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Transfusion Medicine: What Every Emergency Physician Needs to Know

Although potentially lifesaving, the use of blood products can be associated with short and longterm complications. Emergency physicians must be comfortable with transfusion medicine as it relates to patient management using the the currently available blood products. Appropriate indication for these products will be reviewed.

- Recognize the indication for and the use of commonly available blood products for the correction of anemia and coagulation defects in the emergency department.
- List the potential complications of using these blood products

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FACULTY

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Why do I have to bother with crossmatching blood?

- **Transfusion Immunology:** Blood is a complex organ system with O2 carrying RBC, clotting factors, platelets, proteins
  - Each person has unique blood group antigens (Ags)
  - Donor Ag + Patient Lymphs = specific antibody (Ab)
    - RBC Ab: naturally occurring (ABO), immune (Rh), or auto-immune (drug/disease).
  - Cell destruction is intra-(hemolysis) or extravascular (liver/spleen)
- **ABO System**
  - Ag formed at birth: reciprocal Ab by 6-12 months of age
  - ABO genes –codominant→ enzymes to add carbs to RBC membrane
  - ABO System and Blood Selection

Blood Group	RBC Ag	RBC Ab	RBC Choice	Plasma Choice	Plat Choice
A	A	-B	A, O	A, AB	any
B	B	-A	B, O	B, AB	any
AB	A, B	none	A, B, AB, O	AB	any
O	H	-A, -B, -A,B	O	O, A, B, AB	any

- **Rh System**
  - Very immunogenic; if Rh neg receives Rh pos blood = 85% risk of Rh Ab
  - Major Ag is D: D positive = Rh pos; D negative = Rh neg; many other Rh Ag's exist, e.g., C,c, E,e, etc.; alleles at Rh locus→ membrane glycoprotein
  - Rh Ab is always immune
  - Rh group and Blood Selection

Rh group	Rh Ag	Rh Ab	RBC Choice	Plasma Choice	Platelet Choice
Pos 85%	D pos	none	pos or neg	either	either
Neg 15%	D neg	immune -D	neg **	either	neg or either**

Rh neg RBC products should **ALWAYS be given to females of child bearing age to prevent formation of anti-D and subsequent Rh hemolytic disease of the newborn. Males should **ideally** be given Rh negative unless emergent transfusion and insufficient Rh neg blood supplies.

- **Other Blood Groups**
  - Red Blood Cell: more than 30 different systems with more than 350 different Ags: K, Fy(a), etc.; detected by crossmatch and Ab screen
  - HLA System (Tissue Ag): all nucleated cells; over 150 Ags Immune antibody: febrile reactions, transplant rejection

- **Platelet Specific Ag:**

How long does it really take to do a crossmatch and what is the charge? If I crossmatch the blood but don't use it, will it be thrown away?

- **Type and Crossmatch(T&C)** - $240: *Pt serum (Ab) + Unknown cells (Ag)*
  - Ab screen negative: abbreviated crossmatch done; <15 mins.
  - Ab screen positive: expanded crossmatch done; 30-45 minutes.
  - Crossmatched blood is reserved for a specific patient for 48 hrs.
    - **If unused, it returns to general supply**
  - **Order T&C if transfusion seems INEVITABLE**
- **Type and Screen (T&S)** - $125: *Type and Rh with Ab screen*.
  - Ab screen negative: no blood crossmatched;
    - If blood needed - < 10 minutes
  - Ab screen positive and Ab is clinically relevant: complete crossmatch done; fully compatible blood is held on reserve for patient.
  - **Order T&S when POSSIBILITY of blood transfusion exists**

What tests are done on donor blood before it is released for use?

- **Update on Blood Donation:**
  - 8 million blood donors; <5% of healthy Americans/year
  - Tests performed: ABO, RH, antibody screen, antibodies against Hep B, C, HIV, HTLV and syphilis and antigens for hepatitis B and P24 for HIV.
- **Current US Blood Transfusion Practice**
  - 8 million PRBC transfused/yr; 7 million components transfused/yr.
  - Preop autologous blood donations: 600,000 units/yr; <50% transfused
  - 3.5 units transfused/pt; 67% units transfused as PRBC
  - 1.5 crossmatched/transfused ratio is ideal; 2.0- acceptable

What should I tell my patient about the safety of blood transfusion?

