdisorders.com/about/how-blood-clots-coagulation
Interpreting coagulation studies. https://medschool.co/tests/coagulation/interpreting-coagulation-studies

Coagulation Cascade



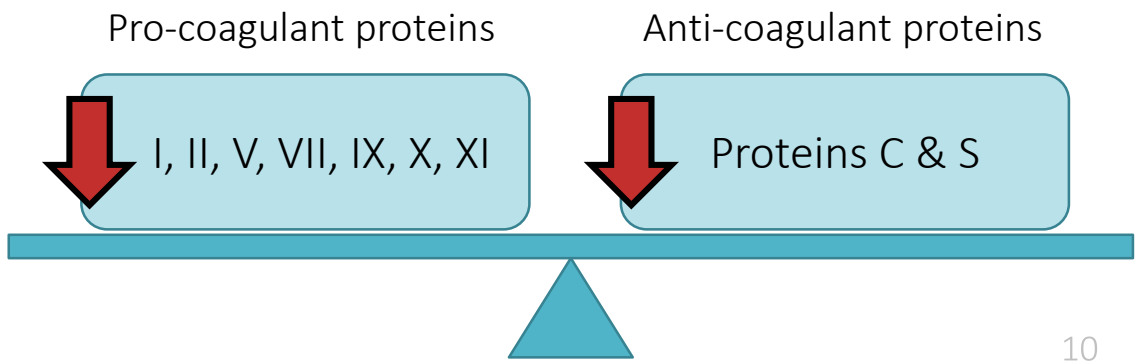
Prothrombin time (PT)	Clotting time that measures extrinsic and common pathways
International normalized ratio (INR)	Correction of PT to account for various reagents used in labs
Activated partial thromboplastin time (aPTT)	Clotting time that measures intrinsic and common pathways
Fibrinogen	Amount of Factor I present in blood



Sources: Bates et al. Coagulation Assays. *Circulation* 2005;112:e53–e60.
Interpreting coagulation studies. https://medschool.co/tests/coagulation/interpreting-coagulation-studies

Coagulation in Liver Failure: A Fine Balance

- The liver is the primary site of synthesis for clotting factors
- Common misconceptions
  - Conventional coagulation assays (CCA) are good measures of coagulation status
  - All patients with liver disease are auto-anticoagulated and at risk of bleeding
- In chronic liver disease, relative deficiencies in clotting factors combined with decreased production of endogenous anticoagulants such as proteins C&S lead to “re-balanced” homeostasis
- Many factors to consider when assessing bleeding/clotting risk:
  - Sepsis
  - Acute inflammation
  - Surgical intervention
  - Other organ dysfunction, comorbidities
  - Severity of liver disease



Sources: Al-Doezi et al. *Thrombosis* ePub 2013;807526:1-7.
Smith et al. *J Hosp Med* 2013;8(10)569-573.
Northup et al. *Clin Gastroenterol Hepatol* 2013;11:1064-1074.

New Guideline Updates

March 2020

Society of Critical Care Medicine
The Intensive Care Professionals

Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary, and Renal Considerations

Rahul Nanchal, MD, MS, FCCM (Co-Chair)[1]; Ram Subramanian, MD, FCCM (Co-Chair)[2];

January 2021

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases

Patrick G. Northup,[1] Juan Carlos Garcia-Pagan,[2-4] Guadalupe Garcia-Tsao,[5,6] Nicolas M. Intagliata,[1] Riccardo A. Superina,[7] Lara N. Roberts,[8] Ton Lisman,[9] and Dominique C. Valla[10,11]

Sources: Nanchal R et al. *Crit Care Med* 2020;48(3):e713-e191.
Northup et al. *Hepatology* 2021;73(1):366-413.

Take Home Message:

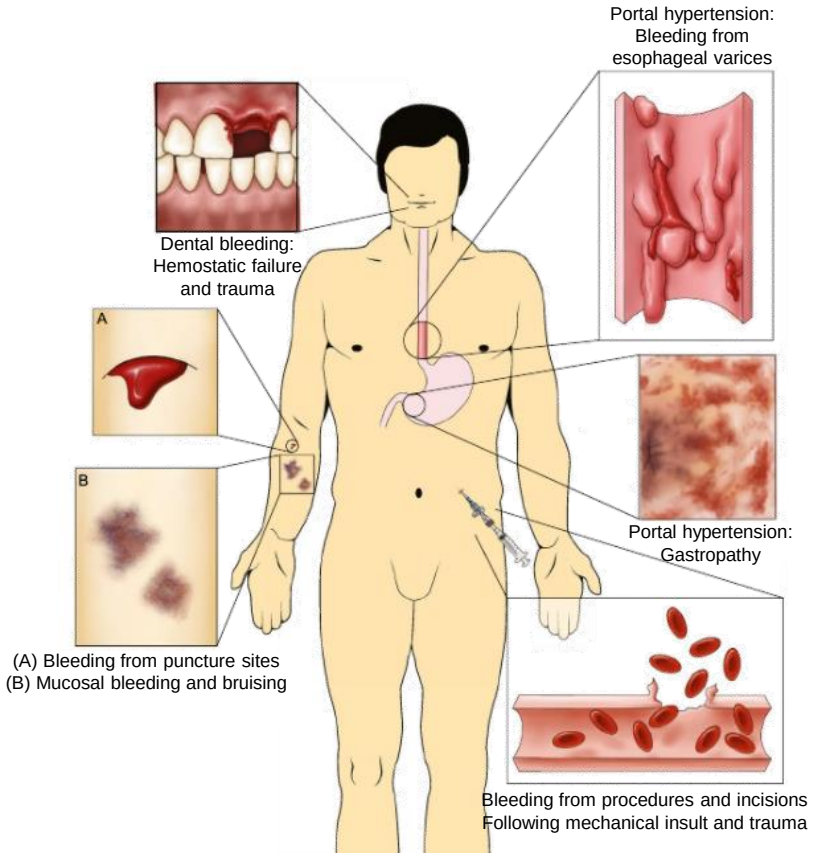
- Patients with **chronic** liver disease are at a new set point between bleeding and thrombosis
- The idea of “auto-anticoagulation” should not preclude patients from getting anticoagulants or DVT prophylaxis if they also have a high risk of thrombosis

Reversal of Coagulopathy in Liver Failure

Indications for Reversal of Coagulopathy in Liver Failure

- **Active Bleeding or Surgical Procedures**

Types of Bleeding Seen in Patients with Cirrhosis



AASLD List of High Bleeding Risk Procedures in Patients with Cirrhosis

Percutaneous	• Biliary intervention (cholecystostomy or percutaneous biliary drain) • Liver biopsy • Tumor ablation • Non-liver intra-abdominal solid organ or intrathoracic biopsy • Nephrostomy tube placement • CNS procedures • Intra-ocular procedures • Intra-articular injections
Vascular	• TIPS • Angiography or venography with intervention • Transjugular venous biopsy • Transhepatic arterial chemoembolization or radioembolization • Therapeutic coronary angiography
Endoscopic	• Endoscopic polypectomy • Endoscopic stricture dilation or mucosal resection • Balloon-assisted enteroscopy • Percutaneous endoscopic gastrostomy placement • Endoscopic retrograde cholangiopancreatography with sphincterotomy • Endoscopic ultrasound with fine-needle aspiration • Cystgastrostomy • Therapeutic bronchoscopy or diagnostic bronchoscopy with biopsy

Source: Northup et al. *Hepatology* 2021;73(1):366-413.

