How do I manage this coagulopathy?

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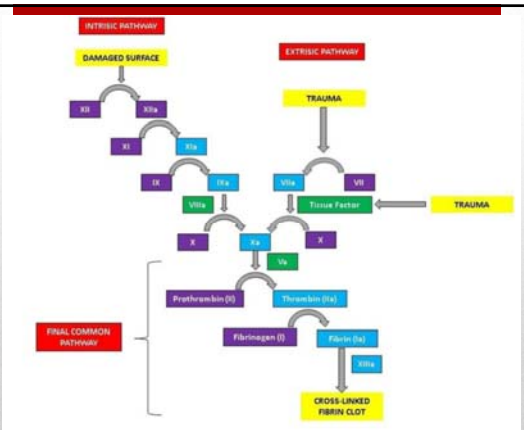
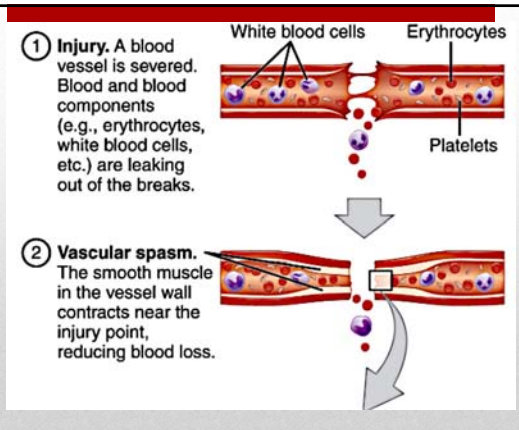
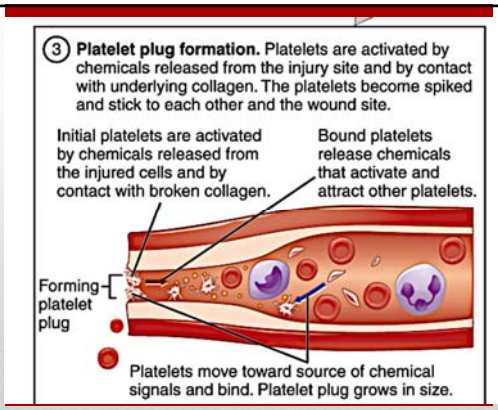
Disclosures: none

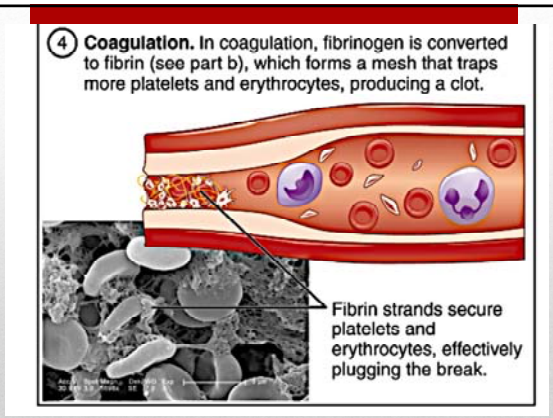
All bleeding stops… eventually

Review of coagulation cascade









- an initial platelet plug is formed when vascular tissue is damaged
- platelets activate and release chemical signals that induce aggregation
- adherence to the subendothelial matrix
- Activated surface receptors interact and protein bridges are created between the subendothelium and activated platelets

Primary Hemostasis

- **extrinsic pathway** begins when trauma to vasculature exposes tissue factor to blood
- activating coagulation factor VII (FVII)
- **active FVII complex** initiates and amplifies the coagulation cascade

Coagulation Cascade

- **intrinsic pathway** activates **factor XII** upon surface damage resulting in downstream
- proteolytic **activation of other coagulation factors**

Coagulation Cascade

- Converge into the common pathway
- activation of factor X cleaves prothrombin into thrombin
- activates fibrinogen into fibrin, reinforcing the platelet

Coagulation Cascade

Derangements in massive bleeding

Uncontrolled bleeding can lead to a combination of
- hemodilution, hypothermia
- consumption of clotting factors
- acidosis

These exert their own negative influences over the clotting process to further exacerbate the problem in a vicious Bloody circle

Dilutional thrombocytopenia

- the most common of the coagulation abnormalities in heavy bleeding
- particularly common with transfusion volumes in excess of 1.5 times their blood volume
- After replacement of one blood volume, only 35% to 40% of platelets remain in the circulation.

