Managing the Bleeding Patient

George A. Fritsma MS, MLS
The Fritsma Factor, Your Interactive Hemostasis Resource
www.fritsmafactor.com; george@fritsmafactor.com

Bleeding Patient Overview

• Managing trauma and massive transfusion
• Acquired multiple procoagulant deficiencies
• Von Willebrand disease
• Hemophilia: inherited single factor deficiency
• Coagulation factor inhibitors
• Disseminated intravascular coagulation

Hemorrhage

• Hemorrhages are uncontrolled bleeds that...
  – Require intervention.
  – May require transfusions.
• Most bleeds are local, caused by...
  – Injury or anatomic abnormality.
  – Incomplete surgical ligation or cauterization.
• A coagulopathy is implied when bleeding is generalized, meaning...
  – From multiple sites.
  – Spontaneous and recurring.
  – Excessive.

Two Types of Coagulopathy

• Mucocutaneous (systemic) hemorrhage
  – Platelet or vascular deficiency
  – Immediately follows event
  – Petechiae, purpura, ecchymoses, epistaxis, menorrhagia, hematemesis
• Anatomic (soft tissue) hemorrhage
  – Coagulation factor deficiency—coagulopathy
  – Delayed or recurrent
  – Joint, muscle, soft tissue, body cavities, CNS

Coagulopathy Etiology

Acquired
• Adult onset
• 2° to event
• Underlying disorder
• Bleeding Hx negative
• Not familial
• Multiple factor deficiency

Congenital
• Childhood onset
• Spontaneous
• Primary
• Previous bleeds
• Found in kindred
• Single factor deficiency

Acute Coagulopathy of Trauma and Shock

• If no coagulopathy is suspected
  – Ligate and treat with colloids and RBCs
    – Dextran: 5% glucose
    – Discourage plasma (P-24, “FFP”)
• If coagulopathy is suspected: standard
  – Plasma to replace multiple coagulation factors
  – Coagulation factor concentrates: VIII, IX
  – Cryoprecipitate (CRYO) for fibrinogen
  – Activated prothrombin complex concentrate
  – Platelet concentrate for thrombocytopenia
  – NovoSeven® recombinant activated factor VII
24-YO ♂, GSW in ED

A 24-YO male arrived in the ED with a gunshot wound causing massive abdominal trauma. He had been given three units of Dextran® in transit to achieve fluid resuscitation but was hemorrhaging. ED ordered and administered four RBC units. Upon the second RBC four-unit batch order the transfusion service director recommended one plasma and onepheresis platelet concentrate. After 8 RBCs, 1 plasma, and 1 platelet, still bleeding, labs were:

- PT: 20.8 s (mean of RI 12.9);
- PTT: 82.5 s (MRI 30.1);
- FG: 130 mg/dL (225–498 mg/dL);
- PLTs: 70,000/µL (mean of RI 225,000–498,000/µL);
- INR: 2.6 (mean of RI 1.6–2.0);
- PTT: 82.5 s (MRI 30.1);
- Plasma: 9 g/dL (mean of RI 8–9 g/dL);
- Platelets: 70,000/µL (mean of RI 225,000–498,000/µL).

Patient expired before additional plasma and platelet concentrate could be administered.

Transfusion 2011; 51: 62–70.


Risks of Intraoperative Transfusion

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Transfusion</th>
<th>No Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>16.4%</td>
<td>9.81%</td>
</tr>
<tr>
<td>Pulmonary complication</td>
<td>12.6%</td>
<td>6.03%</td>
</tr>
<tr>
<td>Wound complications</td>
<td>9.17%</td>
<td>4.65%</td>
</tr>
<tr>
<td>Mortality</td>
<td>6.44%</td>
<td>4.26%</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>4.07%</td>
<td>1.89%</td>
</tr>
<tr>
<td>Renal complications</td>
<td>2.69%</td>
<td>1.85%</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>2.08%</td>
<td>1.40%</td>
</tr>
</tbody>
</table>


How to Treat, How to Monitor?

