# Transfusion Therapy:
## When to Use It and How to Minimize It

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# Disclosures

- None

# Objectives

- Describe basic concepts of anemia
- Define indications for and use of blood components
- Examine potential risks of blood products
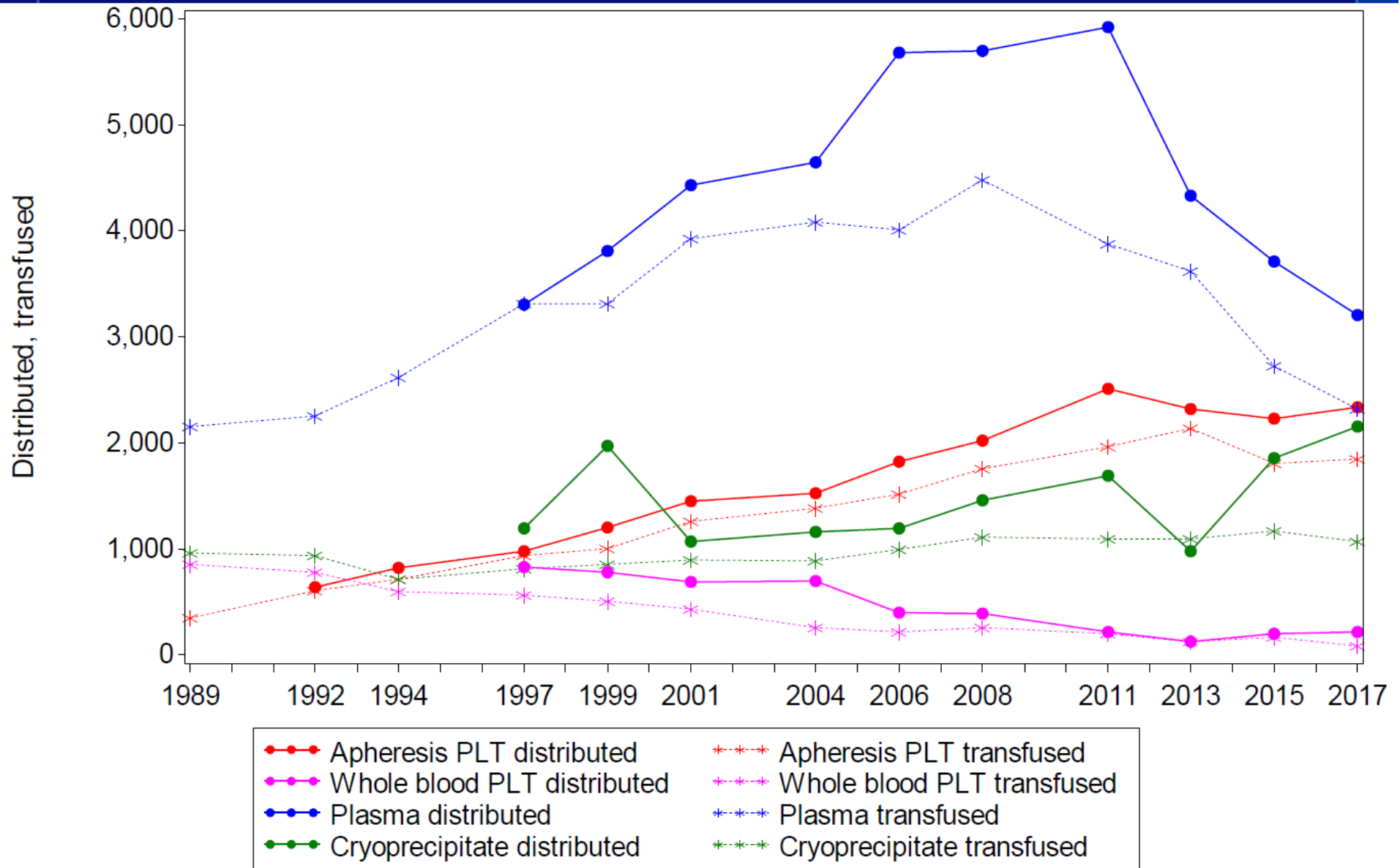- Determine alternatives to blood transfusion

# Key points

- Anemia is common and bad.
  - Iron deficiency is common and easy to fix.
- Transfusions seem to be more bad than good.
- Some low hemoglobins should be tolerated.
  - If you have to transfuse, give one.
- Do not use INR to gauge bleeding risk.
- Do not use plasma to "reverse" mid-range INR.
- Use strategies for less bleeding, more oxygen delivery, and more red blood cell production.

