MASSIVE AND EMERGENT TRANSFUSIONS
Shan Yuan, MD
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I. Definitions of Massive Transfusion:
- Replacement of a patient's total blood volume or more within a 24-hour period
- Transfusion of 10 or more units of blood 24 hours
- Transfusion of 50% TBV in 3 hours.

II. Basic Principles of Fluid and Transfusion Support
A. Traditional Approach
- Replace volume first.
  - When loss is <15%: no treatment is necessary in most patients
  - When loss is 15-30% of TBV:
    - give crystalloids, e.g., Lactate Ringer solution, which rapidly distributes between the intra- and extravascular spaces. Volume of crystalloid needed to restore intravascular volume is 3X of the estimated blood loss
  - When loss is 30% or above:
    - Give crystalloids and RBCs
    - Give FFP when more than 5-10 RBC units have been given
B. Newer Approach (based on experiences and better survivorship data in combat settings):
- If patient recognized as a bleeder, start giving FFP and RBCs and platelet concentrates in a 1:1:1 ratio to replete all components lost during bleeding simultaneously
- Challenges:
  - Optimal ratio of various products yet to be conclusively established
  - Require coordination with blood bank. Delay of plasma products may be a problem due to the time required for thawing (30 min)

III. Issues in Massive Transfusion
A. Can the blood bank keep up?
- Blood bank may establish policy to abbreviate the testing and paperwork requirements in order to expedite the provision of blood component in trauma cases
- Compatibility testing should proceed as fast as possible
- When time permits, provide ABO/Rh identical or compatible, and crossmatch compatible. Otherwise give O negative (universal) or type-specific (if blood type is known) uncrossmatched units
- If time does not permit, cut back testing as necessary
Get a blood type specimen and determine blood type as soon as possible so type-specific RBC units can be given. O negative RBCs is a precious resource that needs to be utilized judiciously.

- If a patient has already been transfused with 10-12 units of RBCs, it may no longer be possible to determine the patient’s blood type with confidence.

- Antibody screen/identification and crossmatch further reduce risks of transfusing incompatible RBCs in patients with pre-existing alloantibodies. But may be skipped in emergencies. Consider the following:
  - Prevalence of alloantibody formation is not high in the average patient:
    - individuals who have never been transfused or pregnant: 0.04%
    - In previously transfused/multiparous females: 0.3%
    - In chronically transfused (sickle cell, thalassemia patients): 5-30%
  - Most, although not all clinically significant non-ABO antibodies are IgG, thus do not fix complement; they mediate extravascular hemolysis rather than life-threatening, intravascular hemolysis.
  - If antigen positive RBCs given to a patient with pre-existing alloantibodies, most of the time there are no consequences or only very mild DHTR (delayed hemolytic transfusion reactions) due to the decrease of alloantibody concentration following blood loss and fluid replacement.

- Clinical provider should keep blood bank informed of the urgency of transfusions. Blood bank should communicate abbreviation of testing to the clinicians.

- Testing should always be initiated, and completed. Results should be followed up retrospectively.
  - E.g.; A patient was given uncrossmatched units, later shown to have anti-E, then all the uncrossmatched units that had been transfused should be typed for the E antigen to gauge the potential for delayed hemolysis.
  - Any incompatibility detected should be communicated to the clinicians.
  - In certain high-volume massive transfusion settings where the patient’s serum is so diluted with crystalloid solutions that testing is not useful, and pretransfusion specimen is not available, then complete testing may not get done.

- Estimated turn around times and level of testing completed:

<table>
<thead>
<tr>
<th>Situation</th>
<th>Product Given</th>
<th>Turnaround Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood bank has no specimen, need unit</td>
<td>O negative uncrossmatched RBC. O positive</td>
<td>5 min</td>
</tr>
<tr>
<td>ASAP</td>
<td>units may be given to males or females</td>
<td></td>
</tr>
<tr>
<td></td>
<td>past</td>
<td></td>
</tr>
</tbody>
</table>
**B. Issues with Stored Blood –Significant Concerns in Massive Transfusion**

- Stored blood have decreased:
  - RBC 2,3-DPG: drops down near 0 after two weeks in storage. RBC recovers 2-3DPG quickly after transfusion, back to 24 hours after transfusion. This decrease leads to lower oxygen P50, (left-shift) with increased Hgb oxygen affinity, this causes decreased oxygen release to the tissues
  - pH: due to lactate and citrate
  - ATP (due to consumption by cellular components)
  - Coagulation factors
  - Temperature (stored at 1-6°C)

- Stored blood have increased
  - Potassium: one unit may have 20-30mEq/L K+ after 3 weeks storage, total load is about 7mEq per unit, which rapidly equilibrates as RBC recover in low volume transfusions
  - Free Hemoglobin

**C. Clinical problems with massive transfusion:**

- Coagulopathy: Foremost problem in massive issue. (Also see next section ) several contributing factors
  - Thrombocytopenia due to platelet-poor transfusions.
  - Coagulopathy due to dilution and/or factor-poor transfusions.
  - Further exarcebated by hypothermia and acidosis, which impair coagulation protein functions.

