The Thick and the Thin of It—Coagulation and Massive Transfusion

Rebecca Stoudt, CRNA DNP PhD(c)
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Coagulation and Massive Transfusion

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Objectives

• The participant will be able to
  – Identify the steps involved in the clotting mechanism
  – Discuss the coagulation cascade
  – Develop a massive transfusion strategy using qualitative and quantitative test results
  – Obtain familiarity with diagnostic tests for coagulopathic states
Hemostasis

• Three parts
  – Vascular spasm
  – Primary hemostasis
  – Secondary hemostasis
Hemostasis

• Vascular spasm
  – Sympathetic mediated vasoconstriction
  – Small and medium sized vessels

• Primary hemostasis
  – Platelet plug

• Secondary hemostasis
  – Coagulation of blood
Injury

• Intrinsic--damage within a blood vessel
  – Think stenting, DVT

• Extrinsic--damage that causes tissue trauma
  – Think trauma, surgery

• Vascular spasm for either
Injury

- When an injury occurs to a vessel (either partial or full thickness) collagen fibers are exposed.
Clotting Made Easy

Injury → Vascular Spasm → Platelets → Fibrin → Thrombosis
Primary Hemostasis

• Three stages to platelet plug
  – Adhesion of platelets to wound
  – Release of platelet granules
  – Aggregation (platelet clumping)
Primary Hemostasis

• When a vessel is damaged, collagen fibers are exposed
• Platelets adhere to the collagen via glycoprotein receptors
• Collagen activates the platelets
• The platelet bond is strengthened by vWF, also released by platelet activation
Primary Hemostasis

- Activated platelets release ADP, serotonin, platelet activating factor (PAF), platelet factor 4, thromboxane A$_2$, vWF, which activates other platelets and increases aggregation
  - TXA$_2$ is also a potent vasoconstrictor (ASA)
  - ADP also facilitates fibrin binding (Plavix)
- Shape changes from spherical to stellate, thrombin released
Platelet Activation

- ADP
- Serotonin
- PAF
- vWF
- PF4
- TXA$_2$
- Thrombin
- Glycoprotein IIb/IIIa
Clotting Made Easy

Injury → Vascular Spasm → Platelets → Fibrin

Thrombosis
Look familiar?
<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (Factor I)</td>
<td>Molecular Weight (MW) = 340,000 daltons (Da); glycoprotein</td>
<td>Adhesive protein that forms the fibrin clot</td>
</tr>
<tr>
<td>Prothrombin (Factor II)</td>
<td>MW = 72,000 Da; vitamin K-dependent serine protease</td>
<td>Activated form is main enzyme of coagulation</td>
</tr>
<tr>
<td>Tissue factor (Factor III)</td>
<td>MW = 37,000 Da; also known as thromboplastin</td>
<td>Lipoprotein initiator of extrinsic pathway</td>
</tr>
<tr>
<td>Calcium ions (Factor IV)</td>
<td>Necessity of Ca++ ions for coagulation reactions described in 19th century</td>
<td>Metal cation necessary for coagulation reactions</td>
</tr>
<tr>
<td>Factor V (Labile factor)</td>
<td>MW = 330,000 Da</td>
<td>Cofactor for activation of prothrombin to thrombin</td>
</tr>
<tr>
<td>Factor VII (Proconvertin)</td>
<td>MW = 50,000 Da; vitamin K-dependent serine protease</td>
<td>With tissue factor, initiates extrinsic pathway</td>
</tr>
<tr>
<td>Factor VIII (Antihemophilic factor)</td>
<td>MW = 330,000 Da</td>
<td>Cofactor for intrinsic activation of factor X</td>
</tr>
<tr>
<td>Factor IX (Christmas factor)</td>
<td>MW = 55,000 Da; vitamin K-dependent serine protease</td>
<td>Activated form is enzyme for intrinsic activation of factor X</td>
</tr>
<tr>
<td>Factor X (Stuart-Prower factor)</td>
<td>MW = 58,900 Da; vitamin K-dependent serine protease</td>
<td>Activated form is enzyme for final common pathway activation of prothrombin</td>
</tr>
<tr>
<td>Factor XI (Plasma thromboplastin antecedent)</td>
<td>MW = 160,000 Da; serine protease</td>
<td>Activated form is intrinsic activator of factor IX</td>
</tr>
<tr>
<td><strong>Factor XII (Hageman factor)</strong></td>
<td>MW = 80,000 Da; serine protease</td>
<td>Factor that nominally starts aPTT-based intrinsic pathway</td>
</tr>
<tr>
<td>Factor XIII (Fibrin stabilizing factor)</td>
<td>MW = 320,000 Da</td>
<td>Transamidase that cross-links fibrin clot</td>
</tr>
<tr>
<td>High-molecular-weight kininogen (Fitzgerald, Flajcice, or William factor)</td>
<td>MW = 110,000 Da; circulates in a complex with factor XI</td>
<td>Cofactor</td>
</tr>
<tr>
<td>Prekallikrein (Fletcher factor)</td>
<td>MW = 85,000 Da; serine protease</td>
<td>Activated form that participates at beginning of aPTT-based intrinsic pathway</td>
</tr>
</tbody>
</table>
The “New” Cascade

