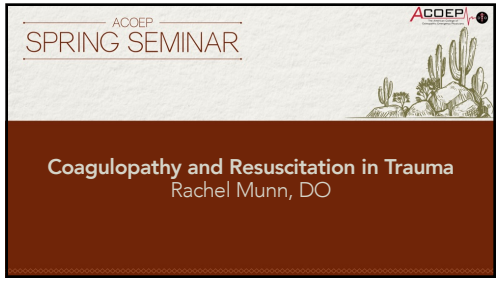
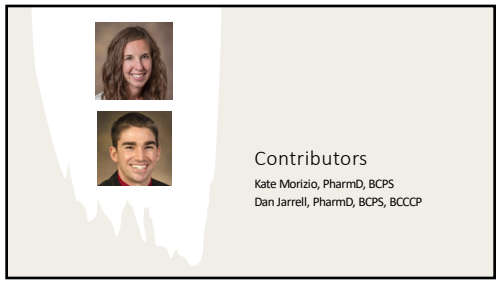

ACOEP
SPRING SEMINAR
PHOENIX, ARIZONA
April 1-5, 2023
ACOEP

1


ACOEP
SPRING SEMINAR
ACOEP
Coagulopathy and Resuscitation in Trauma
Rachel Munn, DO

2


Contributors
Kate Morizio, PharmD, BCPS
Dan Jarrell, PharmD, BCPS, BCCCP

3

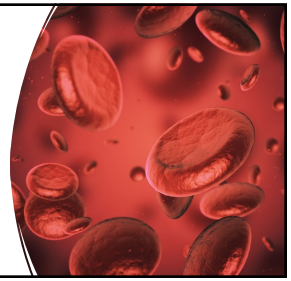
Objectives

Review	Identify	Discuss	Reference
Review basic physiology of coagulation and associated disorders	Identify commonly used anticoagulants, their mechanism of action, monitoring parameters, and reversal agent (if available)	Traumatic coagulopathy and its treatment	Reference guidelines for coagulopathy treatment in traumatic injuries

4

Pathophysiology

... and definitions surrounding bleeding & coagulopathy



5

What is Coagulopathy?

- A defect in any of the components of hemostasis:
  - Vasculature
  - Platelets
  - Coagulation factors
  - Fibrinolytic proteins

6

Pathophysiology of Coagulation

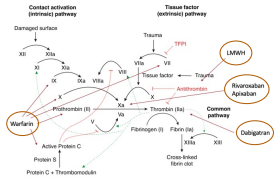


Image: Adapted from Wikimedia Commons

7

What is Major Bleeding?

Definitions differ in non-surgical, surgical, and trauma patients:

In non-surgical patients:

1. *Fatal bleeding, and/or*
2. *Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or*
3. *Bleeding causing a fall in hemoglobin level of 2g/dl or more, or leading to transfusion of 2 or more units of whole blood or RBCs.*

International Society of Thrombosis and Hemostasis

8

What is Major Bleeding?

- A patient who requires massive transfusion?
- A patient who fits into the ACS classification of hemorrhagic shock?

Class	Volume Loss	HR	BP / PP	RR	Other
I	15% (750mL)	Normal to ↑	Normal	Normal	
II	15 – 30% (750 – 1500mL)	↑	Normal to ↓ / Narrow	↑	
III	30 – 40% (1500 – 2000mL)	↑↑	↓ / Narrow	↑	AMS ↓ UOP ↓ Capillary refill
IV	> 40% (> 200mL)	↑↑	↓↓ / Narrow	↑	AMS ↓ UOP ↓ Capillary refill

Heart rate (HR); Blood pressure (BP); Pulse pressure (PP); Respiratory rate (RR); Altered mental status (AMS); Urinary output (UOP)

Adapted from: Hooper N, Armstrong TJ. Hemorrhagic Shock. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-.

