Alternatives to Allogeneic Blood Transfusions

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Outline

Communications
Avoidance: medical and surgical
Volume Expanders
Pharmacologic Agents-
Recombinant Growth Factors: Erythropoietin, GCSF
DDAVP
Antifibrinolytic agents: EACA, Aprotinin and TxA
Autologous Donation
Intraoperative hemodilution and salvage
Hemoglobin based oxygen carriers
ROLE OF TECHNOLOGISTS in Blood Conservation
  • Strategies to minimize exposure
  • Components and Fractions
  • Appropriateness
  • Contraindications
Issues of communications in TM

• Doctor and Patient (P/Maternalistic doctors vs inquisitive patients or family members)
• Nurse and Technologistist (mutual understanding and respect vs confrontational)
• Doctor and Technologistist (happens when demands not met)
• Technologistist and Pathologist/Hematologist (when techs want their help or they need special tests/products from the blood bank)
• Pathologist/Hematologist and Doctor
Transfusion Algorithm

• Avoid Transfusion: medical and surgical
• Alternatives
  replacement fluids: crystalloids and non plasma colloids over plasma pharmacologic agents to reduce bleeding
• Autologous donation
• Minimize exposure to allogeneic transfusion
Transfusion Algorithm

It is possible to avoid transfusion?

Medical:
Treat underlying cause of asymptomatic anemias:
Nutritional deficiencies-supplements
Chronic GI bleeds-medications
Renal failure- erythropoietin
Transfusion Algorithm

Is it possible to avoid transfusion?

Surgical:
Excellent surgical skill (Factor XIV!=avoid tissue trauma, attention to hemostasis, utilize avascular plane etc)
Use of topical hemostatic agents in OR
Eg. Fibrin Glue- Fibrin sealant :Tisseel
Collagen- platelet adhesion: Avitene
Russell’s viper venom: Stypven
Seaweed Extract: Alginate
Transfusion Algorithm

• When transfusion is deemed necessary, a physician must obtain informed consent from patient.

• “Informed Consent to the administration of blood and blood products involves the following: an explanation by the physician in language the patient will understand of the risks and benefits of, and options to, an allogeneic blood transfusion” - Mr. Justice Krever
Informed Consent- patient decides

- Information provided by physician:
  1. product description.
  2. Benefit and potential risks.
  3. Alternatives if available-including risks and benefits.
  4. Risks of refusing transfusion
- Opportunity for questions and clarification
- Patient’s documentation of consent or refusal
Transfusion Algorithm

Strategies to minimize exposure to allogeneic transfusion
1. replacement fluids - crystalloids and non plasma colloids
2. pharmacologic agents to reduce bleeding
3. Autologous Transfusion
Acute Blood Loss

Mild 10-15%  Contraction of great veins  None or mild and transient

Mod 30%  Decreased cardiac output  Thirst hypotension
Thachycardia  weakness etc

Severe >30%  All of the above plus  Air hunger, Loss consci
<50% card op  lacticacidosis
<table>
<thead>
<tr>
<th>Estimate % Blood Loss</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Up to 20%</td>
<td>Volume replacement (crystalloid)</td>
</tr>
<tr>
<td>20-50%</td>
<td>&lt;3RCC+ volume rep</td>
</tr>
<tr>
<td>50-90%</td>
<td>&gt;3RCC+colloid+?FFP</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>RCC+FFP+PC(if&gt;1.5 body volume)</td>
</tr>
</tbody>
</table>

Reference: Vox San 1992;63:241
Replacement Fluids

• Crystalloids eg. Saline, D5W, Ringer’s lactate- not as effective to expand plasma as colloids but they are less costly

• Colloids eg. Hydroxyethyl starch: Pentaspan and Hexpan, Dextrans (D40 and D70) and Gelatins- maintain blood volume longer, may cause circulatory overload (TACO)- these products are preferred by blood bankers– why?
Transfusion Algorithm

Strategies to minimize exposure to allogeneic transfusion

1. replacement fluids- crystalloids and non plasma colloids
2. pharmacologic agents to reduce bleeding
3. Autologous Transfusion
4. Minimize allogeneic donor exposure in neonatal transfusion
Pharmacologic Agents

• Recombinant Growth Factors
  1. Erythropoietin EPO
  2. Colony Stimulating Factors CSF

• Hemostatic vasopressin DDAVP

• Antifibrinolytic agents:
  1. Epsilon aminocaproic acid EACA
  2. Tranexamic acid
  3. Aprotinin

• Recombinant VIIa NiaStase/NovoSeven
Recombinant Growth Factor: Erythropoietin: EPO Eprex

- 165 aa glycoprotein produced in the kidney to stimulate RBC production
- Normal Level: 0.01-0.03U/ml - increase 100-1000x in hypoxia and anemia; decrease level of EPO is seen in patients with end-stage CRF requiring dialysis and transfusions.
- Weekly injection of EPO in >90% of patients with CRF will become transfusion independent.
- EPO injection and autologous donations are effective in minimizing allogeneic transfusion in anemic patients going for effective orthopedic and open-heart surgeries
Recombinant Growth Factors: GCSF-Filgrastim-Neupogen

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology.