Vitamin K (Phytonadione)

- Dietary intake of vitamin K is necessary to form coagulation factors II, VII, IX, and X

- Administration of vitamin K to reduce INR in patients with cirrhosis has been a routine practice in the United States for decades for two reasons
  - Patients with cirrhosis are all thought to have vitamin K deficiencies
  - Vitamin K perceived to be a benign and inexpensive approach to reversing coagulopathy

- Outside of advanced malnutrition states or cholestasis, vitamin K replacement has no measurable effect on INR in patients with cirrhosis

Sources:Hunt BJ. *N Engl J Med* 2014;370(9):847-859.
Aldrich et al. *Pharm Ther* 2019;44(3):131-136.
Northup et al. *Hepatology* 2021;73(1):366-413.

Fresh Frozen Plasma (FFP)

- Contains all clotting factors, proteins C&S, fibrinogen (400-900 mg/unit), albumin, antithrombin, and tissue factor pathway inhibitor
- Current standard of care for reversal of coagulopathy in hemorrhage associated with liver disease and before high-risk surgical procedures
- Routine reversal of coagulopathy with FFP prior to low or moderate risk procedures is not well established in guidelines
- Dose to correct coagulopathy associated with liver disease is not well established
  - Trauma, anticoagulation reversal: 15-30 mL/kg = ↑ in factor levels by about 20%
  - AASLD guidelines: 20-40 mL/kg
  - Society of Interventional Radiology guidelines: 10-15 mL/kg
- Less expensive than prothrombin complex concentrates (PCC)

Source: Northup et al. *Hepatology* 2021;73(1):366-413.

Prothrombin Complex Concentrates (PCC)

- 3 factor PCC contains factors II, IX, X
- 4 factor PCC contains factors II, VII, IX, X and proteins C & S
- Consider thrombosis risk in patients who receive PCCs
  - Associated with repeat dosing (dosing affects the safety profile)
  - Long half-life of factor II (prothrombin) leads to accumulation
- PCC have been used off-label in Europe and in some United States institutions for the reversal of coagulopathy associated with liver disease

SCCM guidelines state “There is insufficient evidence to issue a recommendation for or against PCC”

Sources: KCENTRA [package insert]. Kankakee, IL: CSL Behring; 2013.
Nanchal R et al. *Crit Care Med* 2020;48(3):e713-e191.

Potential Advantages of PCC over FFP

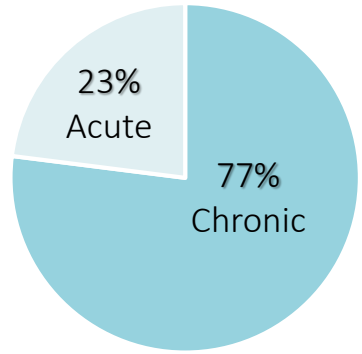
	FFP	PCC
Volume	Larger volume required to achieve comparable reduction in INR may not be tolerated in certain patients (e.g., renal failure, heart failure, liver patients with large volume ascites and 3rd spacing)	Smaller total volume than FFP due to concentrated factors
Preparation	Must be thawed by blood bank Requires blood type screening	No thawing or type/screen required
Administration	Longer administration time: Each unit of FFP infused over 30 min	Shorter administration time: Administered up to 8.4 mL/min

PCC

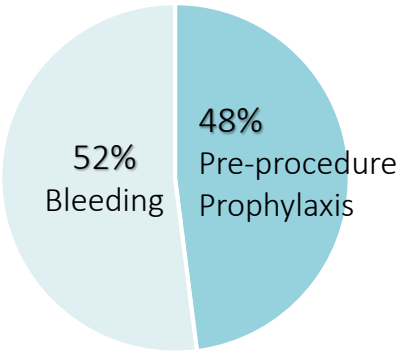
Case Series

- Retrospective analysis characterizing 194 4F-PCC administrations in 105 patients with liver-related coagulopathy in London
- Median dose of PCC administered: 22 IU/kg (~1,500 IU)
  - Beriplex P/N® & Octaplex® used; dose rounded to nearest whole vial
- Cryoprecipitate or fibrinogen concentrate administered when plasma fibrinogen <200 in bleeding patients and ≤150 in patients undergoing surgical procedures

Type of Liver Failure



Indication for PCC



Clinical Outcomes

- PCC therapy produced statistically significant reductions in PT and INR regardless of the administration of cryoprecipitate/fibrinogen concentrate

No concurrent fibrinogen or cryoprecipitate

	Pre-PCC Median (IQR)	Post-PCC Median (IQR)
PT	27 (23-34)	23 (20-26)
INR	2.3 (1.9-2.9)	1.8 (1.6-2.1)
INR to ≤1.5	6% of patients	22% of patients

Concurrent fibrinogen or cryoprecipitate

	Pre-PCC Median (IQR)	Post-PCC Median (IQR)
PT	30 (23-54)	21 (18-28)
INR	3.1 (2.0-7.0)	1.9 (1.5-2.8)
INR to ≤1.5	4% of patients	25% of patients

Source: Drebes et al. *Hepatol Commun* 2019; 3(4):513-524.

PCC

Case Series (continued)

Safety Outcomes

Thrombotic Events

- No cardiovascular adverse events or strokes were recorded during the 4-week follow up period after administration of PCC
- Three patients (~3%) developed venous thromboembolic events

Mortality

- 46 patients died of causes determined to be unrelated to PCC treatment (44%)
- Higher mortality rates observed in patients admitted with decompensated liver disease and those with Child-Pugh grade C liver disease

Author's conclusion: PCC was effective in improving coagulation tests without an excess of thrombotic events

Source: Drebes et al. *Hepatol Commun* 2019; 3(4):513-524.

