Pharmacotherapy Resuscitation in Acute Traumatic Coagulopathy: Ready for Prime Time?

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Disclosures

- No conflicts of interest to disclose

Objectives

- Define the pathophysiology and monitoring of acute traumatic coagulopathy (ATC)
- Analyze the role of tranexamic acid (TXA) in ATC
- Describe the developments and recommendations in coagulation-factor concentrate (CFC) therapy for the treatment of ATC

Pathophysiology of ATC

- Hemorrhagic shock
- Activation of anticoagulant & fibrinolytic pathways
- Tissue injury

Traumatic Hemorrhage

- Traumatic injury is the leading cause of death in patients under the age of 45
- Three leading causes:
  - Traffic accidents
  - Suicides
  - Homicides
- Hemorrhage following trauma accounts for 40% of deaths in the civilian setting
- About one-third of bleeding trauma patients show signs of coagulopathy on admission
- Patients who develop ATC → 3-4x ↑ mortality rate

References

2. Rossaint et al. Crit Care 2016; 20: 100
Diagnosis of ATC

- **Standard laboratory tests:**
  - PT, INR, APTT, platelets, fibrinogen
  - No consensus definition for ATC

- **Viscoelastic Testing:**
  - Assesses physical properties of clot
  - Mechanical-electrical transducer
  - Can test thrombosis through fibrinolysis
  - Rotational thromboelastometry (ROTEM) & thromboelastography (TEG)

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**Alpha angle**

- Speed of fibrin formation
- Normal: 53-72°
- If alpha angle decreased → fibrinogen deficiency

**Maximum Amplitude (MA)**

- Ultimate strength of the clot
- Normal: 50-70 mm
- If MA decreased → platelet dysfunction
Fibrinolysis

Coagulation

Fibrolysis

LY30

Percentage of clot lysis at 30 minutes

Normal: 0-8%

If LY30 increased → excess fibrinolysis


Complete TEG

R Time

Alpha Angle

MA

LY30

TEG

R Time

Alpha Angle

MA

LY30


FAHBT, Factor Xa

FFP: Fresh frozen plasma

PCC: Prothrombin complex concentrate

INR: International Normalized Ratio

Treatment of ATC

ACUTE TRAUMATIC COAGULOPATHY

Stop hyperfibrinolysis

Support clot formation & increase thrombin generation

Pharmacologic treatment of fibrinolysis

- TXA
  - Antifibrinolytic 
  - Inhibits conversion of plasminogen to plasmin
  - Benefits:
    - Clot stabilization
    - Preserves platelet function
    - Reduces myocardial oxygen demand
  - Aminocaproic acid
    - 10x less potent than TXA 
    - Use only when TXA not available
    - ↑ adverse events
  - Aprotinin

Impact of Fibrinolysis

ACUTE TRAUMATIC COAGULOPATHY

Stop hyperfibrinolysis

- In ATC, fibrinolysis may be pathological → hyperfibrinolysis
  - Develops in ~25% of trauma patients
  - Intermediate/severe hyperfibrinolysis → mortality rate >90%

Recommendations: Monitoring of ATC

EUROPEAN TRAUMA GUIDELINES:

Early and repeated monitoring of coagulation is recommended using EITHER standard laboratory tests (1A) and/or viscoelastic testing (1C)

JOURNAL OF TRAUMA CONSENSUS GUIDELINES:

Consideration should be given to using viscoelastic testing during early trauma resuscitation

Viscoelastic testing is highly specific for fibrinolysis and thus should be used to identify hyperfibrinolysis in trauma patients


Inaba et al. J Trauma Acute Care Surg 2015; 78: 220

European Trauma Guidelines:

IN THE JOURNAL OF TRAUMA CONSensus Guidelines:

Consideration should be given to using viscoelastic testing during early trauma resuscitation

Viscoelastic testing is highly specific for fibrinolysis and thus should be used to identify hyperfibrinolysis in trauma patients