Dilution of coagulation factors

- dilution of procoagulant factors is seen with
  - fluid resuscitation
  - transfusion

Hypothermia

hypothermia causes
- platelet dysfunction
- alteration of coagulation enzyme kinetics
- disruption of fibrinolytic balance
- Prolongation of clotting time

Hypothermia

At a temperature of 33° C
- impairment in coagulation is equivalent to a factor IX deficiency of 33% of normal level
  - Similar to Hemophilia B
- greater degree of clot lysis due to the impairment of intrinsic inhibitors of fibrinolysis

Hypotension

- Strong correlation between the development of coagulation abnormalities and duration of hypotension
- hypoperfusion is associated with
  - Consumptive coagulopathy
  - prolongation of aPTT
  - Decreased factor V activity
  - microvascular bleeding

Laboratory analysis of coagulation status

- designed to test for coagulation factor deficiencies
  - not for predicting risk of bleeding or guiding hemostatic management.
- Slow turnaround times
- Typically performed with just plasma
- conducted outside the effect of *in vivo* physiology
- do not convey clot stability or fibrinolysis
- Delayed results may not reflect the current state of hemostatic physiology

Standard lab tests (SLTs)

- integrity of intrinsic and common coagulation pathways
- invented to monitor heparinization in the treatment for thromboembolic disorders
- affected by
  - levels of fibrinogen & factors II, V, VIII, IX, XI, and XII
  - temperature
  - pH
- large variation in calibration, difficult standardization
- empiric cut-off value for therapeutic intervention
  - aPTT 1.5–1.8x above normal upper limit

Standard lab tests- aPTT

- Integrity of extrinsic and common pathways
- created to monitor and adjust the doses of coumarins
- affected by levels of fibrinogen and coagulation factors II, V, VII and X
- standardized by conversion to an international normalized ratio (INR)
- empirical cut-off value for therapeutic intervention
  - PT less than 40 % of normal

Standard lab tests- PT/INR

PT and aPTT assess only the speed of fibrin strand formation, not the mechanical or functional properties of the clot over time

aPTT and PT/INR

- Fibrinogen
  - essential for effective coagulation
  - the first factor to be depleted during massive bleeding and hemodilution
- Excessive bleeding with fibrinogen levels below 50–100 mg/dl

Standard lab tests- fibrinogen

Standard lab tests- platelet count

- Does not measure activity of the platelets
- Platelet function, more than number, is critical in the perioperative setting
- The empirical cut-off value for platelet transfusion is a platelet count of 50–100

Viscoelastic point-of-care monitoring

Thromboelastogram (TEG)

- Uses whole blood
- More representative of *in vivo* coagulation.

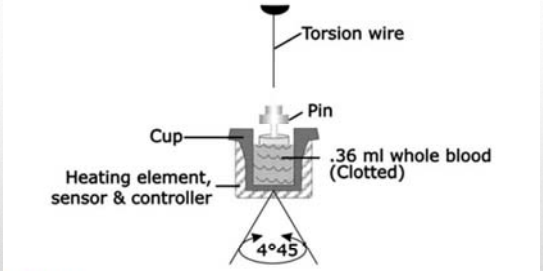


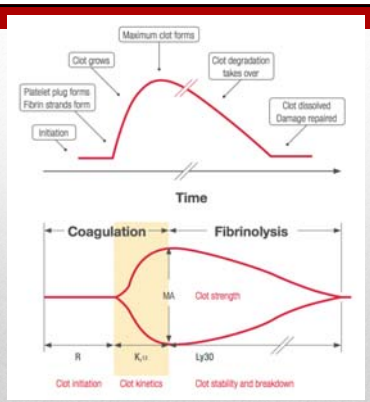
Figure 2. A depiction of a TEG device in which a pin suspended from a torsion wire is immersed in a cup of whole blood. The cup is held in a heating block and continually oscillates through 4° 45′ every 5 sec. Changes in viscoelastic clot strength are directly transmitted to the torsion wire and detected by an electromechanical transducer.