- Disease transmission
  - Hep B 1/200,000 transfusions; 1 million carriers -25% chr active hepatitis
  - Hepatitis C 1/4000 transfusions; chronic liver disease results frequently
  - HIV risk: l in 600,000
- Fatalities 1/100,000 immune hemolysis
  - 51% ABO (38% wrong pt); 15% TRALI
- Overall < 1% risk of harm/unit; 5-18% if >5 units

Why can't I just use Whole Blood? After all, my patient is bleeding whole blood!

- **Whole Blood = RAW Material;** contains all cellular and plasma constituents
  - Anticoagulant CPDA-1/2 (citrate, phosphate, dextrose, adenine) = 35 day expiration; Adenine additive (AS-1) = 42 day expiration

- 70% survival; HCT 40%
- **No FRESH whole blood**
- **Undesirable effects**: volume overload, increased leukocyte exposure, increased amounts of waste products, allergic reactions, citrate toxicity.
- **NO Universal WB Donor**- Group O RBCs are universal RBCs but group O plasma can only be given to group O patients

- **The Storage Lesion (Cold Lesion) Problem**
  - RBC products are stored at 1-6 C; rigidly controlled.
  - Membrane loses deformability due to aging and cold lesion
  - Aging cells hemolyze→ increased K, LDH, free Hgb; decreased viable red cells; decreased Factor V, VIII, platelets
  - Increased waste products: dec Ca, inc ammonia cellular/protein debris
  - Increased lactic acid (anaerobic metabolism) --> ACIDIC environment: depletes ATP, inactivates 2,3 DPG
- **The Passenger WBC Problem**
  - Stimulates HLA antibodies - febrile reactions, (TRALI), platelet antibodies
  - Transmits infections: CMV, EBV, HTLV
  - Causes generalized immunosuppression - altered macrophages have decreased chemotaxis and IL-2. Long lasting effects: increased survival of graft in patients transfused pretransplant, decreased survival of HIV pts and recurrence of CA after heterologous transfusion
  - Increases infection rate in patients receiving heterologous transfusion
  - Graft vs Host Disease (GVHD) - Immunocompetent donor lymphs reject immunosuppressed patient. Seen in transfusion of BM transplant, fetus, neonate, cancer patient.
    - **Irradiated Products:** Gamma irradiation- 2500 cGy/dose
    - Absolute indications: fetal, premature infants <1200g, neonate, immunosuppressed, directed donor to relative,
- **The CMV Problem:**
  - CMV is devastating to immunuosuppressed patients
  - CMV negative blood is given to immunosuppressed patients- e.g., HIV, premature, CMV neg pregnant females, fetuses, transplant candidates
  - Leukocyte-reduced RBC are frequently to reduce risk of CMV transmission

How do I know when to transfuse, help my patient, and keep Utilization Review off mv back?

Evaluation of Anemia: When to Transfuse?

- Clinical assessment is indirect: BP, HR, CO, O2 sat, U/O, Hgb
- O2 carrying capacity dependent upon cardiopulmonary status, Hgb conc/ O2-Hgb binding, tissue O2 needs
- Mechanism of Injury: rate, chronicity, extent
- Patient's reserve: age extremes, chronic anemia, cardiopulmonary status
- Physiologic signs: HR, BP, mentation, capillary refill, urinary output
- Response to therapy: IVF, O2, decreased tissue demand
- Remember in an acute bleed: Hgb inaccurate

What are the guidelines for Red Blood Cell Transfusion?

Transfusion guidelines:

- Symptomatic anemia in normovolemic Hgb 6-10 g/dl
- Acute blood loss with evidence of inadequate O2 delivery; > 25%
- Preoperative Hgb < 8 g/dl and operative procedure with major blood loss
- Hgb < 9 g/dl in patient on chronic transfusion regimen
- In general, anemia well tolerated to 7-8 g/dl for acute, stable, healthy patient; 8-10 g/dl preoperative patient; 4-5 g/dl chronic stable patient.
- Chronic anemia: treat cause; increased risks due to increased sensitization

What alternative Red Blood Cell products are available and when would it be appropriate to order them?