PCC

Retrospective Cohort Study

- 45 critically ill adults with hepatic impairment (INR >1.5) who received either FFP alone, PCCs, or rFVIIa prior to a surgical intervention or procedure

	FFP (n=15)	PCC (n=15)	rFVIIa (n=15)	p-value
Mean dose administered ± SD	1.1 ± 0.5 units	2523 ± 861 units	2.6 ± 0.9 mg	N/A
Primary outcome Achieved INR <1.5 at time of procedure, n(%)	4 (27)	12 (80)	13 (87)	p<0.05 FFP vs. PCCs or rFVIIa
Primary outcome Mean absolute change in INR from 12h before procedure to time of procedure ± SD	0.5 ± 0.8	1.6 ± 0.9	1.8 ± 0.7	p<0.05 FFP vs. PCCs or rFVIIa
Median time to procedure, hours	2.1 ± 1.4	1.3 ± 0.5	1.3 ± 0.6	p<0.05 FFP vs. PCCs or rFVIIa

Source: Kwon et al. *Pharmacotherapy* 2016;36(10):1047-1054.

PCC

Retrospective Cohort Study (continued)

- Safety Outcomes

	FFP (n=15)	PCC (n=15)	rFVIIa (n=15)	p-value
Hypervolemia, n (%)	14 (93)	6 (40)	5 (33)	p<0.05 for FFP vs. PCC or rFVIIa
TRALI, n (%)	4 (27)	0 (0)	1 (7)	Not reported
Major bleeding, n (%)	3 (2)	4 (27)	4 (27)	Not reported
Minor Bleeding , n (%)	12 (80)	11 (73)	10 (67)	Not reported
Thromboembolic event, n (%)	0 (0)	1 (7)	2 (13)	Not reported

Author's conclusion: PCC and rFVIIa reduced INR faster and more effectively than FFP in patients with coagulopathy associated with liver impairment. Bleeding rates were similar across all groups.

Source: Kwon et al. *Pharmacotherapy* 2016;36(10):1047-1054.

Recombinant Factor VIIa (NovoSeven®)

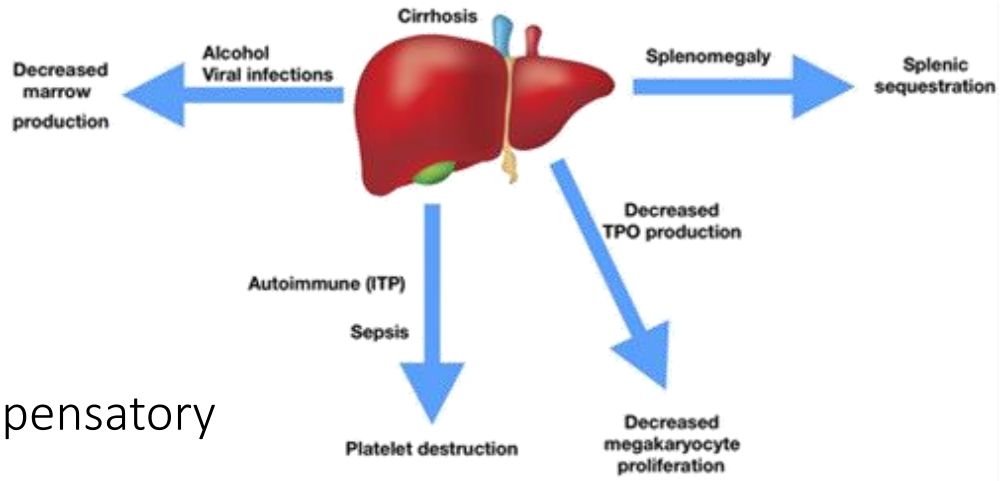
- FDA-indicated for patients with hemophilia and congenital factor VII deficiency
- Historically used off-label to correct elevated INR and coagulopathy associated with liver disease, but has since been largely replaced by PCC since their development
- In a randomized trial of Child-Pugh class B and C patients with cirrhosis and variceal bleeding, rFVIIa had no impact on the primary composite endpoint
  - Failure to control 24-hour bleeding or failure to prevent rebleeding or death at day 5
- rFVIIa potentially increases risk of arterial thrombosis
  - One meta-analysis analyzed n = 4,468 who received either rFVIIa or placebo for off-label indications
  - Rates of arterial thromboembolic events were higher among those who received rFVIIa compared to placebo (5.5% vs. 3.2%, P=0.003)

Sources: Bosch et al. *Hepatology* 2008;47(5):1604-1614.
Levi et al. *N Engl J Med* 2020;363(19):1791-1800.

Platelets

- Thrombocytopenia is a common complication of chronic liver disease
  - Affects 6% of patients without cirrhosis and 70% with cirrhosis

- Platelets normally have two functions
  - Support thrombin generation by assembling coagulation factors on their surface
  - Adhere to damaged vessel wall through interaction with the adhesive protein Von Willebrand factor (vWF)



- In thrombocytopenia associated with liver disease, a compensatory restoration of platelet function occurs
  - Increased levels of vWF and reduced levels of ADAMTS 13

Sources: Giannini et al. Clin Gastroenterol Hepatol 2010; 8(10):899-902.
Tripodi et al. *New Engl J Med* 2011;365:147-56.

Platelets

- Platelets may be a better predictor of bleeding risk than PT/INR in patients undergoing invasive procedures
- Literature suggests a serum platelet count of 50-60k is required for a sufficient thrombin burst to form a clot
- In vitro data suggests there may not be an additional benefit with replacement to >100k

Guideline	Platelet Count Target
SCCM 2020	No recommendation
AASLD 2021	No routine pre-procedure correction
Society of Interventional Radiology 2019	> 30 x 1,000µ/L
American Gastroenterological Association 2019	> 50 x 1,000µ/L
American College of Gastroenterology 2020	> 50 x 1,000µ/L

Sources: Northup et al. Clin Gastro and Hepatology 2013;11:1064-1074.
Northup et al. *Hepatology* 2021;73(1):366-413.

Packed Red Blood Cells (PRBC)

- SCCM guidelines suggest a transfusion threshold of 7 mg/dL for critically ill patients with ALF or ACLF
- Recommendation based on single-center RCT that compared a restrictive transfusion target (7 mg/dL) vs. a liberal strategy (9 mg/dL) in 889 patients with acute GI bleed
  - Stratified for the presence or absence of cirrhosis and found no significant difference between transfusion targets with respect to death by 6 weeks (HR, 0.57; 95% CI, 0.30–1.08; p = 0.08)
  - Study also suggested a mortality benefit in Child-Pugh Class A and B cirrhosis (HR, 0.30; 95% CI, 0.11–0.85)
- RBC transfusions are an independent predictor of mortality post liver transplantation
  - Endogenous erythropoietin levels are elevated in cirrhosis and contribute to portal hypertension
  - Transfusion or more erythropoietin may theoretically worsen thrombosis risk

Source: Nanchal R et al. *Crit Care Med* 2020;48(3):e713-e191.