Appendix C

Appendix E

Maegle et al. Transfusion 2016; 56: S157

Crash 2 collaborators. Lancet 2010; 376: 23

CRASH-2 Trial

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, placebo-controlled trial</td>
<td>n = 20,211</td>
<td>Primary outcome: death in hospital within 4 weeks of injury</td>
</tr>
<tr>
<td>Evaluating the efficacy of TXA in traumatic hemorrhage</td>
<td>1 gram TXA over 10 minutes + IV infusion of 1g over 8 hours versus 0.9% saline</td>
<td>Secondary outcomes:</td>
</tr>
<tr>
<td>274 hospitals</td>
<td>Included: adult trauma patients within 8 hours of injury with significant hemorrhage or at risk for significant hemorrhage (SBP &lt;90, HR &gt;110)</td>
<td>• Vascular occlusive events</td>
</tr>
<tr>
<td>40 countries</td>
<td></td>
<td>• Receiving blood transfusions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Number of units transfused</td>
</tr>
</tbody>
</table>

CRASH-2 Trial - Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n = 10,067)</th>
<th>TXA (n = 10,060)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td>Balanced with respect to all characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11% were from Europe, Australia, and North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1,613 (16%)</td>
<td>1,463 (14.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Death due to bleeding</td>
<td>574 (5.7%)</td>
<td>489 (4.9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vascular occlusion</td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Blood product transfused</td>
<td>5,160 (51.3%)</td>
<td>5,067 (50.4%)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Secondary Analysis of CRASH-2

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examined the effect of TXA on death due to bleeding according to treatment time</td>
<td>Intention-to-treat population</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of death due to bleeding</th>
<th>Time from injury to TXA</th>
<th>Placebo</th>
<th>TXA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 hour post-injury</td>
<td>7.7%</td>
<td>5.3%</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>1-3 hours post-injury</td>
<td>6.1%</td>
<td>4.8%</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>&gt;3 hours post-injury</td>
<td>3.1%</td>
<td>4.4%</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

Criticisms of CRASH-2

- Population
  - Majority from low- to middle-income countries
  - Heterogeneous
- Methods
  - No injury severity scores reported
  - Did not monitor laboratory parameters for coagulation
- Outcomes
  - Absolute reduction in mortality was small (1.5%)
  - Possible underreporting of adverse events

Clinical Questions Following CRASH-2

1. Should TXA be used in all bleeding trauma patients?
2. Are there subgroups who may receive increased benefit from TXA?
**TXA Benefit**
- Pre-specified analysis of CRASH-2
  - Examined if benefit of TXA varied according to baseline risk of death
  - Created prognostic model for mortality

| All-cause mortality in patients with traumatic bleeding according to treatment with TXA: |
|---|---|---|
| No of patients (%) | TXA | Placebo | Odds ratio (99% CI) |
| <5% | 337/438 (12%) | 466/573 (13%) | 0.78 (0.49 to 1.21) |
| >5% | 234/384 (14%) | 464/573 (13%) | 0.83 (0.56 to 1.22) |
| All | 571/822 (18%) | 930/1,146 (18%) | 0.85 (0.57 to 1.26) |

If TXA use is restricted to patients who need massive transfusion or patients at highest risk, miss ~40% of the possible benefit of TXA

**TXA Use Abroad**
- European Trauma Guidelines on TXA:
  - TXA should be administered as early as possible to the bleeding trauma patient (1A) within 3 hours of injury (1B)
  - Dose: 1 gram over 10 minutes, followed by 1 gram over 8 hours
- Economic evaluation of TXA
  - Hospital cost of TXA ~$10/gram
  - TXA is considered ‘very cost effective’ in 3 markets: Tanzania, India, and the UK

**Safety of TXA**
- No difference in venous thromboembolisms (VTE) between the TXA and placebo groups in CRASH-2 trial
  - Low rates of VTE
  - Authors stated could have underreported VTE
- Nishida et al. performed a systematic review of studies looking at VTE with TXA in trauma patients
  - Nonsignificant increase in the risk of VTE with TXA
- Hypothesized fibrinolysis shutdown
  - Mechanism unknown
  - TXA may increase mortality due to organ failure in this population