9

Hemophilia A, B		Clinical Presentation
Mild	5-40 U/dL, 5-40% normal activity	Prolonged bleeding with major trauma or surgery Rare spontaneous bleeding
Moderate	1-5 U/dL, 1-5% normal activity	Severe bleeding with minor trauma or surgery Occasional spontaneous bleeding
Severe	<1 U/dL, <1% normal activity	Spontaneous bleeding

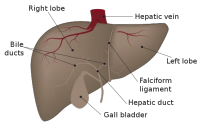
Hereditary Disorders

- **Von Willebrand Disease** – deficiency or dysfunction of vWF (the most common bleeding disorder, found in up to 1% of the U.S. population)
- **Hemophilia A** – deficiency of Factor VIII, most common (~1 in 5000 male births), generally males are affected; female carriers may have mild disease and rarely severe disease
- **Hemophilia B** – deficiency of Factor IX, less common (~1 in 15 – 30,000 male births), generally less severe disease

10

Cirrhosis

- Advanced cirrhosis is another frequent cause of coagulopathy in ED patients.
- Complex pathophysiology with varied levels of both pro and anti coagulant factors.
- INR is frequently elevated, but does not correlate with degree of coagulopathy.



11

Class & Medication	Monitoring Parameter	Reversal	Onset & Half-life
Vitamin K Antagonists			
Warfarin	PT/INR	Vitamin K, 4-Factor PCC	1 – 3 days & 2 – 5 days (PO)
Heparins			
UFH	aPTT	Protamine sulfate	Immediate & Avg 90 min. (IV)
LMWH	Anti-Factor Xa*	Protamine sulfate	3 – 5 hrs & 4.5 – 7 hrs (SubQ)
Factor Xa Inhibitors			
Fondaparinux	Anti-Factor Xa	rFVIIa	2– 3 hrs & 17 – 21 hrs (SubQ)
Rivaroxaban, Apixaban, Edoxaban, Betrixaban**	Anti-Factor Xa	Andexanet alfa, 4-Factor PCC	2 – 4 hrs & 5 – 9 hrs (rivaroxaban, PO) 2 – 4 hrs & 8 - 15 hrs (apixaban, PO)
Direct Thrombin Inhibitor			
Dabigatran*** Argatroban, Bivalirudin	Thrombin Time (TT) / dilute Thrombin Time (dTT) / Ecarin Clotting Time (ECT)	Idarucizumab	1 – 2 hrs & 12 - 17 hrs (dabigatran, PO)
Antiplatelets			
Aspirin	Platelet Function Assay	Platelets / DDAVP	20 min. – 4 hrs & 3– 10 hrs**** (PO)
Clopidogrel	Platelet Function Assay	Platelets	Dose dependent; 2 hrs – 2 days & 4 hrs – 14 days

Anticoagulants

12

Traumatic Coagulopathy

- Multifactorial:
  - Shock & hypoperfusion
  - Tissue injury-related thrombin generation
  - Activation of anticoagulant & fibrinolytic pathways & factor consumption
  - Acidemia
  - Hypothermia
  - Hemodilution

13

Coagulopathy in the ED

- Relevant in the ED when a patient has symptomatic bleeding plus:
  - Hereditary disorder
  - Anticoagulant use
  - Traumatic coagulopathy
  - Chronic medical condition (i.e., cirrhosis)
  - Requires an urgent procedure

14

15

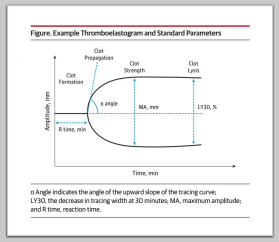
Tests

Test	Characteristics
PT/INR	Measures extrinsic and common pathways INR is calculated and standardized for warfarin
aPTT	Measures intrinsic and common pathways
Anti-Factor Xa	Must be calibrated for specific anticoagulants
Thrombin Time / Ecarin Clotting Time	Measures fibrin formation
Viscoelastic assays (VEAs) (TEG®, ROTEM®)	Measure a variety of coagulation steps
Platelet aggregation	Evaluates platelet function

16

Thromboelastogram (TEG)

- R value = reaction time (s)
- K = kinetics (s)
- alpha = angle (slope of line between R and K)
- TMA = time to maximum amplitude(s)
- MA = maximum amplitude (mm)
- A30 or LY30 = amplitude at 30 minutes
- CLT = clot lysis time (s)



17

18

The Fall of FFP

- "In contrast to FFP, PCCs require a lower infusion volume and shorter infusion time, are associated with a lower risk of pathogen transmission, and have a more rapid impact on INR."