Cryoprecipitate / Fibrinogen Concentrate

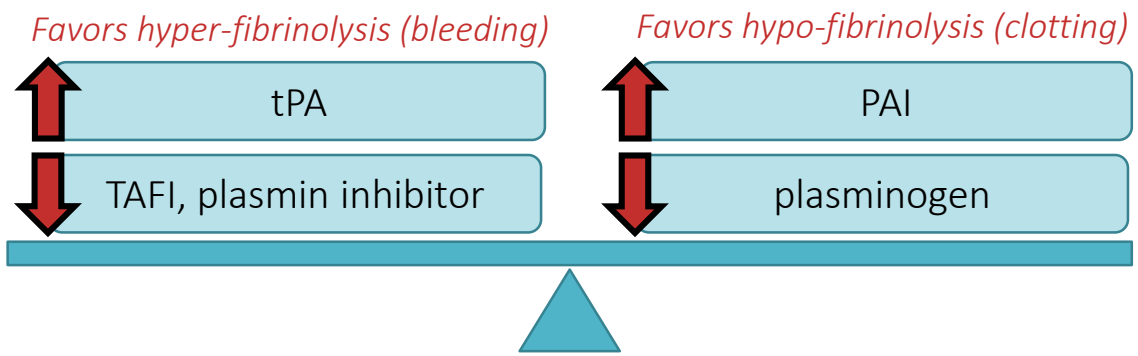
- Low levels of fibrinogen are common in patients with cirrhosis
  - Low levels of fibrinogen can suggest hyperfibrinolysis, and levels <100 mg/dL are concerning for risk of bleeding
  - Not predictive of DIC in this patient population- patients with low fibrinogen can be stable and nonbleeding
  - Fibrinogen is an acute phase reactant and can fluctuate
- Cryoprecipitate contains factors VIII, XIII, vWF, and fibrinogen
  - 1 unit cryoprecipitate ~250mg fibrinogen
- Fibrinogen concentrate (Fibryga®, RiaSTAP®) indicated for congenital fibrinogen deficiency; has been used off label in other countries for coagulopathy in liver disease

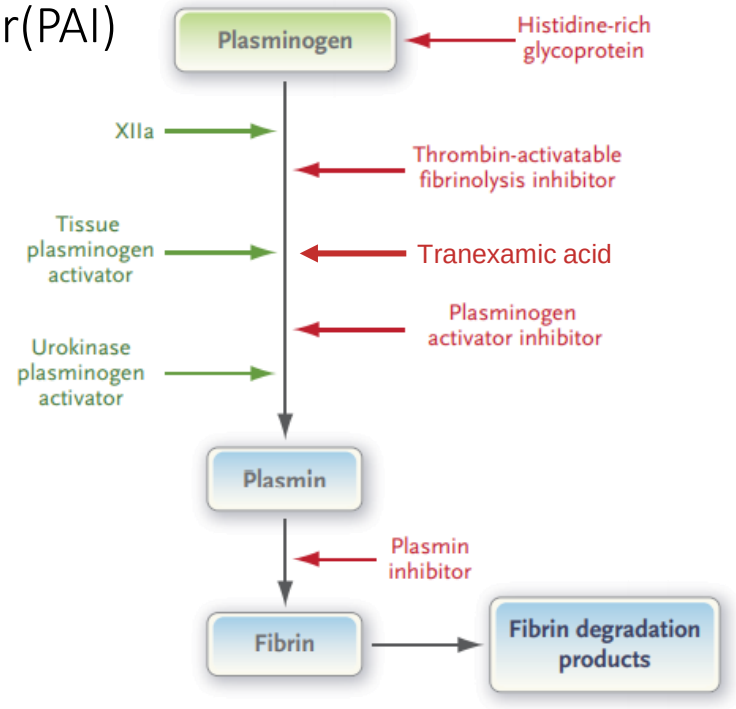
Guideline	Fibrinogen Target
SCCM 2020	No routine pre-procedure correction; Use TEG
AASLD 2021	No routine pre-procedure correction
Society of Interventional Radiology 2019	> 100 mg/dL
American Gastroenterological Association 2019	>120 mg/dL
American College of Gastroenterology 2020	>120-150 mg/dL

Source: Northup et al. *Hepatology* 2021;73(1):366-413.

Antifibrinolytic Agents

- The conversion of plasminogen to plasmin is normally regulated by pro-fibrinolytic drivers such as tissue plasminogen activator (tPA) and factor XIIa
- This system is balanced by anti-activators such as plasminogen activator(PAI) and thrombin-activatable fibrinolysis inhibitor (TAFI)
- Cirrhosis has been associated with both hyper- and hypo-fibrinolysis