- **Packed Red Blood Cells - $80;** component of choice for acute bleed
  - 250 ml volume; HCT 70%
  - Expected increment rise: 1 g/dl or 3% HCT increase/unit
  - Use standard blood filter - may dilute with 0.9 NS to run faster
  - Obtain pre and post transfusion hemoglobin values
- **Leukocyte Reduced RBC-** 1-3 billion WBC/unit WB;
  - Leukocyte reduction filter: inline at collection, or at administration: 99.9% wbc removed; WBC adsorption onto cotton wool fibers..
  - Indications: repeated nonhemolytic febrile reaction, chronic transfusion, reduce risk of CMV transmission, decrease viral infection, delay platelet refractoriness; prevent GVHD, reduce immunosuppression
- **Stem Cells (pluripotential hematopoietic cells)**
  - Indications: repopulate the BM after treatment of leukemia, lymphomas and other malignancies and genetic defects
  - Given as allogenic (HLA matching required) or autologous
  - Methods of collection:
    - bone marrow aspiration (traditional method)
    - apheresis of donor peripheral blood following multi-dose CSF
    - cord blood from placenta and umbilical cord
      - effective- more undifferentiated cells, inexpensive, widely available
      - ethical issues - Pandora's box
- **Washed RBC**: allergic reactions, PNH
- **Frozen/Deglycerolized RBC**: rare blood groups

When are Granulocyte Concentrates appropriate for transfusion?

- **Granulocyte Concentrate: -**apheresis
  - Transfusion indications
    - Bacterial infection unresponsive to 48 hrs of antibiotics if ANC <500.
    - Progressive infection with severe neutrophil dysfunction.
    - Minimal dose: 1X10(10) neutrophils/transfusion
    - Transfuse QD until infection resolves or ANC >500

When should I consider using FFP and how much should I give?

- **Fresh Frozen Plasma - $42**

- Replaces coagulation (not VIII) and fibrinolytic factors and provides complement in congenital deficiency with bleeding, massive transfusion, DIC, TTP, neonates, warfarin reversal, liver disease
- 250 ml volume random donor; 400 ml apheresis
- Transfuse as ABO plasma compatible
- Transfusion guidelines:
  - Nonbleeding, undergoing invasive procedure: PT/PTT > l.5 X mean normal value eg., PT > 20, PTT > 61 with INR 2.7
  - Massively transfused patient with microvascular bleeding (pt given >1 blood volume) and PT/PTT not yet available
  - Warfarin overdose with major bleeding or impending surgery
  - TTP, deficiencies of protein C, protein S, or antithrombin III
- Goal: raise to 30% factor activity; usual dose 15 ml/kg or 2-4 units
- Monitor with PT, PTT pre and post transfusion
- Inappropriate use: stable non bleeding pt, before invasive procedure if PT/PTT <1.5 X mean normal, volume expander or immunoglobulin source
- Risks: volume overload, allergic reaction

I've seen in the newspaper that virus free FFP is available. What is it?

- **Pooled Plasma, Solvent/Detergent Treated (PLAS+SD)** $125/unit
  - First plasma product to use viral inactivation technology. Approved 5/98
  - Pooled plasma (2500 donors) treated with a solvent and a detergent
  - Indications: same as for FFP; contains at least 0.7 units/ml of factors V, II, X, XI, and XIII and 18 mg/ml of FBG. Lacks the largest vWF multimers
  - More than 3 million units of PLAS+SD in Europe and 12 million units of other SD blood products, including IV immunoglobulin, Factor VIII and IX.
  - No case of viral transmission of hepatitis B or C or HIV has been recorded. Viral lipid envelope is destroyed preventing the cell surface receptors from infecting host cells**. It does not destroy non lipid enveloped viruses, eg., parvovirus, Creutzfeldt-Jacob disease or other nonviral diseases**
  - Other methods: for inactivating viruses in blood components are under development, including photosensitizing dyes and heat treatment.

My patient has a platelet count of 25,000 but is hemodynamically stable. When do I give platelets, and if so, how many?