**Taxx Applicability in the United States**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Population</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanin et al.</td>
<td>Retrospective, single center trial, N = 1,032</td>
<td>Trauma patients &gt;15 years old with evidence of hyperfibrinolysis (LY30 &gt;2.9%); TXA v. no TXA</td>
<td>Primary outcome: mortality</td>
<td>• Unadjusted in-hospital mortality was higher in TXA group (40% v. 17%; p&lt;0.01) • Logistic regression failed to find a difference in mortality among those receiving TXA (p = 0.88)</td>
</tr>
<tr>
<td>Moore et al.</td>
<td>Prospective, single center trial, N = 232</td>
<td>Adult, severely injured trauma patients (new ISS &gt;15); Analyzed physiological (LY30 &gt;3.3% or hyperfibrinolysis &gt;4%)</td>
<td>Primary outcome: mortality</td>
<td>• TXA does not benefit adult trauma patients • TXA was a significant predictor of mortality for patients with physiological fibrinolysis (p=0.02)</td>
</tr>
</tbody>
</table>

**Clinical Questions Following CRASH-2**

1. Should TXA be used in all bleeding trauma patients?
   **Likely**
2. Are there subgroups who may receive increased benefit from TXA?

**Mandatory TXA in modern trauma centers is not appropriate**

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**Ongoing TXA Trials**

<table>
<thead>
<tr>
<th>Title</th>
<th>Study Design</th>
<th>Location</th>
<th>Objective</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAMP</td>
<td>Phase II, multicenter, prospective, randomized, double-blind trial of TXA versus placebo</td>
<td>United States</td>
<td>To determine if pre-hospital TXA given during medical transport to a level 1 trauma center in patients at risk of hemorrhage is associated with a lower 30-day mortality</td>
<td>Recruiting</td>
</tr>
<tr>
<td>PATCH</td>
<td>Multicenter, randomized, double-blind trial of TXA versus placebo</td>
<td>New Zealand, Australia</td>
<td>To determine if giving TXA (pre-hospital) improves chances of survival and recovery at 6 months</td>
<td>Recruiting</td>
</tr>
<tr>
<td>TAIPIT</td>
<td>Single-center, prospective, randomized trial</td>
<td>United States</td>
<td>To evaluate the effects of TXA on the immune system, TXA pharmacokinetics, and safety and efficacy in trauma patients</td>
<td>Ongoing, not recruiting</td>
</tr>
</tbody>
</table>
Clinical Questions Following CRASH-2

1. Should TXA be used in all trauma patients?

2. Are there subgroups who may receive increased benefit from TXA?

MATTERs Study

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective observational study comparing TXA to no TXA in patients receiving at least 1 unit of pRBCs</td>
<td>n = 896 (military)</td>
<td>Primary outcome: mortality</td>
</tr>
</tbody>
</table>

Secondary outcomes:
- Transfusion requirements
- Incidence of thrombotic events

MATTERs - Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Results</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>144 (23.9%)</td>
<td>51 (17.4%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (0.3%)</td>
<td>8 (2.7%)</td>
</tr>
<tr>
<td>VTE</td>
<td>1 (0.2%)</td>
<td>7 (2.4%)</td>
</tr>
</tbody>
</table>

In the massive transfusion group, TXA use was independently associated with survival.

Impact of Fibrinogen and Thrombin in ATC

- **Fibrinogen** → marker of clot firmness
  - Decreased fibrinogen
    - Independent predictor of poor outcome
    - Associated with increased severity of shock
  - **Thrombin** → potent activator of coagulation factors
    - Persistent bleeding after improved clot firmness → sign of thrombin deficiency
    - Deficit associated with mortality
    - Hard to detect with viscoelastic testing
Fixed Ratio Resuscitation

- Fixed ratio of 1 unit pRBC: 1 unit plasma: 1 unit platelets mimics whole blood
  - PROPR trial performed in 12 US trauma centers showed more patients achieved hemostasis and had less exsanguination using a 1:1:1 ratio vs 2:1:1

**Disadvantages**
- Diluted concentrations of coagulation factors II, VII, IX, X
- Risk of over-transfusion → transfusion-related acute lung injury
- Not individualized
- Temperature sensitive
- Limited shelf-life
- Limited supply
- Time to obtain from blood bank

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Coagulation Factor Concentrate Resuscitation