Extrinsic

Intrinsic

Factor VII → Factor VIIa + Tissue factor
Factor X → Factor IX
Factor IXa + Factor VIIIa
Factor VIII

Factor Xa + Factor Va
Factor V

Prothrombin
Thrombin activatable fibrinolytic inhibitor (TAFI) activation
Protein C activation
Platelet aggregation
Endothelial cell effects

Fibrinogen → Fibrin monomer → Fibrin polymer → Cross-linked clot

Factor XI
Factor XIa
Factor XIII
Factor XIIIa
Simplified Clotting Cascade

Extrinsic Pathway:
- Damage to tissue outside the vessel
  - Tissue Thromboplastin
  - Inactive Factor X
  - Activated Factor X
  - Prothrombin
  - Fibrinogen
  - Thrombin

Intrinsic Pathway:
- Damage to the blood vessel
  - Cascade of clotting factors
  - Fibrinogen
  - Fibrin
  - Blood Clot

Factor XIII:
- Blood Clot
Secondary Hemostasis

- Fibrinogen molecules have caps on the ends so the molecules can’t stick to each other when they’re not supposed to
- Thrombin removes the caps
Secondary Hemostasis

- Adding calcium allows the rough edges of the fibrin to stick together
- Add Factor XIII, and you have a stabilized fiber meshwork (ie, thrombosis)
Destroying/regulating the clot

- Normal blood flow—clears activated factors
- tPA—Fibrinolysis
- TFPI—Tissue factor inhibition
- PGI$_2$—Platelet aggregation inhibition, vasodilation
- Proteins C and S—inactivates factors V & VIII
- Heparin-like material binds to antithrombin
Endothelial Cell Effects

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**Procoagulant**
- Thrombin activatable fibrinolytic inhibitor (TAFI)
- Activated TAFI
- Thrombin / thrombomodulin
- Expression of tissue factor

**Anticoagulant**
- Tissue factor pathway inhibitor (TFPI)
- Protein C
- Activated protein C (APC)
- Thrombin / thrombomodulin
- Heparin-like material

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Subendothelial matrix

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Endothelial lining of vessel
Thrombin

- Promotes platelet aggregation
- Cleaves fibrinogen to fibrin
- Initiates intrinsic arm and common pathway
- Activates clot regulating factors (Proteins S & C)
- Anticoagulant target (Warfarin and Heparin)
Thrombin

• Factor II
  – One of the Vitamin K dependent factors
  – Found in FFP and prothrombin complex concentrate
  – Recombinant thrombin available in powder form for topical application for small vessel bleeding
Injury to vessel

Activation of platelets by contact to injured endothelium and subendothelium and formation of platelet plug

Activation of coagulation pathway with ultimate generation of thrombin and fibrin clot stabilizing the platelet plug

Fibrinolysis and clot removal

Control of clot extension by antithrombotic mechanisms

Healing and repair of injury
Hemorrhage Classifications

• Class I Hemorrhage
  – Loss of <15% of blood volume
  – No hemodynamic changes
  – Elective surgeries, controlled bleeding
  – Crystalloid replacement, if needed
Hemorrhage Classifications