19

Prothrombin Complex Concentrate

- FDA approved for reversing warfarin-induced coagulopathy.
- 3F- PCC includes factors II, IX, and X (inactive)
- 4F-PCC includes factors II, VII, IX, and X (inactive); small amounts of heparin and protein's C and S
- aPCC includes inactive factors II, IX, and X but activated factor VII
  - FEIBA (factor eight inhibitor bypassing activity) is the only approved product in the U.S. and is approved for prevention & treatment of surgical bleeding in hemophilia patients.

20

Certain factors may be utilized independently for hereditary coagulopathies.

Single Factors

Type	Factor deficiency
Haemophilia A	Factor VIII
Haemophilia B (or Christmas disease)	Factor IX
von Willebrand's disease	von Willebrand's factor leading to low factor VIII activity and reduced platelet adhesion

21

Vitamin K

- IV administration recommended for major bleeding associated with warfarin-induced coagulopathy.
- Necessary to allow activation and utilization of coagulation factors.

22

Platelets

- The 2016 PATCH trial did not demonstrate improved outcomes with platelet transfusion in spontaneous cerebral hemorrhage in patients on aspirin or clopidogrel.
  - Excluded trauma patients, patients on warfarin, or with thrombocytopenia.
- A 2019 meta-analysis of 10 studies failed to demonstrate consistently improved outcomes with platelet transfusion in patients with TBI.
  - A single study demonstrated improved outcomes, a retrospective database review done at the U of A:
    - Decreased progression of ICH
    - Decreased neurosurgical intervention
    - Decreased discharge to SNF
    - Decreased mortality

23

Platelets

Transfusion Thresholds	
Active bleeding	goal > 50,000/microL
Major surgery	goal > 50,000/microL
Central line	goal > 20,000/microL
Lumbar puncture	goal > 10,000 to 20,000/microL in patients with hematologic malignancies and >40,000 to 50,000 in patients without hematologic malignancies
Neurosurgery or ocular surgery	goal > 100,000/microL
Preventative (spontaneous bleeding)	goal > 10,000/microL (some recommend 15 – 20,000/microL in patients with sepsis)

24

DDAVP

- Standard use is in von Willebrand's disease and hemophilia A.
  - Increasing serum level of vWF and factor VIII and enhances platelet adhesion.
- Interest in its use in other conditions including drug-induced coagulopathy and bleeding occurred due to observations of a shortened aPTT and bleeding time in patients given DDAVP.
  - Recent studies in TBI patients taking antiplatelet agents have reported mixed results.

25

TXA

- Inhibits fibrinolysis
- Robust efficacy and safety data in bleeding secondary to acute trauma, reduces mortality if given within 3 hours of injury:
  - MATTERS trial
  - CRASH-2 trial
- Safe to administer in the pre-hospital setting
  - STAAMP trial
- 2g bolus non-inferior than original 1g bolus + 1g infusion dosing regimen
  - Rowell et al. 2020

26

Idracuzimab

- RE-VERSE AD Study
- "…among 503 patients who were receiving dabigatran, had uncontrolled bleeding or were about to undergo an urgent procedure, and had a prolonged diluted thrombin time at baseline, idarucizumab reversed anticoagulation rapidly and completely (to a median maximum percentage of 100%) in more than 98% of the patients."
- 4.8% rate of thrombotic complications

27

Andexanet Alfa

- ANNEXA-4 study
- "In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours"
- 10% rate of thrombotic complications

28

Up & Coming

- **Ciraparantag** as a reversal agent for Factor Xa inhibitors (Phase 2 Clinical Trial):
  - Jack Ansell, Sasha Bakhru, Bryan E Laulicht, Gregory Tracey, Stephen Villano, Daniel Freedman, Ciraparantag reverses the anticoagulant activity of apixaban and rivaroxaban in healthy elderly subjects, *European Heart Journal*, Volume 43, Issue 10, 7 March 2022, Pages 985–992, https://doi.org/10.1093/eurheartj/ehab637