- FEIBA® plasma
- Cryoprecipitate
- Tranexamic acid
- Aspirin, clopidogrel, coumadin, heparin

T >37°C; pH >7.2; HGB >8 mg/dL; Ca++ >10 mmol/L

Surgical intervention: suture, compress, and pack


Plasma Administration in Adults

<table>
<thead>
<tr>
<th>Reason for Plasma</th>
<th>n=4635</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardiac surgery</td>
<td>21%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>19%</td>
</tr>
<tr>
<td>GI, ICH, childbirth, sepsis, renal failure</td>
<td>16%</td>
</tr>
<tr>
<td>Coumadin reversal</td>
<td>14%</td>
</tr>
<tr>
<td>Massive hemorrhage</td>
<td>13%</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>13%</td>
</tr>
<tr>
<td>Cancer</td>
<td>10%</td>
</tr>
<tr>
<td>Trauma</td>
<td>3%</td>
</tr>
<tr>
<td>DIC</td>
<td>3%</td>
</tr>
</tbody>
</table>


Plasma Efficacy in Adults

<table>
<thead>
<tr>
<th>INR</th>
<th>Median FFP</th>
<th>Median Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>11.4 mg/kg</td>
<td>–2.6 s</td>
</tr>
<tr>
<td>≤1.5</td>
<td>10.9 mg/kg</td>
<td>0.0</td>
</tr>
<tr>
<td>1.6–1.7</td>
<td>10.9 mg/kg</td>
<td>–0.2</td>
</tr>
<tr>
<td>1.8–1.9</td>
<td>12.1 mg/kg</td>
<td>–0.3</td>
</tr>
<tr>
<td>2.0–2.1</td>
<td>11.4 mg/kg</td>
<td>–0.4</td>
</tr>
<tr>
<td>2.2–2.5</td>
<td>11.6 mg/kg</td>
<td>–0.6</td>
</tr>
<tr>
<td>2.6–2.9</td>
<td>12.3 mg/kg</td>
<td>–0.9</td>
</tr>
<tr>
<td>3.0–4.9</td>
<td>11.5 mg/kg</td>
<td>–1.8</td>
</tr>
<tr>
<td>≥5.0</td>
<td>10.5 mg/kg</td>
<td>–2.0</td>
</tr>
</tbody>
</table>


USA hospital in Baghdad Green Zone

- Retrospective w/o controls but extensive, accurate data
- Confounding data: soldiers who received >10 RBCs but died before plasma could thaw are counted in this arm
- Receiving 1 plasma for every 4 RBCs: 65% mortality
- Receiving 2 plasma for every 3 RBCs: 19% mortality
- Surgeons report less bleeding and edema
- Now everyone is implementing 1:1:1 plasma/RBC/PLT
- Anticipated adverse effects; none recorded
- But requires ~15 hours to resolve coagulopathy
- TrALI, anaphylaxis, ARDS, MOF, thrombosis, no

Use TXA, CRYO, and PCC (Not plasma or rVIIa)

- Rapid, effective, predictable rise in factor activity
- Or RiaSTAP FG concentrate CLS Behring 12/11
- Requires a small volume, no TACO
- No risk of incompatible transfusion
- Avoid 58% of massive transfusions
  - Massive transfusion avoidance protocol
  - Reduce plasma use by 90%
- Effective viral inactivation
- Reduce RBC Tx by 8.4%
- No risk of TRALI
- Avoid 58% of massive transfusions
  - Massive transfusion avoidance protocol
  - Reduce plasma use by 90%
  - Effective viral inactivation
  - Reduce RBC Tx by 8.4%
  - No risk of TRALI
- Never use rVIIa