• Class II Hemorrhage
  – Loss of 15-30% of blood volume
  – DBP increases (vasoconstriction)
  – HR increases to maintain CO
  – Crystalloid or colloid replacement
  – If need blood = Class III
Hemorrhage Classifications

• Class III Hemorrhage
  – Loss of 30-40% of blood volume
  – Consistent low BP
  – Compensatory vasoconstriction and tachycardia ineffective
  – Metabolic acidosis
  – PRBC to restore tissue perfusion and oxygenation
  – Damage Control Resuscitation?
Hemorrhage Classifications

• Class IV Hemorrhage
  – Loss of >40% of blood volume
  – Life threatening
  – Unresponsive, profound hypotension
  – Trauma-induced coagulopathy
  – High likelihood of death
  – Damage Control Resuscitation
  – Get help, role delineation
Damage Control Resuscitation

• Developed by the military to treat combat wounds

• Not from randomized controlled trials—real life results

• Addresses trauma-induced coagulopathy
Trauma-Induced Coagulopathy

- In 25% of trauma patients, TIC is present before resuscitation
- Independent risk factor of death
- Related to base deficit 6 mEq/L or greater
  - 20% vs 2% in developing TIC
  - Progressive coagulopathy as base deficit increases
Damage Control Resuscitation

• To halt/prevent the triad of coagulopathy, acidosis, and hypothermia related to hemorrhagic losses

• Old method—use crystalloid first, then PRBCs, then plasma only after large amounts of PRBCs to treat the resultant coagulopathy
Damage Control Resuscitation

• New method—start treating with plasma and platelets immediately to prevent coagulopathy

• Current guidelines advocate 1:1:1 ratio of plasma, platelets, and RBCs
  – Ex. 6 units RBCs, 6 units FFP, 6 pack platelets
  – After 6 PRBCs, check fibrinogen level. Give 20 units of cryoprecipitate if <100 mg/dl
Damage Control Resuscitation

• Need to check labs frequency to check progress and guide therapies

• Derivation of massive transfusion protocols are highly recommended
Massive Transfusion Protocol

- Improves survival from trauma
- Reduces total blood product utilization in first 24 hours
- Reduces acute infectious complications
- Decreases post-resuscitation organ dysfunction
Massive Transfusion Protocol

• How much?
  – 6 units PRBCs, 6 units FFP, 1 apheresis unit of Plts

• Who initiates?
  – Trauma service, ER, anesthesia
  – Reordering?
  – Assessment of Blood Consumption (ABC) Score
ABC Score

• Four variables
  – Penetrating injury
  – SBP <90 mmHg
  – HR >120 bpm
  – Positive focused assessment with sonography for trauma (FAST)
    • Looks for free fluid in perihepatic and perisplenic spaces, pericardium, and pelvis
Calculating Allowable Blood Loss

<table>
<thead>
<tr>
<th>Age</th>
<th>Average Blood Volume (ABV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td></td>
</tr>
<tr>
<td>Premature</td>
<td>95 ml/kg</td>
</tr>
<tr>
<td>Full-term</td>
<td>85 ml/kg</td>
</tr>
<tr>
<td>Infants</td>
<td>80 ml/kg</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>75 ml/kg</td>
</tr>
<tr>
<td>Women</td>
<td>65 ml/kg</td>
</tr>
</tbody>
</table>

**EBV**

\[ \text{EBV} = \text{Weight (kg)} \times \text{ABV} \]

**Allowable Blood Loss (ABL)**

\[ \text{ABL} = \text{EBV} \times \left( \frac{\text{H}_i - \text{H}_f}{\text{H}_i} \right) \]

\[ \text{H}_i = \text{Initial HCT}, \text{H}_f = \text{Final HCT} \]
Replacement Considerations

- Crystalloid 3-4:1
- Colloid 1-2:1
- PRBC 1:1

- Crystalloid redistribution half-life 20-30 min
- Colloid redistribution half-life 3-6 hrs
Blood Products