NEUPOGEN® is the Amgen Inc. trademark for Filgrastim, which has been selected as the name for recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF).
G-CSF

• Mobilization of donors in allo BCT: G-CSF to promote release of stem cells from bone marrow into peripheral blood (300/480mcg/vial)

• Mobilization of patients in auto BCT: chemotherapy followed by G-CSF

• G-CSF reduces average engraftment (Plt>10;WBC>500) from 20-30 days in BMT to 10-14 days, less RBC and PC transfusion support
Hemostatic vasopressin 1 desamino-8-D-arginine DDAVP-Stimate

• A synthetic analog of hormone arginine vasopressin which releases Factor VIII:C and von Willebrand Factor from the endothelial cells at a rate of 2-20X normal. It is effective between 1/2-6 hrs and a repeated dose in 12-24 hour is equally effective.

• Platelet membrane expression of GP1b and GPIIb/IIIa is also enhanced.
DDAVP

- DDAVP has been shown to reduce perioperative bleeding in mild-moderate Hemophilia and Type 1 vWD
- Stimate is contraindicated in severe HA and vWD type II A/B and type III
- DDAVP is also effective in patients with dysfunctional platelet: cirrhosis, uremia, aspirin and heparin induced platelet dysfunction
- Common side effects include facial flushing and water retention
Antifibrinolytic Agents: Epsilon Aminocaproic Acid EACA- Amica; Tranexamic Acid TXA- Amstat, Amcha and 20+ other brands

- EACA and TXA are synthetic lysine analog that binds plasminogen lysine binding sites to prevent fibrinolysis. They also block plasmin receptors on platelets.
- EACA was first used in the 50’s in cardiac surgeries to reduce blood loss.
- TXA is 10x more potent than EACA and it is effective in controlling bleeding in oral surgeries on patients with HA and vWD. Both drugs are effective in reducing blood use in liver transplant and orthopedic surgeries.
Aprotinin-Trasylol

- Aprotinin is serine protease inhibitor isolated from bovine and porcine lung. It inhibits plasmin, activated protein C and thrombin as well as preserving platelet GP1b and IIb/IIIa.
- Aprotinin has been used in cardiac surgeries to reduce blood transfusion.
- Side effects include allergic reaction and reversible renal impairment.
FACTOR VIIA (FVIIA) FORMS AN ACTIVE COMPLEX WITH TISSUE FACTOR (TF). TISSUE FACTOR IS PRESENT IN THE SUBENDOTHELIAL LAYER OF THE VASCULAR WALL, AND HENCE IS NOT NORMALLY FREE TO COMPLEX WITH CIRCULATING FACTOR VIIA. FOLLOWING INJURY, THE SUBENDOTHELIUM IS EXPOSED AND TISSUE FACTOR IS FREE TO BIND FVIIA. THIS TF:VIIA COMPLEX ACTIVATES FACTORS IX & X.

FACTOR VIIA CAN ALSO ACTIVATE FACTORS IX & X ON THE PLATELET MEMBRANE, IN THE ABSENCE OF TISSUE FACTOR. ALTHOUGH THIS IS A LOWER AFFINITY REACTION FOR GENERATION OF FACTOR XA, FACTOR IXA SUBSEQUENTLY ACTIVATES FACTOR XA AND AMPLIFIES THIS PATHWAY DRAMATICALLY. THIS REACTION IS OFTEN REFERRED TO AS THE 'THROMBIN BURST' AND IS THOUGHT TO BE RESPONSIBLE FOR THE MAJORITY OF FIBRIN GENERATED IN RESPONSE TO A LOCAL INJURY.

FACTOR XA, COMPLEXED WITH FACTOR V FORMS A COMPLEX CALLED PROTHROMBINASE. PROTHROMBINASE CLEAVES PROTHROMBIN TO FORM THROMBIN, WHICH THEN GENERATES FIBRIN FROM FIBRINOGEN.
Tissue factor (TF)/FVIIa, or TF/rFVIIa interaction, is necessary to initiate haemostasis.

At pharmacological concentrations rFVIIa directly activates FX on the surface of locally activated platelets. This activation will initiate the “thrombin burst” independently of FVIII and FIX. This step is independent of TF.