- Hyperkalemia: may cause cardiac arrhythmia, exacerbated by hypoperfusion and acidosis

- Hypocalcemia: Ca is lowered by the citrate present in the transfused unit. Rate of citrate infusion can exceed the liver’s metabolic capacity. May need to monitor ionized calcium. This can lead to symptoms of hypocalcemia including paresthesia, tingling, and arrhythmias in severe cases

- Hypothermia: cold blood lowers body temperature, which further causes: left shift of HgB-Oxygen dissociation curve, increased intracellular K+ release, impaired coagulation, cardiac arrhythmias, etc. Blood warmers can help, or mixing blood with warmed normal saline is an alternative if blood warmer is not available.
Acidosis: acidosis may be already pre-existing due to shock. Metabolism of lactate and citrate will generate HCO$_3^-$, which will correct acidosis to some degree.

Hemoglobin Changes:
- “p50” = partial pressure of oxygen where hemoglobin is 50% saturated.
- “Shift to the left” = decreased $p50 = \text{increased}$ oxygen affinity
- “Shift to the right” = increased $p50 = \text{decreased}$ oxygen affinity
- In massive transfusion: Decreasing pH in blood from glycolysis moves curve to the right, but decreased 2,3 DPG moves curve to the left.
- End result: 2,3-DPG decline outweighs the pH decline, so curve is left-shifted in transfused blood.

D. Management of Coagulopathy of Massive Transfusion
- Results as a consequence of the combination of consumption, hypothermia seen in trauma, and dilution effects of transfused fluids or RBCs.
- One approach is to manage by closely monitoring fibrinogen level, platelet count, PT aPTT, and select blood components accordingly. This is difficult to achieve in real life because of the rapidly changing clinical status of many patients and the slow TAT of lab tests.
- Alternatively, a formulaic approach may be used. Exact formula varies depending on institution:
- E.g. One unit of FFP after after 2-3 units of RBC in trauma
- E.g. Two units of FFP following every unit of RBC in liver transplant (due to lower baseling coagulation factor levels and ahepatic phase of the surgery)
- E.g. Platelet:FFP:RBC or 1:1:1 ratio in trauma patient
- E.g. “trauma pack” consisting of 6 unit of RBC, 4 units of FFP, one unit of single donor aphereis, one pool of 5 units of cryo in massively bleeding trauma patients.

♦ Whether using the formulaic approach or relying laboratory values as a guide, make sure all components are considered and replaced if necessary: RBC, platelet, coagulation factors (FFP), fibrinogen (FFP and cryo). Inadequate therapy is associated with higher mortality.

♦ Off-label use of recombinant Factor VII (NovoSeven)
  - Often used in this setting at a dose of 90ug/kg as a last resort when bleeding is controllable despite correction of anatomic defects and restoration of coagulation to normal or near normal with component therapy
  - Efficacy and safety yet to be demonstrated
  - Optimal dosing uncertain
  - Very expensive! $5000-10,000 dose, often not reimbursed due to off-label use

IV. Transfusion of ABO or Rh incompatible RBCs

A. Patients with less common ABO blood type (AB, B) may receive RBCs of a more common type. E.g.: Type B patient can receive O RBC, type AB recipients can receive A RBCs

B. Patient can be switched back to original ABO type when:
  - Inventory permits
  - Bleeding has slowed or stopped
  - Crossmatch with using recent patient serum/plasma specimen is compatible.
This is to ensure for example, the type B patient above who received type O RBC, did not get too much passively transferred anti-B from the donors.