# Trends in RBC collections and transfusion per 1000 population, 1992–2017



Population data from US Census Bureau (http://www.census.gov/popest/data/index.html)

NBCUS, 2017
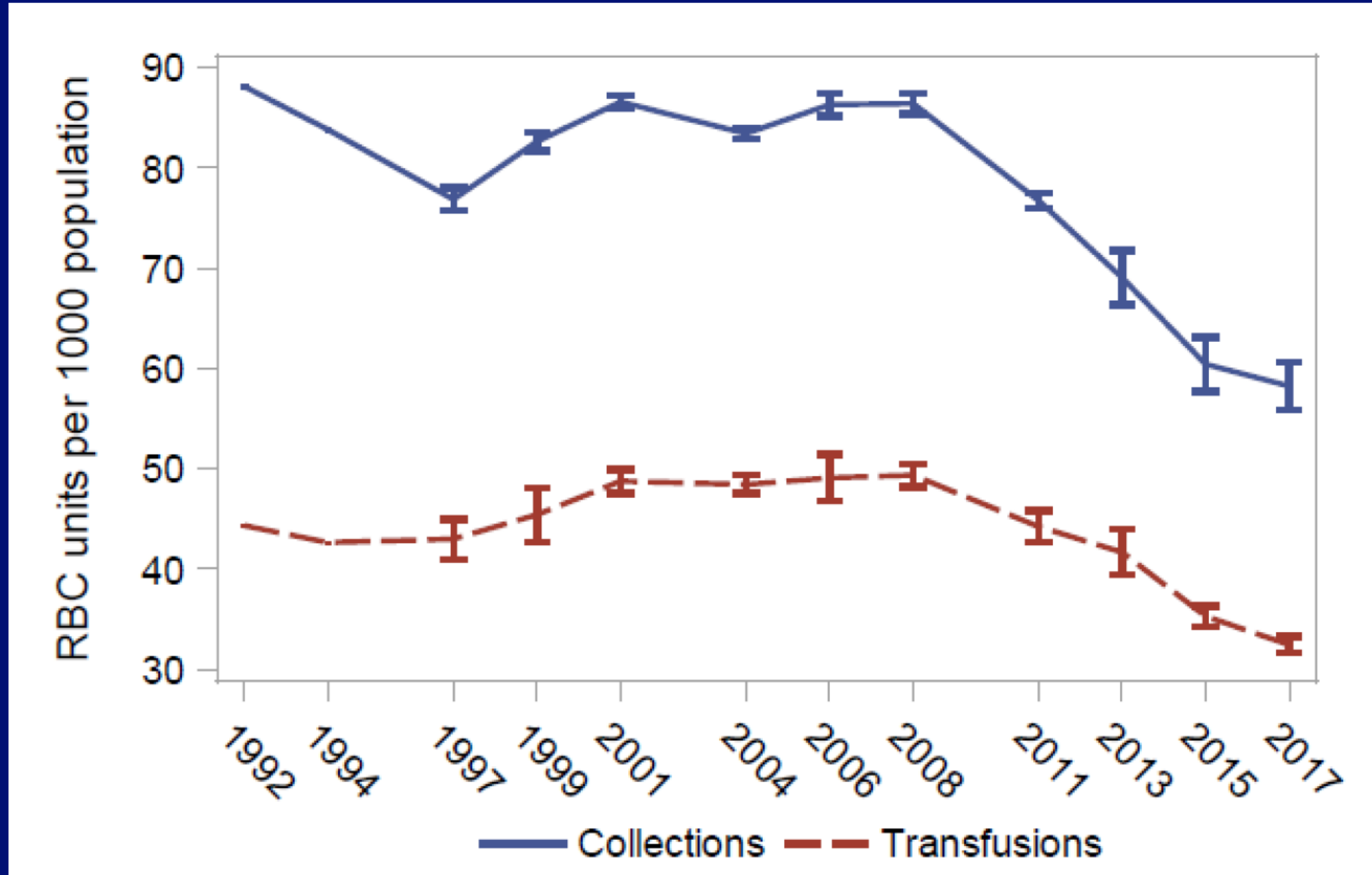
**Trends in platelets, plasma, and cryoprecipitate distribution and transfusion, 1989–2017**