The thrombin burst leads to the formation of a stable clot.
Recombinant Factor VIIa in blunt trauma

- Dose: 35-90 ug/kg, Q2 until bleeding stops
- Availability: 1.2, 2.4 and 4.8 mg/vial
- Significant reduction in use of RBC, PC, FFP and Cryo
Transfusion Algorithm

Strategies to minimize exposure to allogeneic transfusion
1. replacement fluids - crystalloids and non-plasma colloids
2. pharmacologic agents to reduce bleeding
3. autologous transfusion
Autologous Transfusion

Canadian Blood Services

• Preoperative Autologous Donation PAD (Hospital Recovery Room)
• PAD on High Risk Patients (Hospital Operating Room)
• Acute normovolemic hemodilution ANH
• Intraoperative collection
• Postoperative collection
Advantages of Autologous RBC

• Prevents transfusion associated diseases
• Prevents alloimmunization
• Reduce demand on donor units
• Reduce some risk of transfusion reaction eg. Febrile, allergic and hemolytic Tx Rx
• Psychological benefits to some patients
Disadvantages of autologous RBC

• Similar risk of bacterial contamination
• Similar risk of clerical error
• More costly
• More wastage
• Anxiety to some patients
• Higher incidence of adverse reactions in donation
• Perioperative anemia and side effects of iron supplementation
PAD Complications

• Venous access
• Pediatrics- low volume challenges
• Donor adverse reactions
• Clerical errors leading to the use of regular donors before autologous units
• Over transfusion
Acute Normovolemic Hemodilution

- Crystalloid 1:3; Colloid 1:1
- Properly labeled units are stored at RT for up to 8 hours, unused units must be stored within 8 hours at 1-6 C, outdates in 24h
- Re infuse units in reverse order to provide maximum hemostatic functions
- ANH is equivalent to PAD in radical prostatectomy, knee and hip replacement
Intraoperative Blood Collection

• Salvage of shed blood from sterile surgical field, washed with saline to remove debris and anticoagulant, concentrate (Hct .5-.6) and reinfuse using a microscreen filter (40 microns)
• Surgical procedures using large quantities of RBC eg. open Heart, liver transplant and vascular surgeries are most cost effective
• Complications are rare but have been reported- DIC, hemolysis due to high pressure suction and mechanical compression in roller pumps
Postoperative blood collection

• Recovery blood from surgical drains followed by reinfusion with or without processing (limit to 1400ml)
• Most common in orthopedic procedures such as hip or knee replacement.
Minimizing Exposure of Allogeneic RBC in Neonatal and Pediatric Transfusion

• Single Donor Assignment 1:2-4 patients O Pos and O Neg CMV-, irradiated RBC
• Reduce “dead volume” by using syringe pump instead of IMED pump
• Irradiate before issuing (>28 days)
• Directed Donation may be allowed under special circumstances. Eg. Maternal alloantibody to high incidence antigen
Blood Substitutes

Ideal: good O2 carrier, non immunogenic, non toxic, storage stable, acceptable in vivo retention (half life in weeks or months), non infectious, low viscosity for reperfusion of ischemic organs during strokes, MI and in organ transplants, can be massively produced to reduce cost.

NO SUCH LUCK SO FAR!
Blood Substitutes

O2 Carrier
- Perfluorocarbons
- Diaspirin-x-linked HB
- Recombinant HB
- Liposome-encapsulated
- Polymerized HB
- PEG conjugated HB
- Raffinose-x-linked HB

Trade Name, Manufacturer
- Fluosol-DA, Green Cross
- Hemassist, Baxter
- Optro, Eli Lilly
- Hemopure, Biopure
- PolyHeme, Northfield Lab
- ?, Enzon
- Hemolink, Hemosol
Role of Technologists in Blood Conservation

• Recycle of near OD units
• Use of near outdated non ABO identical but compatible units
• Improving yield and quality in component production
• The thirty minute rule
• “Anything is better than nothing!”
• Screening unusual requests- how can we become better gate keepers?
Blood Products
Component vs Fractions

• Components- physical change: Temperature Force, Time Rx- reversible

• Fractions- chemical change: pH, ethanol concentration Temperature Rx- irreversible
Components vs Fractions

- Red Blood Cells LR
- Platelets or apheresis platelets LR
- FFP or AFFP LR
- FP LR
- Cryo LR
- Cryosupernatant Plasma CSP, LR
- Granulocytes

- Factor Concentrates
- Immunoglobulins Polyspecific Monospecific
- Albumins
Reasons for Red Cell Transfusion

1. Acute Blood Loss

2. Anemia

3. Life-Long Support
Red Cell Transfusion- Is a clinical decision!!!

- Tissue oxygenation does NOT depend on hemoglobin concentration alone!

