PLATELET AND PLASMA TRANSFUSION

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Objectives

- Platelet transfusion
  - Guidelines
  - Evidence behind the guidelines
  - Platelet refractoriness
- Plasma transfusion
  - Guidelines
  - Evidence behind the guidelines
- Risks of transfusion
PLATELETS
Platelets

- Life span approximately 10 days
- Platelets form from megakaryocyte blebs
- 40% in the spleen
- 60% circulate
- Normal counts are 150-400/microliter
- 7-10$x10^3$ are consumed daily

http://www.bloodjournal.org/content/121/13/2379
Platelet Products

- Whole blood, buffy coat or platelet rich plasma derived platelets
  - Suspended in 40-70 mL of plasma or platelet additive solution
  - May be leukoreduced
- Single donor apheresis platelets
- Platelet additive solution (PAS) platelets
  - About 65% of the plasma is removed
Platelet Storage

• Stored between 20-24 C with continuous gentle agitation
• Shelf life 5 days
• 24 hours if open system
• Storage containers allow for oxygen and carbon dioxide exchange to allow for aerobic oxidative phosphorylation and maintenance of pH
Bacterial Testing

- AABB requires methods to limit and detect bacteria in platelet products
- Culture based methods
- Point of issue testing
Quality Assurance

• Whole blood derived platelets
  • 90% of whole blood derived platelets must contain $> 5.5 \times 10^{10}$ platelets and have a pH $\geq 6.2$
  • 95% of leukoreduced whole blood derived platelets must have $< 8.3 \times 10^5$ leukocytes
  • Pooled platelets products must have $< 5.0 \times 10^6$ leukocytes

• Apheresis platelets
  • 90% must contain $> 3.0 \times 10^{11}$ platelets and have a pH $\geq 6.2$
  • 95% of leukoreduced apheresis platelets must have $< 5.0 \times 10^6$ leukocytes
Platelet Transfusion

• Adult Dosing
  • 4-6 whole blood derived pooled platelets
  • One apheresis platelet
  • Expected increase in platelet count 30,000-60,000/microliter

• Pediatric Dosing
  • 10mL/kg or 1 whole blood derived platelet/ 10kg
  • Expected increase 50-100,000/uL

• Post-transfusion increment
  • Affected by fever, sepsis, DIC, splenomegaly, drugs, platelet antibodies, bleeding,…
Product Selection

• ABO compatibility –
  • Should be group specific
  • ABO antigens are present on the surface of platelets
  • Administration of ABO incompatible plasma
    • Titer group O apheresis platelets

• Try to match for RhD but not required
  • RhD is not present on the platelet surface but on residual RBCs in the product
  • Possible to cause alloimmunization to RhD but unlikely
  • Can administer RhIg
Platelet Product Modifications

- **Leukoreduction**
  - Decrease risk of febrile nonhemolytic transfusion reactions, HLA alloimmunization, CMV transmission

- **Irradiation**
  - Prevent transfusion-associated graft-versus-host disease

- **Washed**
  - Decrease risk of allergic/anaphylactic transfusion reactions
  - Remove antibodies in the plasma

- **Volume reduced**
  - Decrease antibodies in the plasma
  - Decrease risk of transfusion-associated circulatory overload

- **Aliquots**
  - Neonatal and pediatric transfusions
Indications for Platelet Transfusion

• Prophylactic Transfusions
  • Stable, nonbleeding patient
    • Platelet transfusion threshold 10,000/uL
    • Higher thresholds with fever or sepsis

• Therapeutic Transfusions
  • Minor bleeding or prior to elective catheter placement or low risk endoscopic procedures
    • Platelet transfusion threshold 20,000/uL
  • Bleeding or invasive procedure
    • Platelet transfusion threshold 50,000/uL
  • Neurosurgical patients and ECMO
    • Platelet transfusion threshold 100,000/uL
  • Massive bleeding or known platelet dysfunction

• Optimal dose is unknown but generally transfuse 1 apheresis platelet or 4-6 pooled platelets
For adults: one apheresis platelet, equivalent to 6-8 units of platelets, is indicated:

1. Platelet count ≤ 10,000/uL as prophylaxis against spontaneous bleeding in all patients including:
   a. Therapy-induced hypoproliferative thrombocytopenia
   b. Bone marrow / stem cell transplant patients

2. Platelet count ≤ 20,000/uL and
   a. Minor bleeding (epistaxis, oral mucosal bleeding, etc.), heparin, fever, sepsis, coagulopathy, anatomic lesion at risk of bleeding
   b. Prior to elective catheter placement*
   c. Heme-Onc inpatients about to be discharged home or outpatients who are platelet transfusion-dependent
   d. Low risk diagnostic endoscopic procedures (diagnostic upper endoscopy, flexible sigmoidoscopy, colonoscopy (including biopsies), biliary stent insertion, diagnostic ERCP)