NBCUS, 2017

# Anemia and transfusion are common

- Anemia is common in critically ill patients due to cumulative blood loss, diminished erythropoiesis, deficient erythropoietin, and hemolysis
  - Estimated incidence in the intensive care unit (ICU) range as high as 95%
- Despite trending decreases in blood collection and transfusion, the most common procedure performed during hospitalization in 2010 among all age groups, except infants, was blood transfusion
  - 11% of hospital stays that included a procedure – ranging from vaccination to parenteral nutrition to surgery – were transfused
  - Transfusion rate is even higher in the critically ill, where various studies show 14.7% to 53.0% of ICU patients are transfused

# Anemia

- Defined as "decrease in red blood cell mass"
- World Health Organization definition
  - Males hemoglobin less than 13 grams / deciliter (g / dL)
  - Females less than 12 g / dL
- Anemia classifications
  - Absolute: related either to impaired red blood cell production or red blood cell loss
  - Relative: such as in pregnancy or other fluid overload.

# Anemia

- A decrease in red blood cell mass *theoretically* impairs normal oxygen and carbon dioxide gas exchange and delivery
  - Oxygen supply to tissue depends not only on hemoglobin concentration, but also on oxygen saturation and affinity.
  - If there is blood loss, the degree and rate of change in blood volume also affects oxygen supply.
- The physiologic response to anemia varies according to acuity and etiology.
  - Gradual onset allows for compensatory mechanisms in patients without marked compromise in cardiovascular or pulmonary systems.
  - Clinical manifestations include easy fatigability, dyspnea on exertion, feeling faint or weak, palpitation, or headache
  - Patients may appear pale, tachycardic, and hypotensive due to an increase in cardiac output as compensation
  - In severest cases, tissue hypoxia can result in shock, hypotension, coronary or pulmonary insufficiency

# Anemia

- Tolerance to anemia is affected by volume status, physiologic reserve, and the etiology and rate of onset of the anemia
- Acute anemia -> increased oxygen demand -> tachycardia and increased contractility
  - However oxygen extraction in the myocardium is already near maximal at rest
- Additional compensatory response
  - preferential distribution of blood to vital organs primarily over the periphery
  - increase in the oxygen extraction ratio (reflected as a decrease in mixed venous saturation)
- Patients with coronary artery disease, heart failure, or acute coronary syndrome may be unable to mount a physiologic response to anemia and, thus, experience myocardial ischemia, infarction, or dysrhythmia

# Iron deficiency

- Iron deficiency is most common in gastrointestinal and cancer patients, but also affects patients with obstetric, renal, and immune disorders.
- Nearly all body systems are affected by iron deficiency
  - fatigue, depression and impaired cognitive function
  - anorexia and nausea
  - low skin temperature and pallor of skin, mucous membranes, and conjunctiva
  - impaired T-cell and macrophage function
  - exertional dyspnea, tachycardia, palpitations, cardiac hypertrophy, and increased pulse pressure
  - menstrual problems and loss of libido

# Diagnosis of anemia

- Exclude relative anemia (pregnancy, macroglobulinemia, fluid balance).
- Consider red blood cell loss
    - Evaluate for obvious or occult bleeding
    - Evaluate for hemolysis (lactate dehydrogenase, haptoglobin, direct Coombs (or direct antiglobulin test), bilirubin (direct and indirect), urinalysis
- Consider impaired production of red blood cells
    - Microcytic anemia : iron deficiency, thalassemia
    - Normocytic anemia : early blood loss, anemia of chronic disease
    - Macrocytic anemia : vitamin B12 or folate deficiency, hematologic malignancy
    - The MCV can thus suggest additional laboratory tests or clinical assessment to further elucidate the cause of the anemia.
- Complete understanding of the cause of the anemia is required in order to determine treatment