- Cardiac performance
- Pulmonary function
- $O_2$ Binding Coefficient
- Demand of Tissue (physical activity)
# Red Cell Transfusion

## Special requirements

<table>
<thead>
<tr>
<th>Condition</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow/Blood Cell Transplant</td>
<td>Gamma irr. CMV sero-&lt;10 days</td>
</tr>
<tr>
<td>Neonates</td>
<td>Gp O; CMV-; irr, fresh</td>
</tr>
<tr>
<td>IgA Deficiency</td>
<td>Washed RBC</td>
</tr>
<tr>
<td>Immune Hemolytic Anemias (IHA)-allo</td>
<td>Antigen negative</td>
</tr>
<tr>
<td>AIHA</td>
<td>Avoid Rh, K….</td>
</tr>
<tr>
<td>Long Term</td>
<td>Phenotypically matched</td>
</tr>
</tbody>
</table>


Clinical Algorithm of Red Cell Transfusion

Is blood required for surgery → Yes → Request Accepted
No

Is patient actively bleeding → Yes → Request Accepted
No

Is patient's hemoglobin < 80g/L → Yes → Treatable Causes Excluded
No

Is patient hypoxic or having angina

Yes
requestAccepted

No
Transfusion not indicated

Is patient at risk of bleeding?

No

Yes

Is anemia chronic and stable?

No

Yes

Is patient hypoxic or having angina

No

request accepted

Yes

Is patient at risk of bleeding

No

Yes

Transfusion not indicated - correct underlying cause
Algorithm of platelet transfusion

Is platelet count below $50 \times 10^9/L$? 
- No → Invasive procedure scheduled → No → Not indicated
- Yes → Is patient bleeding?
  - Yes → known bleeding risk factor present → No
  - No → Is any associated hemostatic disorder being treated?
    - Yes → request accepted
    - No → Discuss request with blood bank physician
      - Yes → request accepted
      - No → Is platelet count below $20 \times 10^9/L$?
        - Yes → Platelet transfusion may be indicated prophylactically. Discuss with blood bank physician
        - No → Not indicated
  - Has immune thrombocytopenia been excluded?
    - Yes → Is surgery or invasive procedure planned?
      - Yes → request accepted
      - No → Not indicated
    - No → request accepted
Algorithm of FFP transfusion

Does patient have coagulation disorder?

Yes

Congenital Deficiency?

Yes

Is factor Conc available?

Yes

Administer appropriate factor conc.

No

Congenital Factor V Deficiency?

Yes

discuss with medical director

No

administer albumin

No

Low serum albumin?

Yes

administer albumin

No

Massive Blood Transfusion?

Yes

documented coagulopathy?

Yes

FFP not indicated
Treat underlying cause of DIC. Give Vit. K if Warfarin toxicity.

No

No

Bleeding or invasive OR scheduled?

Yes

No

No

No

No

FFP not indicated
Treat underlying cause of DIC. Give Vit. K if Warfarin toxicity.
Contraindications and Precautions

RBC

- HB/Hct is NOT the only indicator
- Transfusion Associated Circulatory Overload (TACO)
- “Universal Donors” is only for ABO compatibility eg. Anti-Vel
- Special Requirements CMV- irradiated etc
- Liability if allogeneic blood is used before autologous
Contraindications and Precautions

Platelets

- Immune Thrombocytopenia Purpura (ITP)
- Heparin-Induced Thrombocytopenia (HIT)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Untreated Disseminated Intravascular coagulation (DIC)
- HLA/HPA Alloimmunized- apheresis platelet
- “Platelet Glue”
- Rh- patients with child bearing potential receiving Rh+ platelet
Contraindications and Precautions
FFP/FP/Cryo supernatant

- Volume replacement
- Diagnosed Coagulation Factor Deficiency
- Nutritional protein deficiency
- Cryosupernant in DIC
- Warfarin reversal in non bleeding patient
Contraindications and Precautions

Albumin

- First day after severe burns more than 50% of body surface-crystalloid is preferred unless patient is not responsive
- History of allergic reaction
- 25% Albumin may cause dehydration or volume overload if infused rapidly
- Not indicated in patients with chronic hypoalbuminemia
Contraindications and Precautions

IVIG

- BB MD’s must be consulted on many off-label “indications”: pure red cell aplasia, polymyositis, dermatomyositis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, juvenile RA, Stills disease, toxic epidermal necrolysis, chronic parvovirus infextion, streptococcal toxic shock syndrome, AIHA and NAIT.
- IgA Deficiency with anti-IgA
- Severe allergic reaction to IVIG
Contraindications and Precautions

RhIg

Prophylaxis of Rh alloimmunization:
1. Rh pos recipient
2. Rh neg already developed anti-D
3. History of severe allergic reaction
4. Route of administration of Rh- received Rh+ platelet

ITP
1. Rh- patient
2. History of prior splenectomy
3. Previous severe allergic reaction
Copy?

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