3. Platelet count ≤ 50,000/uL and
   a. Patient with active bleeding (GI bleed, hemorrhagic cystitis, etc.)
   b. Invasive procedure (recent, in-progress or planned nonneuraxial surgery such as thoracotomy, laparotomy, hip replacement, liver biopsy, etc.)
   c. High risk interventional endoscopic procedures (endoscopic polypectomy, endoscopic hemostasis, tumor ablation, treatment of varices, percutaneous endoscopic gastrostomy tube placement)*
   d. Lumbar puncture

4. Platelet count ≤ 100,000/uL with
   a. Bleeding in a closed anatomical space (e.g., CNS, ocular)
   b. Neurosurgical patients
   c. Bleeding after cardiopulmonary bypass
   d. Patients on extracorporeal membrane oxygenation (ECMO)

5. In the setting of massive transfusion, without platelet count

6. In the setting of known platelet dysfunction, with a normal or elevated platelet count
<table>
<thead>
<tr>
<th>WHO Bleeding Grade</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Grade 1           | Oropharyngeal bleeding ≤30 min in 24 h  
|                   | Epistaxis ≤30 min in previous 24 h  
|                   | Petechiae of oral mucosa or skin  
|                   | Purpura ≤1 inch in diameter  
|                   | Spontaneous hematoma in soft tissue or muscle  
|                   | Positive stool occult blood test  
|                   | Microscopic hematuria or hemoglobinuria  
|                   | Abnormal vaginal bleeding (spotting)  |
| Grade 2           | Epistaxis >30 min in 24 h  
|                   | Purpura >1 inch in diameter  
|                   | Joint bleeding  
|                   | Melanotic stool  
|                   | Hematemesis  
|                   | Gross/visible hematuria  
|                   | Abnormal vaginal bleeding (more than spotting)  
|                   | Hemoptysis  
|                   | Visible blood in body cavity fluid  
|                   | Retinal bleeding without visual impairment  
|                   | Bleeding at invasive sites  |
| Grade 3           | Bleeding requiring red blood cell transfusion over routine transfusion needs  
|                   | Bleeding associated with moderate hemodynamic instability  |
| Grade 4           | Bleeding associated with severe hemodynamic instability  
|                   | Fatal bleeding  
|                   | CNS bleeding on imaging study with or without dysfunction  |

CNS = central nervous system; WHO = World Health Organization.  
* From references 18 and 22.
Platelet Transfusion: A Clinical Practice Guideline From the AABB

Richard M. Kaufman, MD; Benjamin Djulbegovic, MD, PhD; Terry Gernsheimer, MD; Steven Kleinman, MD; Alan T. Tinmouth, MD; Kelley E. Capocelli, MD; Mark D. Cipolle, MD, PhD; Claudia S. Cohn, MD, PhD; Mark K. Fung, MD, PhD; Brenda J. Grossman, MD, MPH; Paul D. Mintz, MD; Barbara A. O'Malley, MD; Deborah A. Sesok-Pizzini, MD; Aryeh Shander, MD; Gary E. Stack, MD, PhD; Kathryn E. Webert, MD, MSc; Robert Weinstein, MD; Babu G. Welch, MD; Glenn J. Whitman, MD; Edward C. Wong, MD; and Aaron A.R. Tobian, MD, PhD
Clinical Setting 1: Hospitalized Adult Patients With Therapy-Induced Hypoproliferative Thrombocytopenia

Recommendations

Recommendation 1: The AABB recommends that platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in adult patients with therapy-induced hypoproliferative thrombocytopenia.

The AABB recommends transfusing hospitalized adult patients with a platelet count of $10 \times 10^9$ cells/L or less to reduce the risk for spontaneous bleeding.

The AABB recommends transfusing up to a single apheresis unit or equivalent. Greater doses are not more effective, and lower doses equal to one half of a standard apheresis unit are equally effective.

Quality of evidence: moderate; strength of recommendation: strong.
Clinical Setting 2: Adult Patients Having Minor Invasive Procedures

Recommendations

Recommendation 2: The AABB suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than $20 \times 10^9$ cells/L.

Quality of evidence: low; strength of recommendation: weak.

Recommendation 3: The AABB suggests prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than $50 \times 10^9$ cells/L.

Quality of evidence: very low; strength of recommendation: weak.
Clinical Setting 3: Adult Patients Having Major Elective Nonneuraxial Surgery

**Recommendations**

Recommendation 4: The AABB suggests prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than $50 \times 10^9$ cells/L.

Quality of evidence: very low; strength of recommendation: weak.