| Anemia | Cause | Common analyte abnormality |
|---|---|---|
| Hypoproliferative, microcytic | Iron deficiency | Low ferritin, increased IBC, decreased serum iron, reduced Fe / TIBC ratio, generally increased RDW |
| Hypoproliferative, microcytic | Anemia of chronic disease | Generally high ferritin, normal IBC, decreased serum iron, normal Fe / TIBC ratio, generally normal RDW |
| Hyperproliferative, normocytic | Hemolytic anemia | Schistocytosis, increased reticulocytes, low haptoglobin, elevated carboxyhemoglobin, elevated LD, elevated indirect bilirubin, generally increased RDW |
| Hypoproliferative, normocytic | Aplastic anemia | Leukopenia, thrombocytopenia, hypocellular bone marrow, generally normal RDW |
| Hypoproliferative, normocytic | Renal failure | Elevated BUN and creatinine, low erythropoietin, burr cells, generally normal RDW |
| Hypoproliferative, macrocytic (megaloblastic) | B12 and / or folate deficiency | Low B12 and / or folate, hyperlobulated polymorphonuclear leukocytes, macroovalocytes, increased RDW |
| Hypoproliferative, macrocytic (non-megaloblastic) | Hypothyroidism | Elevated TSH, normal RDW |

Source: McPherson RA, Pincus MR (eds). Henry's Clinical Diagnosis and Management by Laboratory Methods. 21st edition

# Transfusion decision-making

- Goal: maximal benefit and minimal risk to the patient and efficient use of a valuable and finite resource

- Transfuse based on
  - Sound physiologic principles
  - An understanding of relative risks and benefits
  - Evidence-based transfusion guidelines are presented based on the best evidence currently available

# Red Blood Cells

- RBC are transfused with the *purported* effects of increasing circulatory volume, transporting oxygen, and the rheological effect of increasing blood flow / viscosity
- **For hemorrhage**, transfusions are NOT recommended for volume expansion, perhaps with the exception of massive hemorrhage, and may lead to transfusion-associated circulatory overload
  - Blood viscosity may only benefit from rheological support of transfusion in severe hemodilution
  - Significant increase in blood viscosity may actually hinder perfusion
- **For non-hemorrhage,** providers commonly assume that anemia confers a risk for ischemia due to decreased oxygen delivery and, similarly, assume that RBC transfusion can improve oxygen delivery and mitigate the risk of ischemia
  - In actuality, anemia *may* increase the risk of ischemia, and a PRBC transfusion *may* improve tissue oxygenation in some cases of severe anemia but, in many situations, the risk of transfusing RBC appears to be greater than the probability of benefit

# Red Blood Cell transfusion may not enhance oxygen utilization in tissue

- Global oxygen delivery ($DO_2$) is determined by the arterial content of oxygen as well as cardiac output

$$DO_2 = CO \times CaO_2$$

CO = cardiac output and $CaO_2$ = arterial oxygen content

- Arterial oxygen content is dependent on hemoglobin level and hemoglobin saturation

- The ratio of oxygen delivery to global oxygen consumption ($VO_2$), or $DO_2 / VO_2$, is known as the oxygen extraction ratio and <span style="color:red">can be measured by mixed venous saturation ($SvO_2$)</span>

- The oxygen extraction ratio in a homeostatic patient is generally wide, around 20% – 30%, which allows for a broad margin of safety

- With anemia or blood loss, as oxygen delivery decreases and the oxygen extraction ratio narrows, a critical oxygen delivery level is reached when it can no longer keep up with oxygen consumption

# Red Blood Cell transfusion may not enhance oxygen utilization in tissue

- A simple hypothesis postulates that a RBC transfusion, by increasing both cardiac output and arterial oxygen content, would increase oxygen delivery and therefore oxygen consumption
  - However, in actuality consumption seems to demonstrate independence of delivery in circumstances where hypoxia is not severe
  - Studies show conflicting results on whether delivery is actually increased after RBC transfusion
- While a RBC transfusion almost always causes a post-transfusion rise in hemoglobin, which in itself is often associated with increased oxygen delivery, consumption is not always increased and ischemia (measured in terms of blood lactate level) is rarely improved
- The reasons for this are not entirely understood.
  - May be that the increase in hemoglobin after a RBC transfusion, by increasing blood viscosity, dampens the sympathetic response to anemia, decreasing cardiac output
  - May include inability of oxygen to dissociate from hemoglobin based on depleted 2,3-diphosphoglycerate in transfused red blood cells
  - May be decreased functional density of the microcirculation
  - May be that many patients whom receive RBC transfusions do not have severe enough ischemia whereby their oxygen consumption is in the dependent phase with delivery

# Evidence for Red Blood Cell Transfusion

- Restrictive vs Liberal Transfusion Randomized Controlled Trials (RCT)
  - Over 9000 patients enrolled in various trials
  - Many are small but three have >900 patients
  - Results consistently suggest that restrictive transfusion approach is safe
  - No adequately powered RCT in acute coronary syndrome

- A restrictive approach appears safe and is often associated with decreased morbidity and mortality.