- **Platelet Concentrate - $46 random; $595 apheresis**
  - Indication: bleeding due to deficiencies in platelet number or function
  - Determine cause of thrombocytopenia before transfusion; if destruction - transfused platelets will be destroyed also.
  - Risk of bleeding risk: >100 K - no risk, 10-50 K - moderate risk if stressed, <10K - high risk- may develop spontaneous, life-threatening bleed
  - Transfusion guidelines:
    - Documented platelet dysfunction and scheduled invasive procedure
    - Platelets < 5000
    - Platelets < 20,000 with fever, petechiae or during chemo induction
    - Platelets <50,000 with active bleeding or before invasive procedure

- **In general, do not transfuse if stable with a chronically low count**
- Random Platelet Concentrate (RPLC): 6-8 X 10(10) platelets/bag;
  - Dose: one RPLC/10kg; Expected increment rise: 7-10K/unit;
- Single Donor Platelet Concentrate (SDPLC)(apheresis): 3-6 X 10(11) platelets/bag. Dose: one SDPLC/60 kg
- Not ABO matched; +/- Rh compatible
  - l vial RhIG used for 30 units Rh pos Platelet Conc.
- Obtain platelet count pre and l hour post transfusion
- Survive hrs to days; Life span 9.5 days
- Use specific Platelet filter (Teflon): 170 micron;
- Use leukocyte reduced apheresis platelets to prevent HLA Ab
- Risks: refractory due to Ab; risk of platelet thrombi and major thromboses if given to heparin induced thrombocytopenia or TTP; no benefit in uremia.

My patient with von Willebrand's disease has a nosebleed. She says that she usually needs cryoprecipitate. How much should I give?

- **Cryoprecipitate -$46**
  - Indications: actively bleeding patient with vonWillebrand's disease, uremia with prolonged bleeding time, massively transfused, bleeding due to dys- or hypofibrinogenemia. Single unit may be used for fibrin sealant or glue.
  - Rich in VIII, IX, vWF, FBG, Fibronectin
  - Given without regard for ABO or Rh; Pooled product with 24 hour outdate
  - One bag: 80-120 U Factor VIII, 150-250 mg FBG, and 30-50 mg fibronectin
  - Dose: one bag/7-10 kg; Pool of 8-10 units = 2 g FBG
  - Transfusion guidelines:
    - Diffuse microvascular bleeding and FBG < 100 mg/dl
    - Documented vWD with active bleeding or invasive procedure
    - Uremia with BUN >50, Cr >4 and Bleeding time >12
    - In acute blood loss: obtain pre and posttransfusion FBG levels

A hemophiliac presents to the ED after being assaulted with a bat. How much Factor VIII do I need to give? How long is treatment needed?

- **Factor VIII Concentrate**
  - Anti-Hemophilic Factor (AHF) - recombinant Factor VIII (most common)
  - Factor VIII activity (unit/cc): FFP: 1; cryo 3-10; AHF Conc: 25
  - Goal of hemophilia treatment depends upon consequences of bleeding

Minor trauma, hemarthrosis	**25% activity X 1 day**	**12.5 u/kg**
IM hematoma, hematuria, dental	**50% X 2 days**	**25 u/kg**
Major surgery,head injury	**100% X 5-14 days**	**50 u/kg**

  - Factor VIII inhibitors - require massive doses to inactivate antibody
  - Treatment: several days T ½ = 12 hrs

How much Rh Immune Globulin should I order for my Rh negative patient after her spontaneous abortion?

Rho Immune Globulin - $125

- Purified Anti-D; Given IM or IV
- Rh neg female, Rh pos child; 7-8% risk
- IM: 50 mcg - <13 wks; 150 mcg - 28 wk; 300 mcg - within 72 hrs term delivery
- IV: 120 mcg or 300 mcg;
- Indications: abortions, amniocentesis, trauma; recipients of Rh pos platelets
- l vial-->30 ml Rh pos whole blood
- Fetal Maternal Hemorrhage assessment required; may require additional vials.

What other plasma products are available?

Other Plasma Derivatives

- Factor IX Concentrate (Prothrombin concentrate): contains IX, II, VII, X, Protein C; for specific factor deficiencies; monoclonal, disease free
- Albumin: 25%: for severe acute colloid loss, eg., hypovolemic shock, burns
- Immune serum globulin, Hyper Globulin, HBV, rabies, tetanus.
- ATIII, C1 est inhibitor, α1AT, Colony Stimulating Factors

My Jehovah's Witness patient refuses transfusion. Are there alternatives?