Recommendation 5: The AABB recommends against routine prophylactic platelet transfusion for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass (CPB). The AABB suggests platelet transfusion for patients having CPB who exhibit perioperative bleeding with thrombocytopenia and/or with evidence of platelet dysfunction.

Quality of evidence: very low; strength of recommendation: weak.
Clinical Setting 4: Adult Patients Receiving Antiplatelet Therapy Who Have Intracranial Hemorrhage (Traumatic or Spontaneous)

Recommendations

Recommendation 6: The AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous).

Quality of evidence: very low; strength of recommendation: uncertain.
Contraindications to Platelet Transfusion

- Absolute contraindications in the absence of significant or life threatening bleeding
  - Thrombotic thrombocytopenic purpura
  - Heparin induced thrombocytopenia
- Relative contraindications in the absence of significant or life threatening bleeding
  - Immune thrombocytopenia
Platelet Refractoriness

- Immune versus non immune causes
- Anti-human platelet antigen antibodies and anti-HLA Class I antibodies
- Check 1 hour post platelet count
- Calculate corrected count increment

\[ CCI = \frac{\text{Post-Transfusion Platelet Increment} \times \text{Body Surface Area (m}^2\text{)}}{10^{11} \text{ Transfused Platelets}} \]

> 7500 – nonimmune causes  <7500 – immune causes
Normal patient showing platelet level graphed against time. The patient shows an increase at the time of transfusion (red arrow) and a minimal decrease over the following hours. Due to this slow decrease, measurement at both 1 hour and 6 hour post-transfusion (green and black arrows) show similar levels.

Patient with non-immune platelet refractoriness (e.g. fever). The patient shows an increase at the time of transfusion (red arrow) and a slow decrease over the following hours. Measurement at 1 hour (green arrow) and 6 hours (black arrow) show markedly different levels.

Patient with either immune-mediated refractoriness or non-immune refractoriness (e.g. splenomegaly). The patient shows an increase at the time of transfusion (red arrow) and a rapid return to pre-transfusion levels. Measurement at 1 hour (green arrow) and 6 hours (black arrow) show low platelet level.
Platelet Antibody Testing
Platelet Antibody Testing

HPA-1a alloAb

HPA-1a alloAb

HPA-1b alloAb

negative control

A

B

1

2

3

4

http://www.haematologica.org/content/97/5/696
Interpretation

• Chloroquine destroys anti-HLA reactivity.
• If you have a positive reaction, add chloroquine.
• If the reaction is still positive and the reactivity is the same, anti-platelet antibodies are present.
• If the reaction is still positive and the reactivity is decreased, both anti-platelet and anti-HLA antibodies are present.
• If the reaction becomes negative, only anti-HLA antibodies are present.
Management

- ABO matched platelets
- Crossmatched platelets
- HLA matched platelets
- HLA antibody antigen negative platelets
Nonimmune Causes of Platelet Refractoriness

- Fever
- Sepsis
- Antibiotics
- Drugs
- Consumption
- Bleeding
- Hypersplenism
PLASMA
Plasma

- Acellular, liquid part of blood
  - 90% water
  - 7% protein
  - 2-3% nutrients, crystalloids, hormones, and vitamins
- Coagulation factors
  - Fibrinogen
  - Factor XIII
  - Von Willebrand factor
  - Factor VIII primarily bound to vWF
  - Clotting factors II, VII, IX, and X
Plasma

- Collected from whole blood or apheresis
- Frozen and stored at ≤ -18 C
- Shelf-life 1 year frozen
- Thawed in water bath at 30-37 C (20-30 minutes)
  - Shelf life of 24 hours at 1-6 C
  - Can be extended for up to 5 days post thaw
Plasma Products

- FFP
- FP24
- Cryoprecipitate-reduced plasma
- Thawed plasma
- FFP, FP4, and thawed plasma are used interchangeably
## Fresh Frozen Plasma Coagulation Factors*