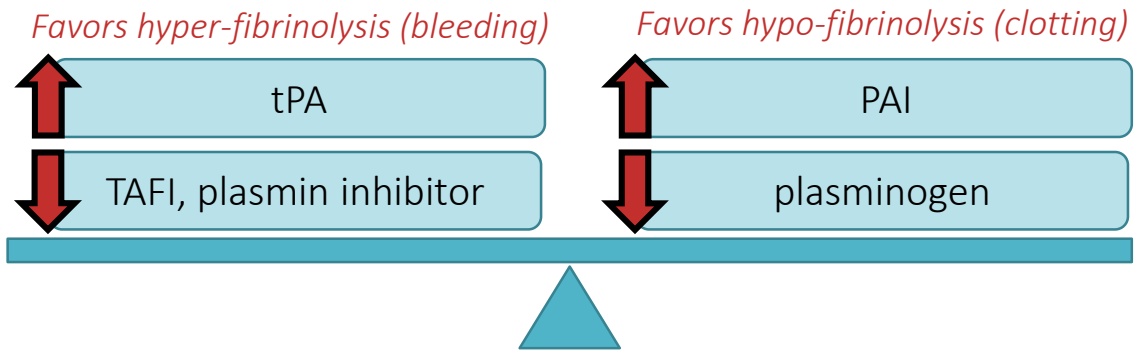


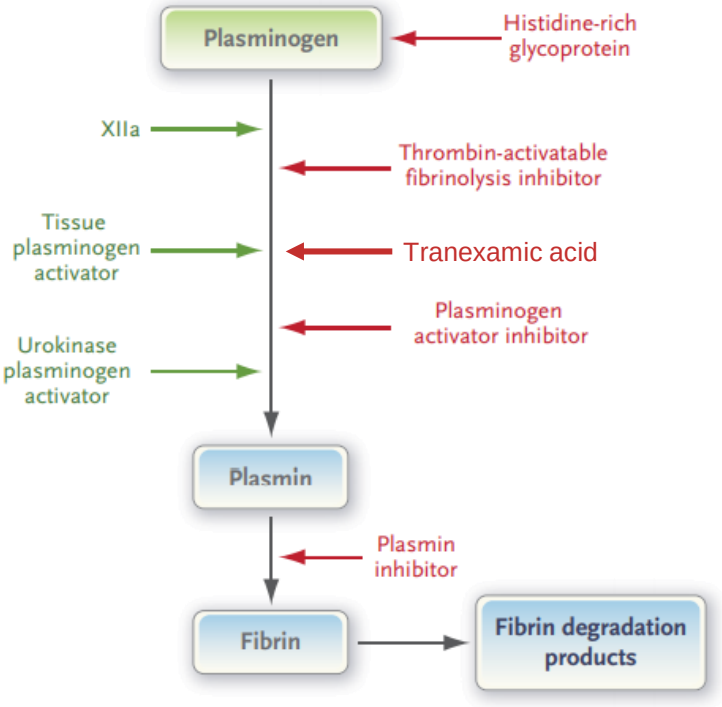


Source: Tripodi et al. *New Engl J Med* 2011;365:147-56.

Antifibrinolytic Agents

- No appropriate lab tests to evaluate summative state of fibrinolysis
- Likely no role for empiric tranexamic acid (TXA) or aminocaproic acid in coagulopathy, may consider in uncontrolled hemorrhage
- No guideline recommendations on use of antifibrinolytics in liver disease due to lack of current evidence





Source: Tripodi et al. *New Engl J Med* 2011;365:147-56.

Take Home Message:

- Small retrospective data suggests efficacy in reducing INR without an increased risk in thrombosis
- The optimal dose of 4 factor PCC for the reversal of coagulopathy associated with acute or acute on chronic liver failure is unknown

Thromboelastography to Guide Management of Coagulopathy

What is TEG/ROTEM?

- Thromboelastography / rotational thromboelastometry are viscoelastic hemostatic assays that assess clot formation and dissolution kinetics

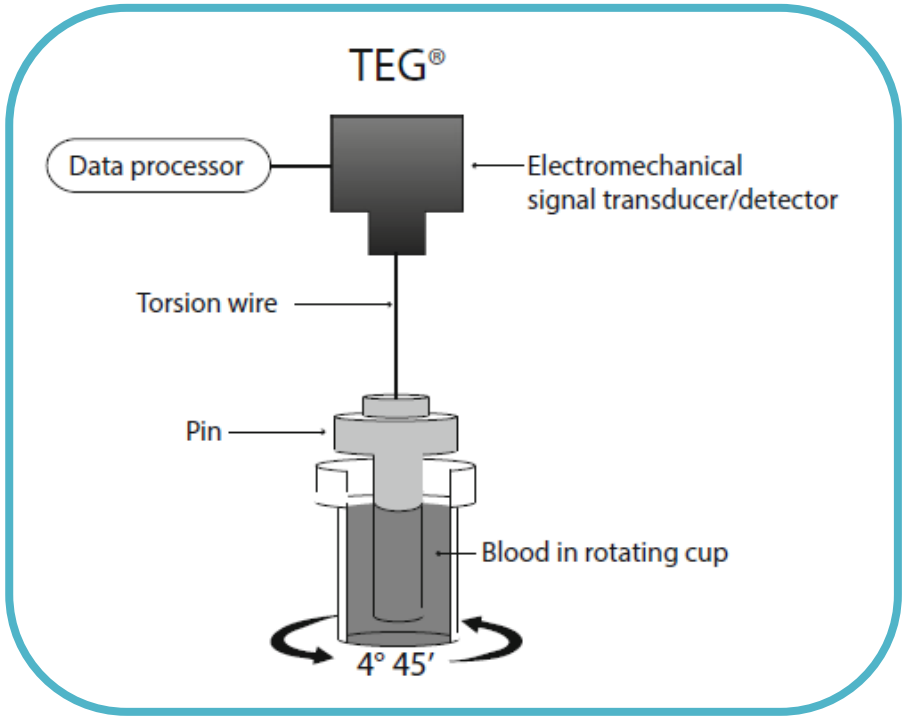
- TEG was initially developed in 1948 by Dr. Hellmut Hartert and has since been studied primarily in the trauma and cardiac surgery population

- Benefits of TEG over CCA
  - Dynamic measure of the coagulation process – measures BOTH clot formation AND clot dissolution
  - Accounts for all components of the coagulation cascade rather than individual pieces
  - Point of Care – may obtain faster results; can be interpreted in real time with appropriate expertise
  - Associated with overall reduction in blood product transfusions in several other patient populations

Source: Kreitzer et al. *Neurocrit Care* 2015;23:427-433.

How does it work?

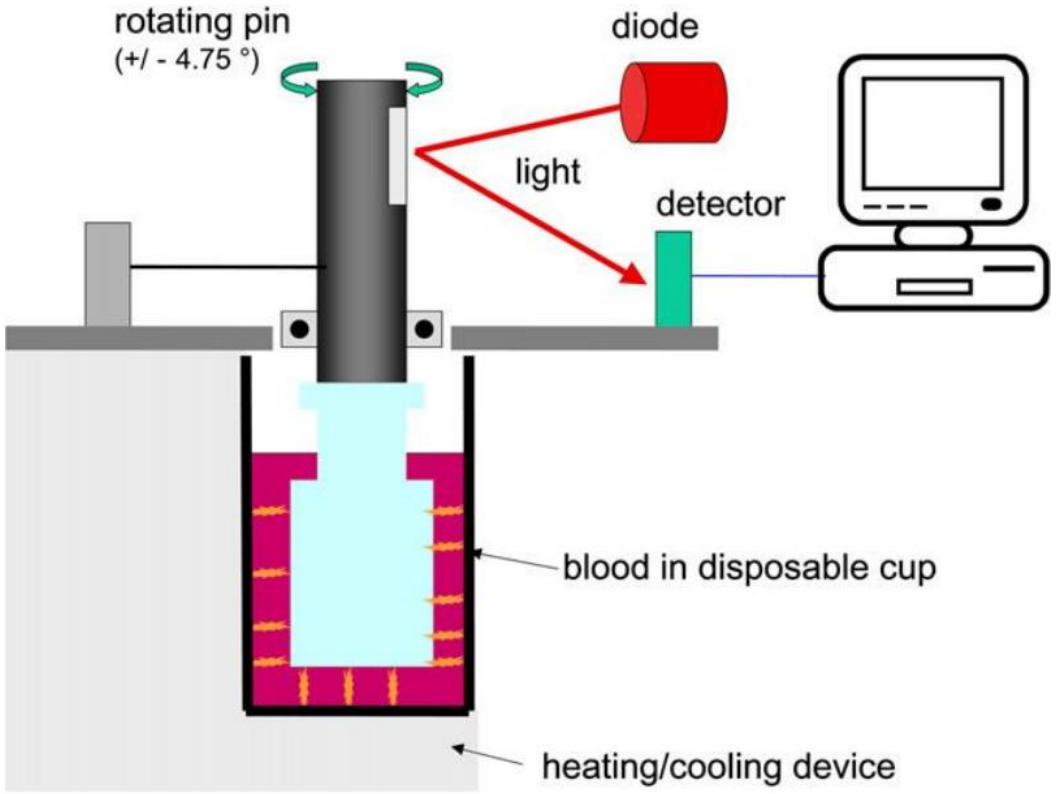
- A small sample of blood (0.36 mL) is added to a cup that is heated to 37°C and slowly oscillates
- A pin connected to a torsion wire is suspended in the cup and measures the mechanical resistance of the blood
- Tracing is developed with parameters that can guide resuscitation