- Alternative to fixed ratio blood product resuscitation
- Viscoelastic testing used to guide the treatment of hemostatic deficiencies
- Schöchl et al. retrospective analysis comparing fibrinogen concentrate + prothrombin complex concentrate (PCC) versus FFP
  - No difference in mortality
  - Decreased pRBC and platelet transfusions in fibrinogen + PCC group

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CFC Pharmacotherapy

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen Concentrate (RiaSTAP®)</td>
<td>15-20 mg/mL per 50-100 mL vials</td>
<td>50-100 mL</td>
</tr>
<tr>
<td>3-Factor PCC (Prothrombin®)</td>
<td>Factors II, IX, X</td>
<td>5-10 mL</td>
</tr>
<tr>
<td>4-Factor PCC (KCentra®)</td>
<td>Factors II, VII, IX, X</td>
<td>20-40 mL</td>
</tr>
</tbody>
</table>

**Advantages**
- Rapid testing
- Targeted/tailored treatment
- Time to therapy
- Decreased risk of volume overload
- Reduced exposure to allogeneic blood products

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RETI Trial

**Study Design**
- Single-center, parallel-group, open-label, randomized trial comparing FFP or CFC for reversal of ATC

**Population**
- n = 100
- FFP group: FFP (15 mL/kg)
- CFC group:
  - Fibrinogen concentrate (50 mg/kg) +
  - Four-factor PCC (20 IU/kg) +
  - Factor XIII (20 IU/kg)

**Outcomes**
- Could receive up to 2 doses of assigned study drug before ‘rescue’ therapy considered
- Inclusion criteria: ISS ≥15, trauma patients aged 18-80, bleeding, and coagulopathy identified by prolonged coagulation time via ROTEM

**Primary endpoint:** multiple organ failure in modified intention-to-treat population

**Secondary endpoints:**
- Reversal of coagulopathy
- Need for massive transfusion
- Length of stay (hospital, ICU)
- Need and duration of hemodialysis
- VTE

---

**RETI – Results**

Study terminated early due to significantly increased treatment failure in the FFP group compared to the CFC group

**RESULTS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FFP (n = 48)</th>
<th>CFC (n = 52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive transfusion</td>
<td>30%</td>
<td>12%</td>
<td>0.04</td>
</tr>
<tr>
<td>VTE</td>
<td>18%</td>
<td>8%</td>
<td>0.22</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>27</td>
<td>28</td>
<td>0.61</td>
</tr>
<tr>
<td>Need for hemodialysis</td>
<td>16%</td>
<td>10%</td>
<td>0.54</td>
</tr>
<tr>
<td>Days of hemodialysis</td>
<td>27</td>
<td>11</td>
<td>0.04</td>
</tr>
<tr>
<td>ISS-adjusted SOFA score</td>
<td>0.20</td>
<td>0.16</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Odds in favor of successful reversal of coagulopathy after single-dose study drug higher in CFC group (OR 8.22, p <0.01)

Author’s Conclusions: CFC resuscitation is superior to FFP
Strengths & Criticisms of RETIC Trial

- Strengths
  + Randomized
  + Clinically relevant
- Criticisms
  - Single center, small sample size
  - Complex study design
  - Only 19% patients received PCC, 21% received Factor XIII
  - Utilization of Factor XIII in based on weak evidence
  - Study not powered to detect differences

Conclusions

RETIC trial shows potential role for fibrinogen concentrate in the treatment of ATC

Further evidence needed for use of PCC and FXIII in treatment of ATC

Disadvantages of CFC Treatment

- Adverse Drug Reactions
  - Fibrinogen concentrate
    - Risks appear low
  - PCC
    - Black box warning for VTE for indication of vitamin K antagonist reversal

Disadvantages of CFC

- Requires additional training
- Cost
- No prospective validation of treatment algorithms

Recommendations for Resuscitation

European Trauma Guidelines:

If plasma-based resuscitation is used, guidelines recommend using FFP to maintain PT and APTT <1.5x normal control (1C)

If concentrate-based strategy is used, use fibrinogen concentrate 3-4 g (2C)

If significant bleeding is accompanied by viscoelastic signs of fibrinogen deficit or a plasma fibrinogen <1.5-2 g/L (1C)