<table>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Plasma Concentration Required for Hemostasis (U/mL)</th>
<th>Half-Life of Factor</th>
<th>Recovery in Blood (as % of Amount Transfused)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (fibrinogen)</td>
<td>100-150 mg/dL</td>
<td>3-6 days</td>
<td>50%</td>
</tr>
<tr>
<td>II (prothrombin)</td>
<td>0.4</td>
<td>2-5 days</td>
<td>40-80%</td>
</tr>
<tr>
<td>V</td>
<td>0.1-0.25</td>
<td>15-36 hours</td>
<td>80%</td>
</tr>
<tr>
<td>VII</td>
<td>0.05-0.2</td>
<td>2-7 hours</td>
<td>70-80%</td>
</tr>
<tr>
<td>VIII</td>
<td>0.1-0.4</td>
<td>8-12 hours</td>
<td>60-80%</td>
</tr>
<tr>
<td>IX (Christmas factor)</td>
<td>0.1-0.4</td>
<td>18-24 hours</td>
<td>40-50%</td>
</tr>
<tr>
<td>X</td>
<td>0.1-0.2</td>
<td>1.5-2 days</td>
<td>50%</td>
</tr>
<tr>
<td>XI</td>
<td>0.15-0.3</td>
<td>3-4 days</td>
<td>90-100%</td>
</tr>
<tr>
<td>XIII (fibrin stabilizing factor)**</td>
<td>0.1-0.5</td>
<td>6-10 days</td>
<td>5-100%</td>
</tr>
<tr>
<td>vWF†</td>
<td>0.25-0.5</td>
<td>3-5 hours</td>
<td>75%</td>
</tr>
</tbody>
</table>

* A dose of 10 ml/kg will typically provide sufficient coagulation factors to achieve hemostasis. Factor levels in donor plasma are variable, but can be assumed to be approximately 1 U/ml. Post-transfusion recovery of transfused factors may be less than expected due to extravascular distribution or consumption.

** Factor XIII is also present in cryoprecipitate, along with factors VIII, vWF, fibrinogen, and fibronectin.

† vWF levels vary with ABO type. Type O blood has less amount of circulating vWF; AB has the most.
FFP vs FP24

- Contains above the minimum clotting factor activity required for surgical hemostasis immediately post thaw
- Improved logistics
- Cost effective processing of whole blood
- Facilitated conversion to male-only plasma
Comparison of Coagulation Factor Activity in FFP and FP24

At Thaw –
- FVIII 23% lower in FP24 (p=0.003)
- PC 18% lower in FP24 (p=0.006)

120 hours -
- PC 17% lower in FP24 (p=0.009)
- PS 13% lower in FP24 (p=0.044)
Comparison of Coagulation Factor Activity in FFP and FP24

Significant decrease in activity of FV, FX, vWF:Rco, and PS at 120 hours post thaw
<table>
<thead>
<tr>
<th>Analyte</th>
<th>HRL reference range*</th>
<th>Thaw (%)</th>
<th>120 hr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FFP</td>
<td>FP24</td>
</tr>
<tr>
<td>FII (IU/dL)</td>
<td>83-145</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>FV (U/dL)</td>
<td>68-135</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>FVII (IU/dL)</td>
<td>68-172</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>FVIII (IU/dL)</td>
<td>60-195</td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td>F IX (IU/dL)</td>
<td>71-141</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>FX (IU/dL)</td>
<td>72-146</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>VWF:Ag (IU/dL)</td>
<td>50-240</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>VWF:RCo (IU/dL)</td>
<td>50-279</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>FGN (mg/dL)</td>
<td>236-484</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>AT (IU/dL)</td>
<td>85-119</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>PC (IU/dL)</td>
<td>81-154</td>
<td>95</td>
<td>64</td>
</tr>
<tr>
<td>PS (IU/dL)</td>
<td>63-138</td>
<td>95</td>
<td>96</td>
</tr>
</tbody>
</table>

* Adult population range.
<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>FP24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thaw 120 hr Change (%)</td>
<td>Thaw 120 hr Change (%)</td>
</tr>
<tr>
<td>Leukoreduced</td>
<td>86 ± 14 (66-101) 10*</td>
<td>84 ± 16 (54-124) 12*</td>
</tr>
<tr>
<td>Nonleukoreduced</td>
<td>83 ± 13 (63-104) 33*</td>
<td>90 ± 14 (61-112) 55*</td>
</tr>
</tbody>
</table>

* p < 0.05 when comparing mean activity at thaw to mean activity at expiration.
Thawed Plasma

- Either FFP or FP24
- Shelf-life 5 days at 1-6°C
- Most clotting factors remain stable
- May have decreased activity of FV, FVII, and FVIII
- Levels remain about minimum activity required for surgical hemostasis
- Cost-effective use of plasma
- Decreased wastage
Cryoprecipitate-Reduced Plasma

- Supernatant expressed during manufacture of cryoprecipitate
- Deficient in FVIII, FXIII, vWF, fibrinogen, cryoglobulin, and fibronectin
- Frozen shelf-life 1 year ≤ 18°C
- Indication: Thrombotic thrombocytopenic purpura
Plasma Transfusion

- 200-280 mL per unit
- 0.7-1 unit/mL of activity of each coagulation factor per mL of plasma
- 1-2 mg/mL of fibrinogen
- Usual dose is 10-20 mL/kg – expected to increase factor levels about 20-30%
- Must consider half-life of the deficient factor that you are correcting
- ABO group matching
Indications for Plasma Transfusion

1. Prevention of bleeding
2. Treatment of hemorrhage
   • Congenital or acquired coagulation defect
## Table 24.3 Screening tests used in the diagnosis of coagulation disorders.