Source: Kreitzer et al. *Neurocrit Care* 2015;23:427-433.

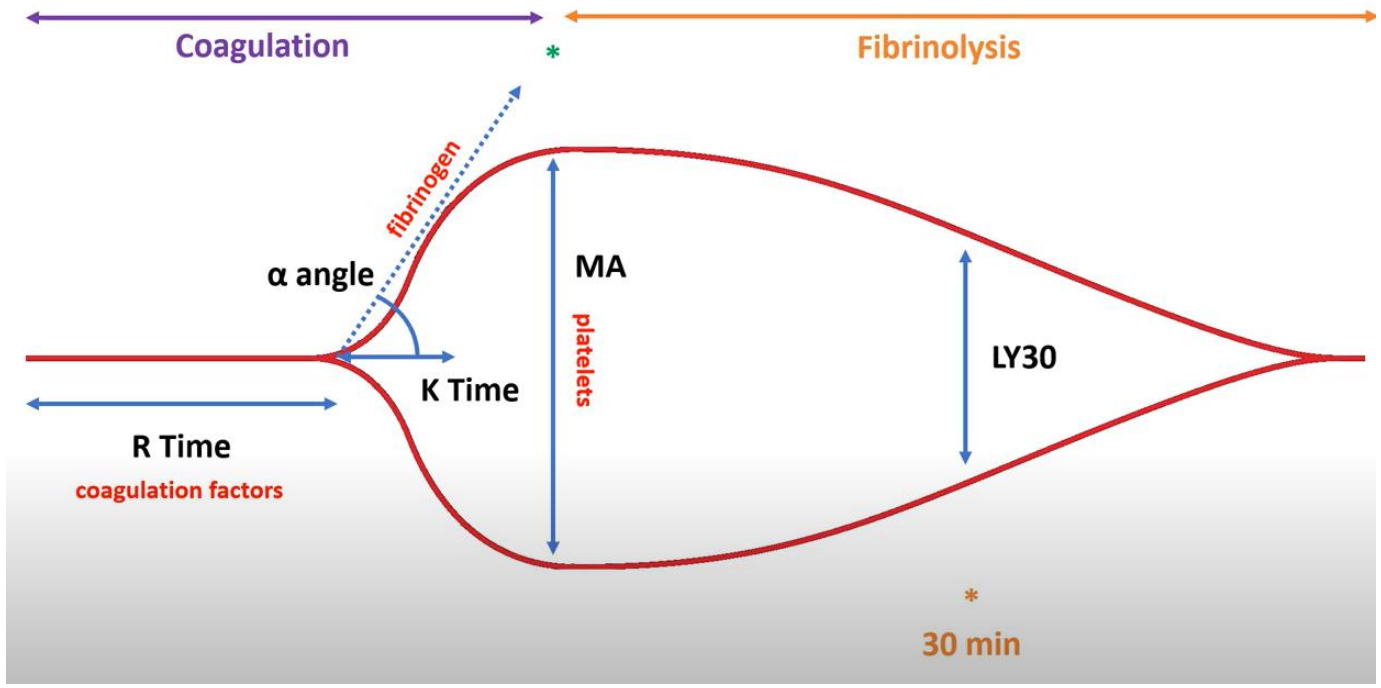
How does it work?

ROTEM®



Sources: https://www.instrumentationlaboratory.com/us/en/rotem-delta
https://www.instrumentationlaboratory.com/us/en/rotem-sigma
https://www.nmthoracic.org/components/com_rseventspro/assets/images/files/DEATON-ROTEM%20in%20Bleeding%20Patient.pdf

Tracing Definitions



- **R time / clotting time**: time from start of test to formation of clot; time to generate fibrin
- **K time / clot formation time**: time it takes to reach a certain level of clot strength (20 mm)
- **α-angle**: tangent line to curve at k-time; represents the speed of clot buildup
- **MA / MCF**: maximum amplitude / maximum clot firmness; point at which clot is most firm
- **LY 30 / clot lysis :** clot lysis 30 minutes after maximum amplitude is reached

Sources: Da Luz et al. *Scand J Trauma Resus and Emerg Med* 2013;21(29):1-8.
Image: https://www.youtube.com/watch?v=zEFszp9DKLE

Interpreting a Tracing

TEG	ROTEM	Normal Value	Interpretation	Treatment
R time	Clotting time (CT)	5-10 min	↑ R –time: deficiency in clotting factors	Give FFP (or PCC)
K time	Clot formation time (CFT)	1-3 min	↑ K –time: deficiency in fibrinogen	Give cryoprecipitate
α angle	α angle	50-75°	Narrow angle <50°: deficiency in fibrinogen	Give cryoprecipitate
Maximum amplitude (MA)	Maximum clot firmness (MCF)	50-70 mm	↓ MA – platelet dysfunction	Give platelets ± DDAVP
LY 30	Clot Lysis (CL)	0-10%	↑LY 30 = increased fibrinolysis	Give TXA ± aminocaproic acid

Source: Mallett SV. *Semin Thromb Hemost* 2015;41:527-537.