C. Rh negative individual may be switched to Rh positive RBCs
  - Ideally avoided in women of childbearing potential – but not at the risk of denying lifesaving transfusions.
    - The D antigen is the most immunogenic non-ABO RBC antigen, and according to some studies, will result in anti-D formation in about 85% of Rh-negative patients receiving >200ml or more Rh positive RBCs.
    - There is some evidence that the alloimmunization rate is not nearly as high in immunosuppressed patients, or those who are stressed (in severe trauma, for e.g, is estimated to be <5%).
    - Should be done if an Rh-negative patient will receive massive RBC transfusion that will deplete the existing ABO compatible, ABO inventory.
    - RhIg (IV form) can be give to prevent anti-D formation in childbearing females following RBC exchange with Rh negative RBCs after the patient stabilizes
Per manufacture recommendation: IV RhIg can be given as long as no more than 20% or the patient’s RBCs are Rh-positive.

When Rh+ RBCs exceeds 20%, the risk of clinically significant hemolysis mediated by the passively acquired anti-D is high.

V. Transfusion of Incompatible RBC/Uncrossmatched RBCs
A. Incompatible or uncrossmatched transfusion of RBC occurs because of limited time for testing and limited inventory, or both.
B. Incompatibility may be discovered retrospectively: patient is found to have previously unknown alloantibody after uncrossmatched units have been given.
C. Even in patients with known alloantibody, antigen positive RBCs may be given anyway due to the clinical urgency.
D. In massive transfused patients in particular, previously formed alloantibodies are “bled out” and/or diluted by transfused blood and crystalloid solutions.
E. In some patients, e.g. those with warm autoimmune hemolytic anemia, crossmatch compatible RBC may never be available.
F. What to do in a case of incompatible transfusion
   - Communicate with clinician: balance the risk of potential hemolysis vs. withholding transfusion. Consider patient’s clinical situation, antibody specificity, and available inventory.
   - Consider premedicating the patient: anti-pyretic, antihistamine etc
   - Clinician/BB physician should sign a release form, in which he or she accepts the responsibility and acknowledges awareness of the transfusion
   - When possible, transfuse at a slow rate (25=50ml in the first 30 minutes)
   - Monitor patient for signs of acute and delayed hemolysis.

VI. Urgent Platelet Transfusions
A. Most patients tolerate severe thrombocytopenia (5,000 -10,000 µ/dL) fairly well, may only have petechiae, purpura, mild GI loss. Thus, low platelet count is not an automatic indication for urgent transfusion.
B. Platelets rarely need to be transfused urgently. Some examples:
   - Neonates with neonatal alloimmune thrombocytopenia. Risk of intracranial hemorrhage greatest in the first 24-36 hours of life
   - DIC with lifethreatening hemorrhage
   - Trauma with thrombocytopenia and active bleeding

VII. Urgent Plasma or Plasma Derivative Transfusions
A. If ABO typing not available, use “universal plasma”, group AB plasma
B. Plasma may be needed for emergent reversal of warfarin (coumadin) in a bleeding patient or in patient about to undergo surgery
C. Other options of correcting the INR in warfarin overdose:
   - Hold warfarin-takes 4 days to be effective
   - Oral, IM or IV vitamin K-takes 3-6h if IV, 24 hours if po
Factor IX complex (prothrombin complex concentrate), recombinant Factor VII

Use of FFP or a coagulation factor preparation in not recommended for prevention of bleeding unless INR is really high

D. May also be indicated for improving coagulation status in patients with liver failure

E. Emergent plasma exchange is indicated in patients with TTP: FFP or cryopoor plasma are the replacement fluids If exchange not possible, simple plasma transfusion is indicated as a “bridging” therapy

F. Thawed plasma

- Plasma can be thawed, refrigerated for up to 5 days before transfusion, labeled as “Thawed Plasma”
- Has decreased levels of FVIII and FV, but other factor levels are okay
- Considered a good alternative to FFP/FP (thaw before use, expire in 24hrs after thawing) as it is already in liquid form. Saves time in urgent transfusion settings.

G. Plasma is NOT indicated for heparin reversal.

- Heparin has short in vivo half life of about an hour, if non urgent, stopping the heparin is sufficient.
- Protamine sulfate can be used to reverse heparin in urgent situations. (0.5mg per 100 unit of heparin if heparing given 30 minutes earlier, 0.25 to 0.375 mg per 100unit of heparin given 2 hours earlier)
- Monitor effectiveness of reversal with aPTT.
- Protamine sulfate has reduced activity against LMWH, higher it still the only antidote to LMWH approved by FDA.
  - 1mg of protamine sulfate is given per mg of enoxaparin administered in the previous 8 hours, or 0.5 mg if given 8-12 hours
  - 1mg of protamine sulfate for per 100 units of anti-Xa activity of dalteparin
- rFVII has been used in this setting as well.