<table>
<thead>
<tr>
<th>Screening tests</th>
<th>Abnormalities indicated by prolongation</th>
<th>Most common cause of coagulation disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin time (TT)</td>
<td>Deficiency or abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs</td>
<td>DIC, Heparin therapy</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>Deficiency or inhibition of one or more of the following coagulation factors: VII, X, V, II, fibrinogen</td>
<td>Liver disease, Warfarin therapy, DIC</td>
</tr>
<tr>
<td>Activated partial</td>
<td>Deficiency or inhibition of one or more of the following coagulation factors: XII, XI, IX (Christmas</td>
<td>Haemophilia, Christmas disease (+ conditions above)</td>
</tr>
<tr>
<td>thromboplastin time (APTT or PTTK)</td>
<td>disease), VIII (haemophilia), X, V, II, fibrinogen</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen quantitation</td>
<td>Fibrinogen deficiency</td>
<td>DIC, liver disease</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; FDPs, fibrin degradation products.

NB. Platelet count and the tests of platelet function are also used in screening patients with a bleeding disorder (p. 328).
Relationship between INR and % Coagulation Factors

![Graph showing the relationship between INR and % Coagulation Factors](http://openi.nlm.nih.gov/detailedresult.php?img=2983046_kjh-45-152-g001&req=4)
Coagulation Tests and Risk of Bleeding

- Abnormal coagulation tests do not predict bleeding
- Normal coagulation factor activity between 50—150%
- About 30% activity needed for hemostasis with a single factor deficiency
- About 40% activity needed for hemostasis with multiple factor deficiencies
- Plasma is indicated when PT or aPTT ≥ 1.5 - 1.7 times normal with bleeding or risk of bleeding
No Evidence for Efficacy

- Mild to moderate elevations in PT/aPTT prior to procedures
- Immunodeficiency
- Burns
- Wound healing
- Volume expansion
- Source of nutrients

- Estimates of inappropriate use of plasma up to 83%
Liver Disease

• May have low levels of vitamin K dependent clotting factors
• May have prolonged PT, aPTT, and TT
• Increase in PT and aPTT correlated with increased risk of bleeding and mortality in these patients

• Plasma transfusion
  • Evidence does not support prophylactic plasma transfusion prior to surgery or liver biopsy
  • Transfusion of plasma for severe liver disease and perioperative liver transplant does not improve outcomes
  • Transfusion decisions should be guided by coagulation testing
Massive Transfusion

- Transfusion of $\geq 10$ units of RBCs within 24 hours
- Acute trauma induced coagulopathy – prolonged PT upon arrival at the ED
- Lethal triad – dilutional coagulopathy, acidosis, and hypothermia
- Associated with increased mortality and increased use of blood products

- Plasma transfusion:
  - Early plasma transfusion appears to improve survival
  - Optimal ratios still being investigated – 2:1, 1:1
Evidence-based practice guidelines for plasma transfusion


Question 1

Should plasma transfusion (vs. no plasma) be used in trauma patients requiring massive transfusion?

Recommendation: We suggest that plasma be transfused to trauma patients requiring massive transfusion (quality of evidence = moderate).
Question 2

Should a plasma : red blood cell (RBC) transfusion ratio of 1:3 or more (vs. <1:3) be used in trauma patients requiring massive transfusion?

**Recommendation:** We *cannot recommend* for or against transfusion of plasma at a plasma : RBC ratio of 1:3 or more in trauma patients during massive transfusion (quality of evidence = low).

The panel strongly endorsed further testing of plasma : RBC transfusion ratio of 1:3 or more (vs. <1:3) in the context of well-designed randomized controlled trials.
Reversal of Warfarin

• Mechanism of action – inhibition of the synthesis of vitamin K-dependent clotting factors by blocking the enzyme vitamin K oxide reductase