Examples and Dose Recommendations

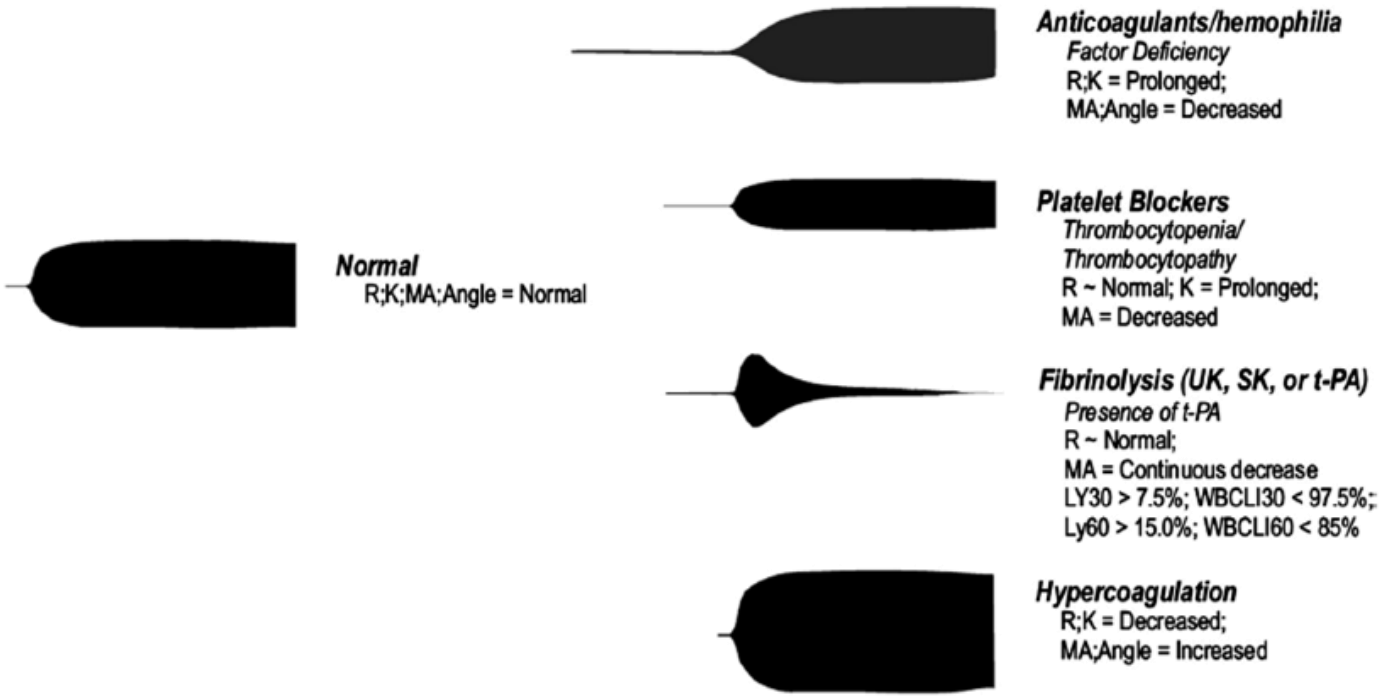


Table 1. Clinical Interpretation of TEG Results as Recommended by Manufacturer

TEG Result	Hemostasis State	Recommended Treatment
Angle		
<45°	Low fibrinogen level	0.06 U/kg cryoprecipitate
Reaction time (R value)		
<4 minutes	Enzymatic hypercoagulability	Anticoagulant
11–14 minutes	Low clotting factors	2 U of FFP
>14 minutes	Very low clotting factors	4 U of FFP
Maximal amplitude		
46–54 mm	Low platelet function	0.3 μg/kg DDAVP
41–45 mm	Very low platelet function	1 U of platelet pheresis
≤40 mm	Extremely low platelet function	2 U of platelet pheresis
>73 mm	Platelet hypercoagulability	Antiplatelet therapy

Sources: Whiting D et al. *Am J Hematol* 2014; 89(2): 228-232.
Redfern et al. *Ann Thorac Surg* 2019;107:1313–8.

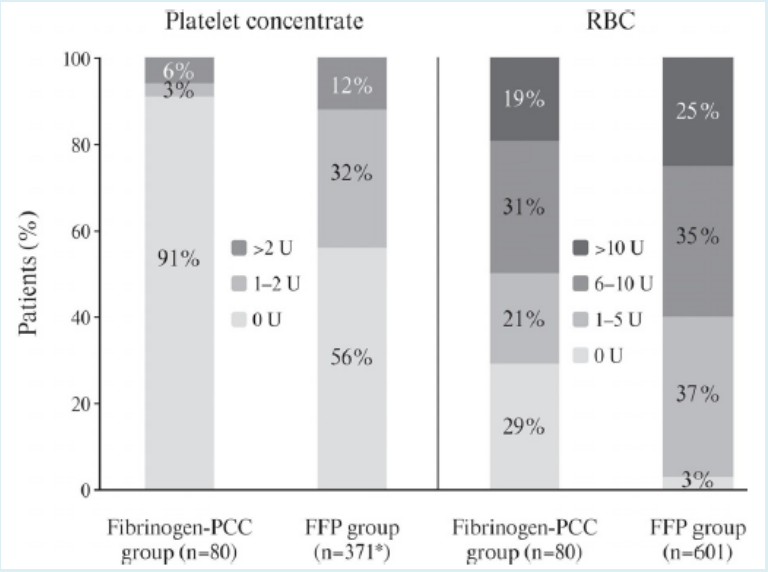
Clinical Data with TEG/ROTEM in patient populations

- Study Design: Retrospective analysis of trauma patients in Austria with injury severity score ≥16

Fibrinogen-PCC group n = 80	vs.	FFP group n = 601
≥1g fibrinogen; ≥500 units PCC *No FFP* *PCC and platelets guided by ROTEM®* *RBC transfused to hemoglobin ≥ 10 g/dL*		*≥2 units FFP* *No additional fibrinogen or PCC* *Platelets given per clinician discretion* *RBC transfused to hemoglobin ≥ 10 g/dL*

- Complete avoidance of RBC transfusion: 29% vs. 3%
  - All patients who avoided RBC in the fibrinogen-PCC group also avoided platelets
  - Proposed theory: ↑FFP causes hemodilution,↑ RBC transfusion requirements
- Platelet transfusion avoided in 91% vs. 56% of patients
  - Baseline platelet count on admission was 178 ±68 vs. 184±79 (p=NS)
  - Proposed theory: high levels of fibrinogen increase maximum clot firmness even in patients with low platelet count, suggesting possible compensation