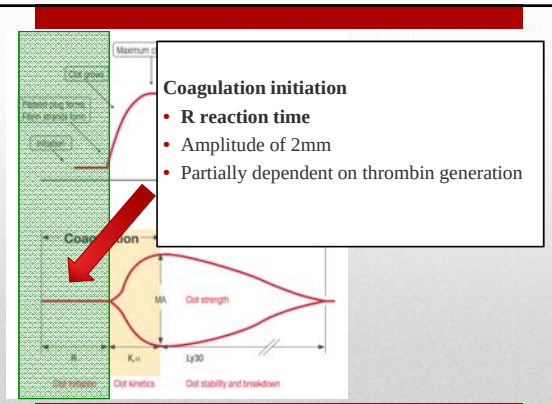
Whiting, *Am J Hematology*, 2014

TEG basics

Thromboelastography measures viscoelastic properties

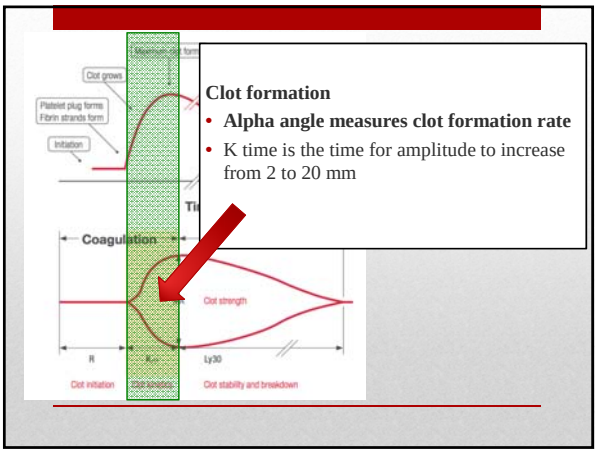
- induction of clotting
- pattern of changes in viscoelasticity
  - thrombus formation
  - clot stability and firmness
  - fibrinolysis

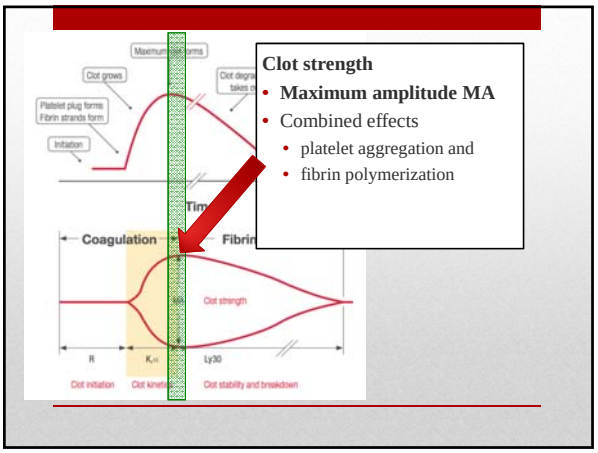


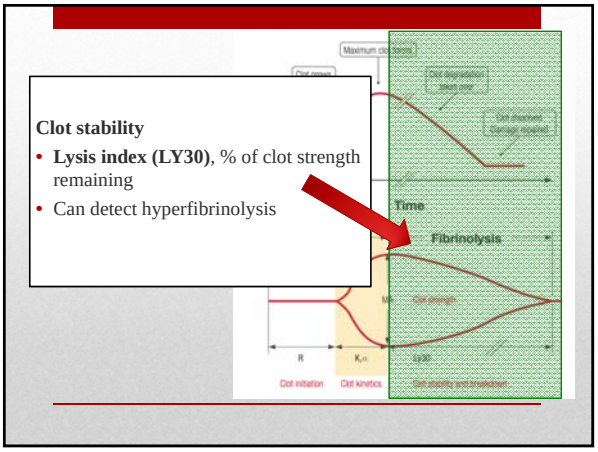


Coagulation initiation

- **R reaction time**
- Amplitude of 2mm
- Partially dependent on thrombin generation







- has been used successfully for screening of primary hemostasis abnormalities such as von Willebrand disease
- can detect disturbances in primary hemostasis by measuring deposition of platelets from whole blood on to an artificial surface
- preoperative platelet function testing can be used to identify decreased platelet function caused by medical conditions and antiplatelet medication