• Functional deficiency in factors II, VII, IX, X, protein C and protein S

• Plasma transfusion –
  • Active bleeding, emergent surgery or trauma
  • PCCs may be more effective due to large volumes of plasma required
  • Considerations for patients at risk for transfusion-associated circulatory overload
<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INR &gt; goal but &lt; 5</strong>&lt;br&gt;No significant bleeding or risk of bleeding</td>
<td>• Lower dose or omit next dose</td>
</tr>
<tr>
<td><strong>INR ≥ 5 or &lt; 9</strong>&lt;br&gt;<strong>AND</strong>&lt;br&gt;No significant bleeding or risk of bleeding</td>
<td>• <strong>Preferred:</strong> Omit next 1-2 doses&lt;br&gt;• Alternatively, omit 1-2 doses and give Vitamin K (1-2.5 mg po)&lt;br&gt;• Alternatively for patients at high risk of thrombosis (i.e. valves), omit 1-2 doses and use FFP 2 units IV – DO NOT use Vitamin K</td>
</tr>
<tr>
<td><strong>INR ≥ 9</strong>&lt;br&gt;No significant bleeding&lt;br&gt;<strong>AND/OR</strong>&lt;br&gt;Low-moderate risk of bleeding</td>
<td>• Hold warfarin therapy&lt;br&gt;• Give FFP 2 units IV&lt;br&gt;• Give Vitamin K (2.5-5 mg po)&lt;br&gt;• In patients with prosthetic heart valves, give FFP 2 units IV and lower dose of Vitamin K (1-2.5mg po)</td>
</tr>
<tr>
<td><strong>Serious bleeding at any elevation of INR</strong>&lt;br&gt;<strong>AND/OR</strong>&lt;br&gt;High risk of bleeding</td>
<td>• Hold warfarin therapy.&lt;br&gt;• Give FFP 4 units IV&lt;br&gt;• Vitamin K 10mg by slow IV infusion&lt;br&gt;• May repeat FFP and Vitamin K as needed&lt;br&gt;• In patients with prosthetic heart valves, FFP is <em>preferred</em> over Vitamin K; use only very low doses of Vitamin K (1mg by slow IV infusion).</td>
</tr>
<tr>
<td><strong>Life-threatening bleeding</strong></td>
<td>• Hold warfarin therapy.&lt;br&gt;• Give FFP 4 units IV&lt;br&gt;• Vitamin K 10mg by slow IV infusion&lt;br&gt;• Consider recombinant Factor VIIa for unresolved coagulopathy&lt;br&gt;• Repeat FFP and Vitamin K as needed</td>
</tr>
</tbody>
</table>

**INR = international normalized ratio**<br>**FFP = fresh frozen plasma**
### TABLE 2: Preoperative Management of Elevated (≥ 1.5 INRs) in Patients on Warfarin (1-7)

<table>
<thead>
<tr>
<th>INR Value</th>
<th>Urgent Surgery or Procedure</th>
<th>Surgery or Procedure Scheduled in 24-48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR ≥ 1.5 but ≤ 1.9</td>
<td>Treatment with FFP</td>
<td>Vitamin K 1mg PO</td>
</tr>
<tr>
<td>INR &gt; 1.9 but ≤ 5 who require reversal for a procedure No significant bleeding</td>
<td>For rapid (&lt; 12 hours) reversal: FFP + Vitamin K 1-3mg slow IV</td>
<td>Vitamin K 1-2.5mg PO If INR still elevated in 24h, repeat</td>
</tr>
<tr>
<td>INR &gt; but &lt; 9 who require surgery No significant bleeding</td>
<td>For rapid (&lt; 12 hours) reversal: FFP + Vitamin K 2-5mg slow IV</td>
<td>Vitamin K 2.5-5mg PO If INR still elevated in 24h, give Vitamin K 1-2mg PO</td>
</tr>
</tbody>
</table>

*NOTE: High-dose Vitamin K should not routinely be given to patients with prosthetic heart valves*

INR = international normalized ratio  
FFP = fresh frozen plasma
Evidence-based practice guidelines for plasma transfusion


Question 5

Should plasma transfusion (vs. no plasma) be used to reverse warfarin anticoagulation in patients without intracranial hemorrhage?

Recommendation: We cannot recommend for or against transfusion of plasma to reverse warfarin in patients without intracranial hemorrhage (quality of evidence = very low).
Question 4

Should plasma transfusion (vs. no plasma) be used for patients with warfarin anticoagulation–related intracranial hemorrhage?

Recommendation: We suggest that plasma be transfused in patients with warfarin anticoagulation–related intracranial hemorrhage (quality of evidence = low).
Other Indications

• Disseminated intravascular coagulopathy
• Coagulation factor replacement in plasma exchange
• Thrombotic thrombocytopenic purpura
• Congenital coagulation factor deficiencies when plasma derivatives are not available
• Other coagulation defects (Bypass surgery, ECMO)
Prophylactic Use

- Use in the absence of bleeding or before surgical procedures to correct PT/aPTT is unlikely to improve outcomes
Evidence-based practice guidelines for plasma transfusion


Question 3
Should plasma transfusion (vs. no plasma) be used in surgical and/or trauma patients in the absence of massive transfusion?

_Recommendation:_ We **cannot recommend** for or against transfusion of plasma for patients undergoing surgery in the absence of massive transfusion (**quality of evidence = very low**).
Question 6

Should plasma transfusion (vs. no plasma) be used in other groups of patients (e.g., in the absence of massive transfusion, surgery, bleeding, or overanticoagulation)?