Medical Conditions Associated with Acquired Coagulopathies

- Malnutrition
- Vitamin K deficiency
- Renal disease
- Platelet dysfunction
- End-stage liver disease
- Chronic DIC
- Thrombocytopenia
- Vitamin K deficiency
- Increased fibrinolysis
- Myeloproliferative neoplasms
- Platelet dysfunction
- Acute promyelocytic or mononuclear leukemia (M3, M5)

Initial Laboratory Assays to Establish Coagulopathy

- Platelet count
  - RI: 150–450,000/µL
  - 50–150,000/µL: bleeding is due to qualitative PLT disorder
  - 10–50,000/µL: bleeding follows trauma
  - <10,000/µL: spontaneous bleeding

- Prothrombin time (PT)
  - RI: 12.4–14.4 s
  - INR RI: 1.0

- Partial thromboplastin time (PTT)
  - RI: 25–35 s

- Thrombin time
  - RI: 17–20 s, 100 mg/dL

- Fibrinogen
  - RI: 220–400 mg/dL

- D-dimer
  - RI: <100 ng/mL

PT or PTT >1.5 × MRI in anatomic bleeding suggests coagulopathy

Drugs Associated with Coagulopathies

<table>
<thead>
<tr>
<th>Drugs Associated with Coagulopathies</th>
<th>Lupus anticoagulant Factor VIII autoantibodies</th>
<th>Decreased synthesis of VK factors II, VII, IX, and X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazines and tricyclic antidepressants</td>
<td>Aspirin, NSAIDs, clopidogrel, prasugrel</td>
<td>Qualitative platelet suppression</td>
</tr>
<tr>
<td>Garlic, vitamin E, ginger, red wine</td>
<td>Antibiotics</td>
<td>Heparin, Coumadin, Dobigatran, Rivaroxaban</td>
</tr>
<tr>
<td>Anticoagulant overdose</td>
<td>Penicillin, sulfonamides</td>
<td>Factor VIII autoantibodies</td>
</tr>
</tbody>
</table>

54 YO Male Following Abdominal Surgery

- Parenteral antibiotics
- NPO one week

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>24.4 s (INR 2.2)</td>
<td>12.4–14.4 s (INR 1.0)</td>
</tr>
<tr>
<td>PTT</td>
<td>29 s</td>
<td>25–34 s</td>
</tr>
<tr>
<td>PLT count</td>
<td>230,000/µL</td>
<td>150–450 x 10^9/L</td>
</tr>
</tbody>
</table>
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The Fritsma Factor, Your Interactive Hemostasis Resource℠
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Prothrombin Time (PT, protime)
- PT reagent (thromboplastin) is tissue factor, phosphatidyl serine, and calcium chloride
- Activates extrinsic pathway at factor VII
- Prolonged by deficiencies of VII, X, V, prothrombin (II), and fibrinogen if <100 mg/dL
- Prolonged in Coumadin therapy
  - Coumadin suppresses production of prothrombin, VII, X, also IX, which is in the intrinsic pathway
  - Factor VII has a 6-hr half-life, thus has the earliest effect upon the PT

Activated Partial Thromboplastin Time (PTT, APTT)
- Reagent is phosphatidyl serine, calcium, and a negatively charged particulate activator; kaolin, silica, or ellagic acid
- Activates the intrinsic contact factor pathway at factor XII
- Prolonged by XII, XI, IX, VIII, X, prothrombin (II), and fibrinogen (if <100 mg/dL deficiency (all but VII))
- Prolonged in unfractionated heparin (UFH) therapy as UFH inhibits thrombin (IIa) and Xa via antithrombin
- PTT is prolonged in the presence of lupus anticoagulant (LA), which inhibits reagent phospholipids
  - PTT reagents vary in sensitivity to LA

Activated Clotting Time (ACT) in Cardiology OR
- Hemochron® or Hemochron Jr®, ITC
- ACT reagent is a suspension negatively charged particulate activator such as kaolin, silica, ellagic acid
- Activates the intrinsic pathway of fresh whole blood at factor XII
- Prolonged by all but VII deficiency
- Used in coronary artery bypass graft (CABG) or angioplasty (percutaneous intervention, PCI, cardiac catheterization) when UFH plasma concentration is 1.0–6.0 units/mL
- ACT RI is 70–180 s, UFH in OR 400–500 s