Platelet function testing

Transfusion product choices

- hemoglobin concentration might influence coagulation
- erythrocytes congregate in the inner lumen of blood vessels
  - resulting in localization of platelets at the vessel wall
- erythrocytes stimulate thrombin generation
  - providing material for clot formation
- no randomized controlled trials have proved that increasing hemoglobin concentration above 9 g/dL reduces bleeding or the number of blood transfusions

Blood products- RBCs

- replace deficient clotting factors when a clotting factor concentrate is not available
- when multiple clotting factors are deficient (e.g., disseminated intravascular, coagulation, massive transfusion)
- when the cause of the coagulopathy is not known

- FFP for volume support is not an accepted indication

Blood products- FFP

Indication is lack of available fibrinogen concentrate for bleeding in the setting of hypofibrinogenemia

Fibrinogen < 75-100 mg/dL

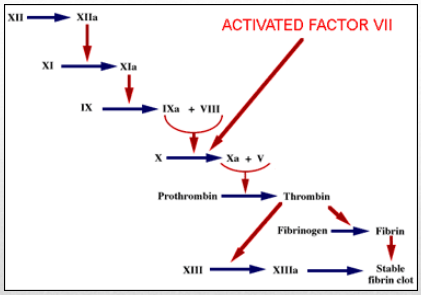
Blood products- cryoprecipitate

To treat or prevent bleeding secondary to
- critical thrombocytopenia or
- a qualitative platelet defect

Blood products- platelets

Licensed for
- hemophilia and inhibitory antibodies or
- Glanzmann thrombasthesia

Recombinant factor VIIa



Recombinant factor VIIa

- rVIIa is increasingly used in off-label indications to control severe bleeding, such as in major trauma, surgical interventions, intracerebral hemorrhage
- locally activating hemostasis at sites of vascular injury
- thrombin burst leads to the formation of a fibrin clot if fibrinogen levels are adequate

Recombinant factor VIIa

Prior to use of fVIIa, all other components of coagulation should be optimized:

1. Fibrinogen
2. Platelets
3. Temperature less than 34 degrees inhibits thrombin generation, fibrinogen synthesis, platelet function, and accelerates fibrinolysis
4. Calcium enhances fibrin polymerization, coagulation factor activity and platelet activity
5. acidosis < 7.1 inhibits thrombin and platelet function, and accelerates fibrinolysis

Recombinant factor VIIa

- Tranexamic acid (TXA) or Aminocaproic acid (Amicar)
- Useful if evidence of hyperfibrinolysis

Antifibrinolytics

- Increases the levels of
  - factor VIII
  - plasminogen activator
  - von Willebrand Factor
- Beware of side effects, especially hyponatremia

Desmopressin (DDAVP)

Are patient outcomes improved by algorithms that incorporate coagulation monitoring for perioperative hemostatic management?

Transfusion choices

Perioperative coagulation monitoring is beneficial only if the results contribute to clinically effective decisions.

Patients with similar conditions may receive different treatments if protocols and triggers for coagulation management are not in place.

Transfusion choices

What about massive transfusion ratios?

Transfusion choices

References:

Behrens, A. M., M. J. Sikorski and P. Kofinas (2014). "Hemostatic strategies for traumatic and surgical bleeding." J Biomed Mater Res A **102**(11): 4182-4194.

Colomina, M. J., A. Diez Lobo, I. Garutti, A. Gomez-Luque, J. V. Llau and E. Pita (2012). "Perioperative use of prothrombin complex concentrates." Minerva Anestesiol **78**(3): 358-368.

Georgiou, C., K. Neofytou and D. Demetriades (2013). "Local and systemic hemostatics as an adjunct to control bleeding in trauma." Am Surg **79**(2): 180-187.

Hong, I. and J. Stachnik (2010). "Unlabeled uses of factor VIIa (recombinant) in pediatric patients." Am J Health Syst Pharm **67**(22): 1909-1919.

Jakoi, A., N. Kumar, A. Vaccaro and K. Radcliff (2014). "Perioperative coagulopathy monitoring." Musculoskelet Surg **98**(1): 1-8.