**Recommendation:** We **suggest against** plasma transfusion in other groups for which data were available (acute pancreatitis, organophosphate poisoning, coagulopathy associated with acetaminophen overdose, intracranial hemorrhage after severe closed head injury in patients without coagulopathy, nonsurgical noncardiac patients in the intensive care unit; quality of evidence = very low).
RISKS OF PLATELET AND PLASMA TRANSFUSION
Table 1. Approximate Per-Unit Risks for Platelet Transfusion in the United States

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Approximate Risk per Platelet Transfusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile reaction</td>
<td>1/14</td>
<td>6</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1/50</td>
<td>7</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>1/75 000</td>
<td>8</td>
</tr>
<tr>
<td>TRALI*</td>
<td>1/138 000</td>
<td>9</td>
</tr>
<tr>
<td>HBV infection</td>
<td>1/2 652 580</td>
<td>Personal communication†</td>
</tr>
<tr>
<td>HCV infection</td>
<td>1/3 315 729</td>
<td>Personal communication†</td>
</tr>
<tr>
<td>HIV infection</td>
<td>0 (95% CI, 0 to 1/1 461 888)</td>
<td>Personal communication†</td>
</tr>
</tbody>
</table>

HBV = hepatitis B virus; HCV = hepatitis C virus; TRALI = transfusion-related acute lung injury.
* The overall risk for TRALI from all plasma-containing blood products is currently estimated to be approximately 1/10 000 (10).
† Notari E, Dodd R, Stramer S. Personal communication.
Table 2 Of the Potential Adverse Effects, the Following Events Were Reported From the Danish, French, and Quebec Hemovigilance System, Recalculated to a Rate per 10,000 Transfusions\textsuperscript{14,16,18}

<table>
<thead>
<tr>
<th>Events per 10,000 Transfusions</th>
<th>Plasma</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-haemolytic transfusion reactions (urticaria, allergic and anaphylaxis symptom)</td>
<td>0.22\textdagger</td>
<td>0\dagger</td>
</tr>
<tr>
<td></td>
<td>0.35\textnatural</td>
<td>1.04\textnatural</td>
</tr>
<tr>
<td></td>
<td>2.35\textnatural</td>
<td>5.42\textnatural</td>
</tr>
<tr>
<td>Congestive heart failure/volume overload</td>
<td>0.1\natural</td>
<td>0.13\natural</td>
</tr>
<tr>
<td></td>
<td>2.06\natural</td>
<td>4.82\natural</td>
</tr>
<tr>
<td>Sepsis due to inadvertent bacterial contamination</td>
<td>0.02\natural</td>
<td>0.28\dagger</td>
</tr>
<tr>
<td></td>
<td>0\natural</td>
<td>0.29\natural</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.41\natural</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury*</td>
<td>0.18\dagger</td>
<td>0.46\natural</td>
</tr>
<tr>
<td></td>
<td>0\natural</td>
<td>1.81\natural</td>
</tr>
<tr>
<td>Posttransfusion purpura</td>
<td>0.04\natural</td>
<td>0</td>
</tr>
<tr>
<td>Viral transmission</td>
<td>0</td>
<td>0.03\natural</td>
</tr>
<tr>
<td>Severe anaphylaxis with Ig A deficiency and anti IgA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transfusion-associated graft-versus host disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Citrate toxicity</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Transmission of other pathogens not tested for or recognised</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Alloimmunisation against HLA-antigens</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

\dagger Reported from the Danish.
\natural Reported from the French.
\natural Reported from Quebec.
\natural NR indicates not reported.
**Table 3** Other Adverse Effects Reported in the Danish, French and Quebec Hemovigilance System, Recalculated to a Rate per 10,000 Transfusions\textsuperscript{14,16,18}