PT and PTT Test Results in Inherited Coagulopathies

<table>
<thead>
<tr>
<th>PT</th>
<th>PTT</th>
<th>Single Factor Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long</td>
<td>Normal</td>
<td>VII</td>
</tr>
<tr>
<td>Long</td>
<td>Long</td>
<td>X, V, II, and fibrinogen¹</td>
</tr>
<tr>
<td>Normal</td>
<td>Long</td>
<td>VIII, IX, XI²</td>
</tr>
</tbody>
</table>

¹PT & PTT prolonged when fibrinogen is <100 mg/dL
²Contact factor deficiencies: XII, prekallikrein (PK, Fletcher), or high molecular weight kininogen (HMWK, Fitzgerald) also prolong PTT results, but do not cause bleeding

54 YO Male, Abdominal Surgery
What Are His Possibilities?
- Congenital factor VII deficiency
  - Rare, symptoms appear in infancy
- Liver disease
  - Deficiency of all but factors VIII, XIII
  - PT is a sensitive measure of liver coagulopathy
  - PTT is less sensitive, later response
  - Liver enzymes
54 YO Male, Abdominal Surgery

**What Are More Possibilities?**

- **Vitamin K deficiency**
  - Hospitalized patients on antibiotics, malnutrition
  - Prolonged PT: deficiency of II, VII, IX, X, proteins C, S, Z
- **Disseminated intravascular coagulation (DIC)**
  - D-dimer is >>240 ng/mL (RI: 110–240 ng/mL)
  - Schistocytes on peripheral blood film
  - Platelet count <150,000/µL
  - PTT likely to be prolonged
  - Fibrinogen <100 mg/dL

**What’s Next?**

- Factor VII activity <10%
- Factor V activity 82%
- RI for most factors 50–150%

**Managing Vitamin K Deficiency**

- **Acute hemorrhage**
  - SQ or IV vitamin K ≤10 mg, monitor with PT
  - Plasma at 10–20 mL/kg or until hemostasis restored
    - May cause TACO
    - Provides little VII
  - NovoSeven “off-label” 25–35 µg/kg q 6 hours IV (157)
    - NovoSeven FDA-cleared dosage is 90–120 ug/kg q 2 hours IV
    - Indication is to treat bleeding in factor VIII or IX inhibitor
  - Minor bleeding, just an elevated PT/INR
    - Oral vitamin K ≤10 mg
    - 4–8 hours to recovery, monitor with PT
  - Next day, factor VII was 73% and INR was 1.2

**Managing Vitamin K Deficiency**

Another patient with serum creatinine 4.5 mg/dL had an INR of 1.9, no therapeutic Coumadin. He was given 10 units of FFP and 6 mg vitamin K IV, but the next day his INR was 1.7. Why didn’t it go back to normal?

**Managing Vitamin K Deficiency**

- Factor VII activity in plasma is small and becomes reduced in comparison to whole blood
  - 6-hour half-life
- In renal failure, plasma Rx causes TACO, dilutes existing plasma procoagulants
- The man was dialyzed and the INR went to 1.3 with no additional plasma

**Management of Bleeding in Liver Disease**

- Plasma at 10–20 mL/kg or until hemostasis is restored
- Vitamin K SQ or IV ≤10 mg
- Monitor for DIC
  - D-dimer >>240 ng/mL indicates abnormal fibrinolysis
  - Fibrinogen <100 mg/dL indicates consumption
**Platelet Disorders**
- RI: 150–450,000/µL
- PLT count in systemic bleeding
  - >50,000/µL: qualitative platelet disorder
  - 10–50,000/µL: bleeding follows trauma
  - <10,000/µL: spontaneous bleeding