Johnson, J. L., E. E. Moore, J. L. Kashuk, A. Banerjee, C. C. Cothren, W. L. Biffl and A. Sauaia (2010). "Effect of blood products transfusion on the development of postinjury multiple organ failure." Arch Surg **145**(10): 973-977.

Karon, B. S. (2014). "Why is everyone so excited about thromboelastrography (TEG)?" Clin Chim Acta **436**: 143-148.

Kashuk, J. L., E. E. Moore, J. L. Johnson, J. Haenel, M. Wilson, J. B. Moore, C. C. Cothren, W. L. Biffl, A. Banerjee and A. Sauaia (2008). "Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer?" J Trauma **65**(2): 261-270; discussion 270-261.

Kashuk, J. L., E. E. Moore, M. Sawyer, T. Le, J. Johnson, W. L. Biffl, C. C. Cothren, C. Barnett, P. Stahel, C. C. Sillman, A. Sauaia and A. Banerjee (2010). "Postinjury coagulopathy management: goal directed resuscitation via POC thrombelastography." Ann Surg **251**(4): 604-614.

Kashuk, J. L., E. E. Moore, M. Wohlauer, J. L. Johnson, M. Pezold, J. Lawrence, W. L. Biffl, C. C. Burlew, C. Barnett, M. Sawyer and A. Sauaia (2012). "Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy." Transfusion **52**(1): 23-33.

Kashuk, J. L., E. E. Moore, M. Wohlauer, J. L. Johnson, M. Pezold, J. Lawrence, W. L. Biffl, C. C. C. Burlew, C. Barnett, M. Sawyer and A. Sauaia (2011). "Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy." Transfusion **52**(1): 23-33.

Kozek-Langenecker, S. A., A. Afshari, P. Albaladejo, C. A. Santullano, E. De Robertis, D. C. Filipescu, D. Fries, K. Gorlinger, T. Haas, G. Imberger, M. Jacob, M. Lance, J. Llau, S. Mallett, J. Meier, N. Rahe-Meyer, C. M. Samama, A. Smith, C. Solomon, P. Van der Linden, A. J. Wikkelso, P. Wouters and P. Wyffels (2013). "Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology." Eur J Anaesthesiol **30**(6): 270-382.

Marietta, M., L. Facchini, P. Pedrazzi, S. Busani and G. Torelli (2006). "Pathophysiology of bleeding in surgery." Transplant Proc **38**(3): 812-814.

Parker, R. I. (2014). "Transfusion in Critically Ill Children." Critical Care Medicine **42**(3): 675-690.

Schochl, H. and C. J. Schlimp (2014). "Trauma bleeding management: the concept of goal-directed primary care." Anesth Analg **119**(5): 1064-1073.

Schulman, S. (1991). "DDAVP--the multipotent drug in patients with coagulopathies." Transfus Med Rev **5**(2): 132-144.

Solomon, C., H. Schochl, M. Ranucci and C. J. Schlimp (2015). "Can the Viscoelastic Parameter alpha-Angle Distinguish Fibrinogen from Platelet Deficiency and Guide Fibrinogen Supplementation?" Anesth Analg **121**(2): 289-301.

Stensballe, J., S. R. Ostrowski and P. I. Johansson (2014). "Viscoelastic guidance of resuscitation." Curr Opin Anaesthesiol **27**(2): 212-218.

Trey, J. E. and I. Kushner (1995). "The acute phase response and the hematopoietic system: the role of cytokines." Crit Rev Oncol Hematol **21**(1-3): 1-18.

Wada, H., T. Matsumoto, Y. Yamashita and T. Hatada (2014). "Disseminated intravascular coagulation: testing and diagnosis." Clin Chim Acta **436**: 130-134.

Waters, J. H. (2014). "Role of the massive transfusion protocol in the management of haemorrhagic shock." Br J Anaesth **113 Suppl 2**: ii3-8.

Whiting, D. and J. A. DiNardo (2014). "TEG and ROTEM: technology and clinical applications." Am J Hematol **89**(2): 228-232.

Wikkelso, A., J. Lunde, M. Johansen, J. Stensballe, J. Wetterslev, A. M. Moller and A. Afshari (2013). "Fibrinogen concentrate in bleeding patients." Cochrane Database Syst Rev **8**: CD008864.