Adjunctive Alternatives to Allogenic Transfusion

- Autologous preop donation- donate 1 unit/wk for up to 6 wks prior to surgery
- Acute Normovolemic Hemodilution -removal of one or more units at beginning of surgery to be transfused during or after surgery
- Intraoperative blood collection – recovered, washed, recycled during surgery
- Postoperative blood collection - postop blood is collected in drainage tube
- Erythropoietin (EPO); recombinant DNA technology
  - EPO stimulates the BM to produce rbcs in response to hypoxemia
  - Indications: anemia in predialysis, end-stage renal failure, HIV, AZT
  - The Jehovah's Witness Watchtower Society's Bible Information Services states that EPO may be acceptable as it is a synthetic hormone and a product of recent technology. Some JW may object due to contamination with a small amount (2.5 mg) of human albumin.
- DDAVP (Desmopressin acetate): Synthetic vasopressin;
  - Transient increase of Factor VIII and plasminogen activator @ 3 hrs; releases Factor VIII from endothelium
  - Indications: treat trauma or spontaneous bleeds in Hemophilia A or von Willebrands with > 5% factor VIII
- Topicals- collagen, thrombin, fibrin glue
- GM-CSF and G-CSF
- Vitamin K
- Antifibrinolytics - EACA, aprotinin; reduces blood needs in cardiac surgery.
- Hydroxyurea

15 minutes into the transfusion, my patient develops a temperature of 101C. Could this be a transfusion reaction?

Nonimmunologic

- Disease transmission, physical destruction, bacterial contamination, volume overload, dilution, hypothermia (cold toxicity), hemosiderosis, citrate toxicity

Immunologic

- Intravascular Hemolysis- usually IgM antibody
  - 1/7000 transfusions; Usually clerical error; **ABO;**
  - **Ag + Ab + Complement** = **hemolysis**
  - May progress to cardiogenic shock, DIC, renal failure
  - Supportive care- pressors, FFP, Plat, diuretics
- Extravascular Hemolysis- usually IgG antibody
  - **Ag + Ab --->splenic or liver sequestration**
  - May be rapid (hours) or delayed (weeks)
  - Spherocytes, positive DAT, bilirubinemia, or failure to obtain post-Hgb rise
- Febrile Reaction - most common
  - Seen in multiparous, multi-transfused patients; due to HLA antibodies
  - Rise of 1-2 C within l hr, chills, malaise
  - Rx: mild- antipyretics; severe: Leukocyte Reduced RBC
- Urticarial Reaction - very common
  - Soluble material in donor plasma + pt Ab--->histamine release
  - Rx: antihistamine, steroids;
  - Hives only: slow transfusion, medicate, observe; Severe: Washed PRBC
- Anaphylactic Reaction
  - Massive histamine- flushing, hyper/hypotension, edema, resp distress
  - Patient has class specific IgA deficiency
  - Rx: antihistamine, epi, steroids, etc; give only IgA deficient plasma, Washed RBC
- Transfusion Related Acute Lung Injury- 15%
  - noncardiogenic pulmonary edema, chills, fever, cyanosis, hypotension
  - HLA Ab mediated; WBC aggregates in lungs; complement activation
  - Rx: steroids, respiratory support, Leukocyte Reduced RBC
    - GVHD

What do I do in case of a transfusion reaction? What does the lab do in case of a transfusion reaction report?

- Stop transfusion and assess
- Supportive care: IVF, pressors, epinephrine, diuretics, antihistamines, steroids, antipyretics
- Send to BB: post transfusion sample, blood bag, first urine, paperwork
- The Blood Bank will reidentify all paperwork, check for hemolysis, test patient direct Coombs, repeat patient ABO, Rh, crossmatch pre and post, examine bag for hemolysis, culture, etc.

Transfusion Pearls for the ED physician:

- Do not mix LR with PRBC: 0.9NS is only **approved** solution for use with blood
- Remember to use T&S and not T&C unless you feel transfusion will be inevitable. Crossmatched blood is **reserved for specific pt for 48 hrs.**
- In an emergency, Rh pos can get either Rh pos or Rh neg blood
- If a transfusion is not begun within 30 minutes of issue, the blood should be returned to the BB for proper storage until ready to be given..
- Most RBC transfusions are given over 60-90 mins, but not longer than 4 hrs. If the patient's condition requires more time, the unit can be split into two parts- the first is given immediately; the other can be stored in the BB until needed.
- Type and Rh all pregnant patients with abortions, amniocentesis, deliveries, trauma . If Rh negative, RhIG should be given.

- Patients may be premedicated with antihistamines, acetaminophen, or steroids 30 minutes before beginning transfusion to reduce risk of reaction.