**Acquired Thrombocytopenia**
- Radiation, chemotherapy
- Post-transfusion purpura (PTP)
- Drug-induced platelet-specific antibody
- All leukemias, myeloma, aplastic anemia
- Idiosyncratic response to hundreds of drugs
- Thrombotic thrombocytopenic purpura (TTP)
- Autoimmune thrombocytopenic purpura (ITP)
- Neonatal alloimmune thrombocytopenia (NAIT)

**Congenital Thrombocytopenia**
- PLT MPV ≥10.2 fl
  - MYH9-associated thrombocytopenia: mutations in non-muscle myosin II A cause May-Hegglin anomaly, Fechtner, Sebastian, Epstein syndromes with Döhle bodies
  - Gray platelet syndrome: absence of α granules confirmed by EM
  - Bernard-Soulier syndrome: decreased expression of GPIb/IX/V
  - Paris Trousseau/Jacobsen syndrome: deletion of key transcription factor in megakaryocytes; cardiac defects and developmental delay; large α granules visible by EM
- PLT MPV ≤6.8 fl
  - Wiskott Aldrich syndrome and X-linked thrombocytopenia
  - Immunodeficiency of T & B cells, eczema, recurrent infections

**Mother and Newborn with Thrombocytopenia**
- 28 YO woman with chronic thrombocytopenia
  - 2 y prior; surgery with PLT count 13,500/µL, no bleeding (as reported by patient)
- Newborn 5 d count 17,200/µL, no bleeding

**What Are The Possibilities?**
- Inherited thrombocytopenia
  - Chronic variable need for PLT concentrate
  - MYH9-associated thrombocytopenia: May-Hegglin anomaly
- Immune thrombocytopenic purpura (ITP)
  - Assay maternal auto-anti platelet antibodies
- Neonatal alloimmune TP (NATP)
  - Assay maternal allo-anti platelet antibodies
  - In either case, immunization ends at birth and infant PLT count reverts to normal in a few weeks

**28 YO Woman 2 M Post-partum**
- Heavy menstrual periods
- Bruises on arms and legs
- Easy bruising from 12 YO to present
- Bruises disappeared during pregnancy
- Reports mother and brother have easy bruising

<table>
<thead>
<tr>
<th>Screen</th>
<th>Result</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>13.1 s (INR 1.0)</td>
<td>12.4–14.4 s</td>
</tr>
<tr>
<td>PTT</td>
<td>49 s</td>
<td>25–35 s</td>
</tr>
<tr>
<td>PLT count</td>
<td>162,000/µL</td>
<td>150–450,000/µL</td>
</tr>
<tr>
<td>HGB</td>
<td>9.8 g/dL</td>
<td>12.0–14.5 g/dL</td>
</tr>
</tbody>
</table>
What are the Possibilities?

- **Unrecorded UFH?**
  - Thrombin time or anti-Xa heparin assay

- **Lupus anticoagulant?**
  - Not seen with bleeding, associates with thrombosis
  - Mixing studies

- **Acquired (non-familial) hemophilia?**
  - Autoantibody to factor VIII usually appears >60 YO, autoimmune disorders, subsequent to a pregnancy
  - Detect antibody in incubated mixing study
  - Confirmed in Bethesda titer

- **DIC: must always consider**
  - PT would be prolonged
  - Schistocytes in peripheral blood film
  - D-dimer >>>>240 ng/mL
  - Fibrinogen <100 mg/dL

- **Single congenital factor deficiency: VIII, IX, or XI**
  - VIII or IX are sex-linked, unlikely
  - XI deficiency is autosomal, 50% of cases in Jews
  - Factor VIII low in von Willebrand disease (VWD)
  - Perform mixing studies and factor assays