If fibrinogen levels are normal, suggest using PCC or plasma in the bleeding patient based on evidence of delayed coagulation initiation on viscoelastic monitoring (2C)

United States Recommendations:

Multicenter, large randomized studies needed to support use of CFC

Pharmacoeconomic analysis needed

Conclusions

- ATC leads to worse outcomes and identification via TEG or standard lab tests is essential
- Early use of TXA is beneficial in patients with bleeding trauma and those requiring massive transfusion
- Further studies needed to support replacement of blood product resuscitation for CFC

As the treatment of ATC shifts from a focus on blood products to pharmacologic-based treatment with CFC, it is important for pharmacists to be knowledgeable of the available evidence.

Treatment of ATC

- Bleeding trauma
- Massive transfusion
- Hyperfibrinolysis

Conclusions

- Evaluator
  - Merry Daniel, PharmD, BCCCP
- Preceptors
  - Mitch Daley, PharmD, BCPS
  - Emily Hodge, PharmD, BCCCP

Acknowledgements
Appendices

A. Abbreviations
B. Pathophysiology of Acute Traumatic Coagulopathy
C. Thromboelastography
D. Rotational Thromboelastometry
E. ATC Treatment Strategies
F. Blood Products
G. Coagulation Factor Concentrates
H. RETIC Treatment Algorithm
I. RETIC Trial Dosing
J. RETIC Trial Bleeding Score
Appendix A: Abbreviations

- APTT: activated partial thromboplastin time
- ATC: acute traumatic coagulopathy
- CFC: coagulation factor concentrate
- FAST: focused assessment with sonography for trauma
- FFP: fresh frozen plasma
- GCS: Glasgow Coma Scale
- HR: Heart rate
- ICU: intensive care unit
- INR: international normalized ratio
- ISS: injury severity score
- LY30: lysis at 40 minutes
- MA: maximum amplitude
- OR: operating room
- PCC: prothrombin complex concentrate
- pRBCs: packed red blood cells
- PT: prothrombin time
- ROTEM: rotational thromboelastometry
- SBP: systolic blood pressure
- SOFA: sequential organ failure assessment
- TEG: thromboelastography
- tPA: tissue plasminogen activator
- TXA: Tranexamic acid
- VTE: venous thromboembolism
Appendix B: Pathophysiology of Acute Traumatic Coagulopathy
## Appendix C: Thromboelastography

### Complete TEG

![Complete TEG Diagram]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Normal Value</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R Time</strong></td>
<td>Time to clot initiation</td>
<td>5-10 min</td>
<td>Deficiency in coagulation factors</td>
<td></td>
</tr>
<tr>
<td><strong>K Time</strong></td>
<td>Time until clot reaches fixed strength</td>
<td>1-3 min</td>
<td>Fibrin deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha Angle</strong></td>
<td>Speed of fibrin formation</td>
<td>53-72°</td>
<td>Fibrinogen deficiency</td>
<td>Platelet dysfunction</td>
</tr>
<tr>
<td><strong>Maximum Amplitude (MA)</strong></td>
<td>Ultimate strength of the clot</td>
<td>50-70 mm</td>
<td><strong>Excess fibrinolysis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>LY30</strong></td>
<td>Degree of clot lysis</td>
<td>0-8%</td>
<td><strong>Excess fibrinolysis</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix D: Rotational Thromboelastometry

**Complete ROTEM**

<table>
<thead>
<tr>
<th></th>
<th>Definition</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clotting Time (CT)</strong></td>
<td>Time to clot initiation</td>
<td>Deficiency in coagulation factors</td>
<td></td>
</tr>
<tr>
<td><strong>Clot Formation Time</strong></td>
<td>Time until clot reaches fixed strength</td>
<td>Fibrin deficiency</td>
<td></td>
</tr>
<tr>
<td>(CFT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alpha Angle</strong></td>
<td>Speed of fibrin formation</td>
<td></td>
<td>Fibrinogen deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Clot Firmness</strong></td>
<td>Ultimate strength of the clot</td>
<td></td>
<td>Fibrinogen deficiency, Platelet dysfunction</td>
</tr>
<tr>
<td>(MCF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clot Lysis at 30 minutes (CL30)</strong></td>
<td>Degree of clot lysis/amplitude reduction at 30 minutes</td>
<td>Excess fibrinolysis</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Lysis (ML)</strong></td>
<td>Maximum clot lysis</td>
<td>Excess fibrinolysis</td>
<td></td>
</tr>
</tbody>
</table>
Appendix E: Treatment of ATC Algorithm