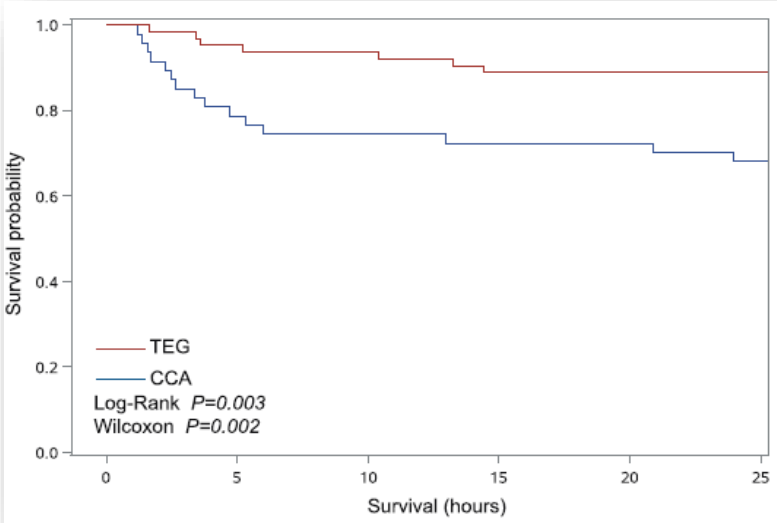
ROTEM guided hemostatic therapy reduced the exposure of trauma patients to allogeneic blood products



Source: Schochl et al. *Crit Care* 2011;15:R83.

Clinical Data with TEG/ROTEM in patient populations

- Prospective RCT that randomized 111 patients who activated MTP at a level I trauma center to be managed by either TEG or CCA
- Demographics, injury severity, and coagulation assays similar at baseline
- Clinicians could administer up to 4 units PRBC and 2 units FFP in either group while waiting for results of coag studies
- Primary outcome: 28-day survival
  - Significantly higher risk of death in CCA group vs. TEG group (Hazard Ratio 2.17; 95% CI1.03-4.58, p=0.04)
  - Survival benefit driven by less hemorrhagic deaths in TEG group (7.8% vs 23.4%, p=0.02)
- Secondary outcomes:
  - No difference in use of PRBC
  - CCA led to significantly more use of plasma and platelets in the first 2 hours of resuscitation; more use of cryoprecipitate overall



Source: Gonzalez et al. *Ann Surg* 2016; 263(6)1051-1059.

Clinical Data with TEG/ROTEM in Liver Disease

- Prospective study of acutely ill patients with severe chronic liver disease (Child Pugh C)
- A total of 109 paired CCA and TEG samples were obtained from 34 patients
- 41% were ICU patients (mean APACHE III score 84) with infection being most common admission diagnosis
- CCA such as PT/INR, platelet counts, and D-dimer had poor correlation with TEG
- The only conventional coagulation parameter that was consistently associated with TEG tracings was fibrinogen

Coagulation Initiation				Correlation
• TEG: R-time	vs.	CCA:	PT	Inconsistent
			INR	Inconsistent
Clot Formation				
• TEG: K-time	vs.	CCA:	fibrinogen	Consistent
• TEG: α-angle	vs.	CCA:	fibrinogen	Consistent
Clot Strength				
• TEG: MA	vs.	CCA:	platelet count	Inconsistent
			fibrinogen	Consistent
Fibrinolysis				
• TEG: LY 30%	vs.	CCA:	D-dimer	Inconsistent

Source: Lloyd-Donald et al. *Clin Appl Thromb Hemost* 2020;26:1-10.

Limitations of Thromboelastography

- Cost and availability
- Parameters are not standardized to one reagent
- Requires experience to interpret tracings

Source: Northup et al. *Clin Gastro and Hepatology* 2013;11:1064-1074.

Take Home Message:

- TEG/ROTEM provides **real time** information about a patient's coagulation status
- Studies have shown a reduction in blood product use with TEG guided vs. CCA- guided resuscitation and reversal of coagulopathy

Conclusion

- CCA such as PT/INR do not accurately reflect bleeding risk in patients with liver failure
- If deciding to replace factors, four-factor PCC may be considered an alternative to conventional fresh frozen plasma
- Viscoelastic testing with thromboelastography (TEG®) should be considered prior to reversal of coagulopathy in patients with liver failure

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Assessment Questions

Question 1

True/False: Patients with chronic liver disease are *always* at a higher risk of bleeding than thrombosis, because their coagulopathy leads to “auto-anticoagulation”

Question 1: Response

True/False: Patients with chronic liver disease are *always* at a higher risk of bleeding than thrombosis, because their coagulopathy leads to “auto-anticoagulation”

FALSE

Question 2

Which of the following has been described in recent literature regarding the use of PCCs in coagulopathy associated with liver disease?

A. The optimal dose of 4 factor PCC (Kcentra®) for reversal of coagulopathy is 50 units/kg
B. More cardiopulmonary complications and volume overload have been found with PCC over conventional techniques like FFP
C. PCCs may lower INR as effectively or more than FFP before surgical procedures
D. The Society of Critical Care Medicine strongly suggests the use of PCCs for reversal of coagulopathy

Question 2: Response

Which of the following has been described in recent literature regarding the use of PCCs in coagulopathy associated with liver disease?

A. The optimal dose of 4 factor PCC (Kcentra®) for reversal of coagulopathy is 50 units/kg
B. More cardiopulmonary complications and volume overload have been found with PCC over conventional techniques like FFP
C. PCCs may lower INR as effectively or more than FFP before surgical procedures
D. The Society of Critical Care Medicine strongly suggests the use of PCCs for reversal of coagulopathy

Question 3

Which of the following is an advantage of using TEG/ROTEM over CCA such as PT/INR, platelets, fibrinogen, etc. for assessing a patient's bleeding and thrombosis risk?

A. More precise identification of patient's coagulation status

B. Potential to use less blood products

C. "Real-time" information available in minutes

D. All of the above

Question 3: Response

Which of the following is an advantage of using TEG/ROTEM over CCA such as PT/INR, platelets, fibrinogen, etc. for assessing a patient's bleeding and thrombosis risk?

A. More precise identification of patient's coagulation status

B. Potential to use less blood products

C. "Real-time" information available in minutes

D. All of the above

Question 4

Case Question: You respond to a Code Trauma in the ER for a patient in hemorrhagic shock for which massive transfusion protocol is initiated. The team decides to perform TEG to guide further resuscitation and you see the following waveform (left).
Which of the following agents should be given?

Decreased MA

Normal

A. Platelets

B. FFP

C. Cryoprecipitate

D. Tranexamic acid

Question 4: Response

Case Question: You respond to a Code Trauma in the ER for a patient in hemorrhagic shock for which massive transfusion protocol is initiated. The team decides to perform TEG to guide further resuscitation and you see the following waveform (left).
Which of the following agents should be given?

Decreased MA

Normal

A. Platelets

B. FFP

C. Cryoprecipitate

D. Tranexamic acid

Thank You!

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