### 28-YO Woman 2 M Post-partum

#### PTT Mixing Study

<table>
<thead>
<tr>
<th>Assay</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin time</td>
<td>17 s</td>
<td>RI 17–20 s, r/o heparin</td>
</tr>
<tr>
<td>PTT patient (as before)</td>
<td>49 s</td>
<td>RI 25–35 s</td>
</tr>
<tr>
<td>PTT normal plasma control</td>
<td>27 s</td>
<td>Commercial PPP</td>
</tr>
<tr>
<td>Immediate 1:1 mix</td>
<td>29 s</td>
<td>Correction ≤10%, r/o LA</td>
</tr>
<tr>
<td>37°C 2 h mix</td>
<td>31 s</td>
<td>Correction ≤10%, r/o inhibitor</td>
</tr>
<tr>
<td>37°C 2 h normal control</td>
<td>30.5 s</td>
<td>Incubate with mix</td>
</tr>
</tbody>
</table>

### 28 YO Woman 2 Mo After Delivery

#### Presumptive Evidence of ?

<table>
<thead>
<tr>
<th>Factor Assay</th>
<th>Result</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII</td>
<td>38%</td>
<td>50–150%</td>
</tr>
<tr>
<td>FIX</td>
<td>96%</td>
<td>110%</td>
</tr>
<tr>
<td>FXI</td>
<td></td>
<td></td>
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</tbody>
</table>

### VWD Profile

<table>
<thead>
<tr>
<th>Assay</th>
<th>Patient</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF-Ag</td>
<td>39%</td>
<td>50–249%</td>
</tr>
<tr>
<td>VWF-RCo</td>
<td>37%</td>
<td>50–166%</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>38%</td>
<td>55–188%</td>
</tr>
<tr>
<td>ABO-related VWF-Ag or VWF RCo</td>
<td>Group O</td>
<td>36–157%</td>
</tr>
<tr>
<td></td>
<td>A, B, or AB</td>
<td>57–239%</td>
</tr>
<tr>
<td>VWF-Act Immunoadsay</td>
<td>41%</td>
<td>50–150%</td>
</tr>
<tr>
<td>VWF-CBA</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>RIPA 0.5 mg ristocetin</td>
<td>&lt;60% Agg</td>
<td>&gt;60% Agg</td>
</tr>
<tr>
<td>VWF multimers</td>
<td>NA</td>
<td>Type 2 only</td>
</tr>
</tbody>
</table>
**VWD Therapy**

- **RICE**: rest, ice, compression, elevation
- **Estrogens**: oral contraceptives, topical salves
- **Stimate®**: see next slide
- **Antifibrinolytics** that complement DDAVP
  - Amicar®, ε-aminocaproic acid (EACA)
  - Tranexamic acid (Cyklokapron®)
    - Injection: 10 mg/kg 3–4 x per day
    - Oral: 25 mg/kg 3–4 x per day
    - Mouthwash: 10 mL of 4.8% aqueous solution for dental procedures
- **VWF concentrate**: Humate P or Wilate

**Desmopressin Vasopressin® (DDAVP®)**

- Releases VWF from EC Weibel-Palade bodies
- **VWD types 1, 2A, 2M**
  - In type 2, individualized response; challenge with pre and post therapy, monitor with VWF:Ag assay, not VWF:RCO
  - Contraindicated in VWD 2B, ineffective in VWD 3
- **3 µg/kg to limit of 28 µg in 15–30 mL saline 15–30m**
- **Stimate® inhaler**, one spray/nostril = 300 µg total
  - 2 h before any procedure, VWF half-life is 12 h
  - Tachyphylaxis if repeated <48 h
- **Monitor 15–20 m after dose**

**VWD Therapy**

- **VWF-rich, intermediate purity fractionated factor VIII concentrate** (Humate-P®, Alphanate®)
  - Cleared 1999, orphan drug
  - VWF:FVIII 2:1
  - Monitor VWF:Ag
- **Wilate® high purity plasma-derived VWF**
  - Octapharma: FDA cleared 7/7/2010 as orphan drug
  - VWF:FVIII ratio 1:1
- **Dosage**: see hemophilia discussion