<table>
<thead>
<tr>
<th>Events per 10,000 Transfusions</th>
<th>Plasma</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor allergic reactions</td>
<td>16,2\textsuperscript{†}</td>
<td>44,6\textsuperscript{†}</td>
</tr>
<tr>
<td>Febrile non-hemolytic</td>
<td>5,3\textsuperscript{†}</td>
<td>24,1\textsuperscript{†}</td>
</tr>
<tr>
<td>transfusion reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions, not further</td>
<td>2,6\textsuperscript{†}</td>
<td>19,8\textsuperscript{†}</td>
</tr>
<tr>
<td>specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunological incompatibility</td>
<td>0,06\textsuperscript{†}</td>
<td>3,4\textsuperscript{†}</td>
</tr>
<tr>
<td></td>
<td>2,9\textsuperscript{†}</td>
<td>1,2\textsuperscript{†}</td>
</tr>
<tr>
<td>Incorrect blood component</td>
<td>0,15\textsuperscript{*}</td>
<td>0\textsuperscript{*}</td>
</tr>
<tr>
<td>issued</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hemolytical transfusion</td>
<td>0,84\textsuperscript{†}</td>
<td>2,0\textsuperscript{†}</td>
</tr>
<tr>
<td>reaction</td>
<td>0\textsuperscript{*}</td>
<td>0\textsuperscript{*}</td>
</tr>
<tr>
<td>Inefficient transfusion</td>
<td>0\textsuperscript{†}</td>
<td>1,4\textsuperscript{†}</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,3\textsuperscript{†}</td>
<td>12,9\textsuperscript{†}</td>
</tr>
<tr>
<td></td>
<td>0,88\textsuperscript{†}</td>
<td>0,12\textsuperscript{†}</td>
</tr>
<tr>
<td>Other reactions</td>
<td>0,31\textsuperscript{†}</td>
<td>0,38\textsuperscript{†}</td>
</tr>
<tr>
<td></td>
<td>0,90\textsuperscript{†}</td>
<td></td>
</tr>
</tbody>
</table>

\* Reported from the Danish.
\ † Reported from the French.
\ ‡ Reported from Quebec.
TRALI MITIGATION
AABB Standard

• “Plasma and whole blood for allogeneic transfusion shall be from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.”
TRALI Mitigation Strategies

• Male-only plasma
• Tested plasma or platelets
• Exclusion of multiparous females
• Deferring antibody positive donors
• Decreasing plasma volume from a single donor
QUESTIONS???
Primary Hemostasis: Formation of the platelet plug

1. von Willebrand factor binds to collagen and triggers platelet adhesion.
2. ADP released by platelets recruits more platelets through the platelet plug formation.
3. Fibrinogen and fibrinogen receptors facilitate the formation of a stable fibrin network around the platelet plug.
Primary Hemostasis: Formation of the platelet plug

1. Platelet adhesion occurs when von Willebrand factor connects exposed collagen to platelets.
2. During the platelet release reaction, ADP, thromboxanes, and other chemicals are released and activate other platelets.
3. Platelet aggregation occurs when fibrinogen receptors on activated platelets bind to fibrinogen, connecting the platelets to one another. The accumulating mass of platelets forms a platelet plug.
Effect of Hematocrit: Decrease in hematocrit can lead to an increase in bleeding time

<table>
<thead>
<tr>
<th>Normal axial red-cell flow, hematocrit ≥30%</th>
<th>Anemia, resulting in loss of axial red-cell flow, hematocrit &lt;30%</th>
<th>Platelet dysfunction due to platelet adhesion and granule release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subendothelial matrix</td>
<td>von Willebrand factor</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>Glycoprotein Ib</td>
<td>Adhesion</td>
<td>Adhesion</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Aggregation</td>
<td>Aggregation</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIA</td>
<td>Platelet</td>
<td>Platelet</td>
</tr>
<tr>
<td>Granule release</td>
<td></td>
<td>Granule release</td>
</tr>
</tbody>
</table>
Secondary Hemostasis: Activation of the coagulation cascade

1. The extrinsic pathway of clotting starts with thromboplastin, which is released outside the plasma in damaged tissue.
2. The intrinsic pathway of clotting starts when inactive factor XII, which is in the plasma, is activated by coming into contact with a damaged blood vessel.
3. Activation of the extrinsic or intrinsic pathway results in the production of activated factor X.
5. Prothrombin is converted to thrombin by prothrombinase.
6. Fibrinogen is converted to fibrin (the clot) by thrombin.
7. Thrombin activates clotting factors, promoting clot formation and stabilizing the fibrin clot.

Stable Clot

http://www.med-health.net/What-Does-Low-Platelets-Mean.html
History: Rule out inherited defect or use of antithrombotic drugs.

Examination: Is bleeding general or local?

General bleeding

Coagulation screening and full blood count

Low platelet count with normal results on coagulation screening

Low platelet count and fragmented red cells (microangiopathic hemolytic anemia)

Normal platelet count with coagulation deficiencies

Low platelet count with coagulation deficiencies

Failed production of platelets

Reduced survival

Increased splenic pooling

Schistocyte

Factor VIII

Acquired hemophilia

Consumption of platelets and clotting factors

Widespread fibrin deposition

Microvascular thrombotic obstruction

Organ failure

Figure 1. Causes of Bleeding among Patients in the ICU.

After the presence of inherited disorders and the use of antithrombotic drugs have been ruled out, the first major question ("Is the bleeding general or local?") combined with a platelet count and coagulation screening, will assist in the identification of the pathogenesis of bleeding.