29

Clinical Scenarios

... and society recommendations & guidelines

30

Intracranial Hemorrhage

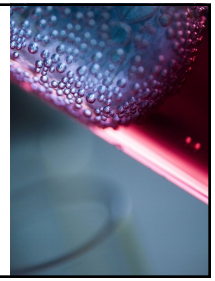
- 2016 Neurocritical Care Society & Society of Critical Care Medicine Guideline
- 2020 AHA Guidelines

- Reversal recommended in most cases of intracranial hemorrhage.
- Agent utilized depends on the anticoagulant.
- Risk : benefit ratio should be assessed in patients with critical thrombotic complication (limb ischemia) or high-risk feature (mechanical heart valve).

31

Major Trauma

- Acute traumatic coagulopathy is common.
- One study noted 34% of trauma patients had coagulopathy (abnormal PT) upon presentation to the ED.
  - Associated with increased prehospital IVF and injury severity score.
- How are we evaluating for and treating this type of coagulopathy?



33

What comes first?

- Are patients with critical injury requiring MTP at higher risk of acute traumatic coagulopathy?
- Is this a combination of separate processes:
  - Acute traumatic coagulopathy
  - Resuscitation induced coagulopathy

34

Major Trauma

- Can we predict who will be at risk? Who will need massive transfusion?
- Assessment of Blood Consumption (ABC) Score
  - Penetrating mechanism of injury
  - Positive FAST
  - SBP of < 90
  - HR > 120
- If 2 or more checked, predicts the need for massive transfusion with 75% sensitivity and 86% specificity.

35

Balanced resuscitation…

- PROPPR Trial
- Among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days.

36

Is a "one size fits all" approach best?

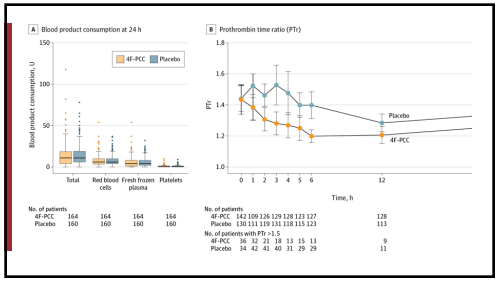
- A 2016 RCT found that using TEG-guided MTP improved survival and led to less utilization of plasma and platelets.
- ITACTIC Trial (2021)
  - Examined if VEA utilization vs conventional coagulation tests in patients requiring MTP improved mortality and other patient outcomes.
  - Negative study.

37

PROCOAG Trial

- Published March 21, 2023
  - France, 2017 – 2021, at 12 level 1 trauma centers
  - Trauma activations age >18
    - receiving at least 1 unit pRBCs prehospital or within 1 hr
    - ABC score > 2,
    - clinical assessment by physician of at risk for massive transfusion
  - Primary outcome: total units of blood products consumed in the first 24 hrs
  - 324 patients randomized / 308 received the study intervention (73% men, mean age 39)

38

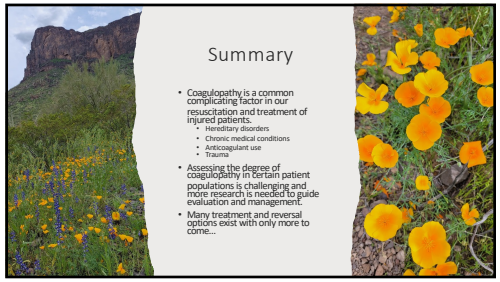


39

PROCOAG Trial

- No reduction in 24 hr blood product consumption or other secondary outcomes
- Higher risk of thromboembolic complications with PCC
- Limitations include giving FFP and PCC may increase thrombotic events
- "These findings do not support systematic use of 4F-PCC in patients at risk of massive transfusion."

40


Summary
Coagulopathy is a common complicating factor in our resuscitation and treatment of injured patients.
Hereditary disorders
Chronic medical conditions
Anticoagulant use
Trauma
Assessing the degree of coagulopathy in certain patient populations is challenging and more research is needed to guide evaluation and management.
Many treatment and reversal options exist with only more to come…

41


Questions?

42