What about blood substitutes --- when and how will we use them?

UPDATE ON BLOOD SUBSTITUTES- the race is on.....

"One of the top 10 advances in the physiology of medicine in the 20th century" C. Everett Koop, MD

- **The problem**:
  - WHO - worldwide demand is 100 million units of blood per year. Every 3.75 secs a U.S. citizen needs blood yet the donation rate has fallen.
  - Blood is complex mixture and it is impossible to ever duplicate all of its roles. The option is to correct only what is dysfunctional.

- **Properties of an ideal red cell substitute-** transport oxygen and carbon dioxide, volume expansion, non-toxic to tissues, especially lungs, stable during circulation- biologically and chemically inert, natural catabolic pathway, no special storage or handling, dwell time (short or long), no infectious disease transmission, non-immunogenic with compatibility to all blood types, immediately available at low cost.

- **Oxygen solubility**: 2% dissolved in plasma; 98% bound to Hgb. O2 can be dissolved or chelated by compounds other than Hgb. The amount of O2 picked up depends upon the partial pressure and the O2 affinity.

- **Potential uses**: reduce demand for banked human blood, risk of disease transmission, and immunosuppression of the recipient.
  - Resuscitation: military conflicts, trauma, blood shortages
  - Limit ischemia/infarct - stroke, MI, arterial occlusions, PE
  - Cancer therapy- enhance radiation efficacy
  - Sepsis, dialysis- improve hemodynamics
  - Sickle cell crisis - reduce pain
  - Transplant organ perfusion, cardioplegia,

  - **Perfluorocompounds**- manmade molecules of carbon and fluorine that act a solvents for gases; can carry oxygen temporarlily ; insoluble in other liquids; emulsified usually in phospholipids (surfactant)
  - Lttle oncotic pressure; electrolytes and volume expanders added
  - Available for coronary angioplasty; combined with autologous donations reduces need for blood during surgery; no special storage/handling
  - Advantage: synthetic, produced in large amounts; no donor source
  - Limitations: maximum conc 0.9g/kg; pt must breathe 70-90% oxygen
  - Side effects: PFC's only removed via lungs; ? long term effect of liver/spleen disorder, F, N/V, myalgia environmental concerns.

- **Modified hemoglobin(HBOC)** Normal hemoglobin is a tetramer; RBC membrane retains 2,3,DPG for release of oxygen as required. Stroma free Hgb breaks down rapidly into subunits that are rapidly excreted by the kidneys (dwell time)- renal toxicity; additionally, outside of the rbc, 2,3,DPG is not available to allow the Hgb to readily release oxygen.
- Hgb modified by microencapsulation or crosslinkage for stabilization and

sterilization; source Hgb- bovine, human, recombinant, transgenic species
- Clinical properties: O2 carrier, volume expander, viscosity, pressor, perfusion
- Adverse reactions: renal failure, increased vascular pressure, anaphylaxis
  - **Crosslinked Hemoglobin**- agent crosslinks hemoglobin into polyhemoglobin to prevent breakdown of tetramers into dimers; 2,3 DPG analogue, pyridoxal phosphate added to improve P50
  - **Encapsulated Hemoglobin**- "artificial cells" ; liposome encapsulated; 2,3,DPG and ATP added, pyridoxal-5-phosphate improves O2 delivery
  - Rapid oxygen transfer to tissue due to small size. Intravascular survival is up to 20 hours. Problem: rapid uptake by RES
  - **Enzyme treated red cells**- ABO and Rh antigens stripped from group A or B red cells to make universal group O negative red cells
  - **Freeze dried red cells**
  - Further refinements- addition of superoxide dismutase and catalase to prevent reperfusion injury, multienzyme systems.

What is on the horizon for transfusion medicine? What changes will I see during my career?

- Increased donor evaluation criteria to decrease disease transmission
- More autologous/directed donors
- More apheresis components
- Hematopoietic cell therapy- peripheral stem cells, cord blood/placenta
- Transfusion gene therapy - killer lymphocytes
- Hematopoietic growth factors and cytokines; clone new growth factors
- Blood substitutes
- Expanded role of regulatory/government
- Fewer indications for transfusion with decreased blood utilization
- Molecular biology- recombinant therapy
- Virus inactivation and removal
- Immunomodulation

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