Acute Traumatic Coagulopathy

Stop hyperfibrinolysis

TXA

Fixed Ratio Resuscitation

Support clot formation & Increase thrombin generation

1:1:1 pRBCs + FFP + platelets

Coagulation Factor Concentrate Resuscitation

Fibrinogen concentrate

PCC
# Appendix F: Blood Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed Red Blood Cells (pRBCs)</td>
<td>• Red cells left from one unit of whole blood after majority of plasma removed</td>
<td>200-350 mL</td>
</tr>
<tr>
<td></td>
<td>• ~195 mL red cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ~155 mL suspending fluid (35 mL plasma)</td>
<td></td>
</tr>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>• Contains about 80% of the plasma from a unit of whole blood</td>
<td>250 mL</td>
</tr>
<tr>
<td></td>
<td>• 500 mg fibrinogen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 200 units of other clotting factors</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>• A unit of platelets suspended in 40 mL of plasma and 10 mL of citrate-sugar solution</td>
<td>50 mL</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>• 250-400 mg fibrinogen</td>
<td>10-15 mL</td>
</tr>
<tr>
<td></td>
<td>• Von Willebrand Factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ~100 Units Factor VIII</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Factor XIII</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix G: Coagulation Factor Concentrates

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Volume</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen Concentrate (RiaSTAP®)</td>
<td>15-20 mg/mL per 50-100 mL vials*</td>
<td>50-100 mL</td>
<td>$1/mg</td>
</tr>
<tr>
<td>3-Factor PCC (Profilnine®)</td>
<td>Factors II, IX, X</td>
<td>5-10 mL</td>
<td>$0.7/unit</td>
</tr>
<tr>
<td></td>
<td>500, 1000, 1500 unit vials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Factor PCC (KCentra®)</td>
<td>Factors II, VII, IX, X</td>
<td>20-40 mL</td>
<td>$1.3/unit</td>
</tr>
<tr>
<td></td>
<td>500, 1000 unit vials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII concentrate (Corifact®)</td>
<td>1000 – 1600 units</td>
<td>20 mL</td>
<td>$11.88/unit**</td>
</tr>
</tbody>
</table>

*varies by manufacturer

**Average Wholesale Price (AWP)
Appendix H: RETIC Treatment Algorithm

- FFP: Fresh Frozen Plasma
- CFC: Coagulation Factor Concentrate
- PCC: Prothrombin Complex Concentrate
- FXIII: Factor XIII Concentrate
Appendix I: RETIC Trial dosing

Weight-based dosing of study drugs

<table>
<thead>
<tr>
<th></th>
<th>45-50 kg</th>
<th>51-70 kg</th>
<th>71-100 kg</th>
<th>&gt;100 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>4 U</td>
<td>5 U</td>
<td>7 U</td>
<td>10 U</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3 g</td>
<td>4 g</td>
<td>5 g</td>
<td>6 g</td>
</tr>
<tr>
<td>PCC</td>
<td>1000 IE</td>
<td>1500 IE</td>
<td>2000 IE</td>
<td>2500 IE</td>
</tr>
<tr>
<td>FXIII</td>
<td>1000 IE</td>
<td>1500 IE</td>
<td>2000 IE</td>
<td>2500 IE</td>
</tr>
</tbody>
</table>

Appendix J: RETIC Trial Bleeding Score

<table>
<thead>
<tr>
<th>Bleeding Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No substantial Bleeding</td>
</tr>
<tr>
<td>1</td>
<td>Injury-related normal bleeding with visible clots</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse microvascular bleeding from wound and catheter insertion sites</td>
</tr>
<tr>
<td>3</td>
<td>Massive bleeding with transfusion of &gt;3 units of pRBCs/hr</td>
</tr>
</tbody>
</table>

*Subjective bleeding score created by authors, not yet validated*