• PRBCs
  – Dose 5-20 ml/kg
  – HCT 70%, increases Hgb 1g/dL (3% Hct)
  – Consider transfusion of Hbg < 7-8 g/dL
  • Below 7 = CO increases to compensate for decreased tissue oxygenation
Blood Products

• PRBCs
  – Stored for 42 days
    • 2,3 DPG degradation shifts oxygen dissociation curve to left
    • Potassium increases d/t red cell apoptosis
  – Citrate binds to calcium
    • Liver converts to NaHCO₃
Blood Products

• PRBCs
  – Type and Screen
    • 45 minutes, mix specimen with known antigenic composition
  – Type and Crossmatch
    • Mixes specimen with donor cells
    • Confirms ABO typing, detects antibodies to other blood group systems and in low titers
  – O negative
    • After 8 units, continue with O neg
Blood Products

• FFP
  – Dose 10-15ml/kg
  – Increases each clotting factor by 2-3%
  – Vit. K dependent factors (II, VII, IX, and X)
  – Factors V and VIII, vWF, fibrinogen
  – ATIII (also available as concentrate)
Blood Products

• Cryoprecipitate
  – Factor VIII and fibrinogen
  – 1 unit/5kg, or 10 units/70kg
    • 10 units of cryo = 1g of fibrinogen
Diagnostic Tests

Quantitative
- PT
- aPTT
- INR
- Fibrinogen
- Platelets
- Antithrombin III (ATII)

Qualitative
- Soluble Fibrin Monomer (SFM)
- Thromboelastography (TEG)
- Rotational thromboelastography (ROTEM)
- Sonoclot
Qualitative

- Soluble fibrin monomer (SFM)—normal = negative
  - A measure of soluble fibrin, a precursor of thrombin activation of fibrinogen
  - Different from D-dimer
The Thromboelastogram

- **R (reaction time)**—minutes from commencement of test to initial fibrin clot formation (reflects factor levels, fibrinogen)
- **Alpha angle**—tangent line to TEG tracing (reflects clot growth rate = fibrin build up and cross linking)
• **MA (maximum amplitude)**—width in millimeters of the widest gap (reflects clot strength = platelet/fibrin interaction)
• **LY30**—% fibrinolysis at 30 minutes after MA (reflects clot stability)
Using the TEG

- Platelets >100
  - MA > 55 = normal function and number
  - MA 49-55 = mild to moderate decreased function
    - DDAVP (0.3 mcg/kg)
  - MA < 49 = severe decreased function
    - 6 pack platelets and DDAVP
Fibrinogen <100

R = 8-12 (normal) \(\rightarrow\) FFP 4 units/70 kg

R > 12 (prolonged) \(\rightarrow\) Cryo 10 units/70 kg
DIC Stage 1

- Short R
- Obtuse alpha angle
- Large MA
- LY30 > 8%

Hypercoagulable with fast fibrinolysis
DIC Stage 1

Plts > 100, Fib > 100, LY30 > 8%

If either ATIII < 69% or SFM + and Cl btw -1 & 2
Correct ATIII to 90 and transfuse as needed

If ATIII > 69% and SFM -
Give antifibrinolytic and/or rFVII at 50 mcg/kg
DIC Stage 2

- Prolonged R
- Acute alpha angle
- Narrow MA
- LY30 stable

Hypocoagulable with factor depletion
DIC Stage 2

Plts < 100, Fib < 100, LY30 < 8%

If either ATIII < 69% or SFM +
- Correct ATIII to 90%
- Plt, FFP and Cryo >100 transfuse as needed

If ATIII > 69% and SFM -
- Plt and Cryo >100
- Consider rFVII 50mcg/kg
Massive Transfusion Recommendations

- Create a protocol for MTP
  - How much, who to initiate?
  - Work with blood bank, trauma teams, other services (vascular, cardiac surgery, perfusion)

- Get help, role delineation
Massive Transfusion Recommendations

• Baseline labs, T&C

• Consider labs after each round
  – Quantitative and qualitative

• Correction of acid/base disturbance

• Correction of coagulopathy
We made it!!!
Thank you!
References