# Restrictive vs Liberal RBC Transfusion

| RCT | n | PATIENTS | RESTRICTIVE | LIBERAL | OUTCOME | RESULT |
|---|---|---|---|---|---|---|
| TRICC | 838 | ICU | 7 | 10 | 30day mort | Not Signif |
| TRACS | 512 | CABG/Valve | 8 | 10 | 30day mort or organ failure | Not Signif |
| FOCUS | 2016 | Hip fracture & CV disease | 8 | 10 | 60day mort or inability to walk 10' | Not Signif |
| CRIT | 45 | ACS | 8 | 10 | 30day mort, MI, revasc | Favor Restrictive |
| MINT | 110 | ACS or CAD with PCI | 8 | 10 | 30day mort, MI, revasc | Not Signif |
| Villanueva | 921 | UGI bleed | 7 | 9 | 45day mort | Favor Restrictive |
| Robertson | 200 | TBI | 7 | 10 | 6 month GCS | Not signif |
| TRISS | 998 | Septic shock | 7 | 9 | 90 day mort, ischemia, life support | Not signif |

# Transfusion of red blood cells

- Decision to transfuse RBC in non-hemorrhaging patients should be based on clinical assessment and not solely on hemoglobin levels
  - Shortness of breath, fatigue, and tachycardia may also be caused by hypovolemia; treat with crystalloids
  - Consider patient age, comorbidity, and evidence or risk of ischemia
  - Persistently high lactate or central or mixed venous saturation less than 60% likely indicates systemic hypoperfusion
- If the combined laboratory and clinical assessment of the non-hemorrhaging patient meet evidence-based guidelines for transfusion, one unit of RBC at a time should be transfused
  - Hemoglobin equilibrates fifteen minutes after transfusion is completed
  - One PRBC unit can be expected to increase hemoglobin by 1 g / dL and hematocrit by 3%.
  - After one unit, hemoglobin and clinical reassessment should be repeated to determine if further PRBC transfusion is necessary.
- The ultimate goal of the RBC transfusion should not be to maintain a hemoglobin number, but to improve patient outcome

# Guidelines for transfusion of RBC

- Active hemorrhage

- Hgb less than 7 gm / dL

- Hgb less than 8 gm / dL for cardiac surgery or acute coronary syndrome

- Systemic hypoperfusion (persistently high lactate or central or mixed venous saturation less than 60%)

# Platelets

- Platelets can be prepared from whole blood or from apheresis
  - Platelet concentrates from whole blood can be transfused singly, often to pediatric patients, but are more commonly pooled together in pools of 4 or 6 concentrates, commonly referred to as a "six-pack"
  - Platelet units from apheresis donors are also known as "single donor platelets" and are considered equivalent to one pooled platelet
- Advantages of single-donor platelets:
  - Exposes the recipient to a single set of foreign antigens versus four to six sets, decreasing the risk of alloimmunization, to human platelet antigens (HPA) or human leukocyte antigens (HLA)
    - Alloimmunization to HPA or HLA can result in platelet refractoriness, potentially necessitating special laboratory evaluation and procurement of costly and time-consuming products such as crossmatched platelets or HLA-selected platelets
  - Bacterial contamination is less likely with single-donor platelets

# Platelet transfusion efficacy

- Efficacy of platelet transfusion may be assessed both by clinical parameters (improved hemostasis) and by following the platelet counts at 1 hour and 24 hours as an estimate of platelet survival
  - 1-hour post transfusion platelet count should increase by 30,000 to 60,000 platelets / $\mu$L
  - Failure of an appropriate rise in platelet count at 1 hour post transfusion is suggestive of immune platelet refractoriness (i.e. alloimmunization)
  - Failure to sustain increased platelet counts in 24 hours post-transfusion is suggestive of non-immune platelet refractoriness (i.e. fever, sepsis, consumption, or splenomegaly)

# Platelet transfusion decision-making

- Most platelet transfusions are given prophylactically to reduce the risk for spontaneous bleeding in thrombocytopenic patients

- The evidence to support platelet transfusion decision-making ranges from low to moderate quality, as there are both observational studies and RCTs

- For therapy-associated hypoproliferative thrombocytopenia
    - Prophylactic transfusions significantly reduced risk for spontaneous grade two or greater bleeding (three RCTs)
    - The most appropriate platelet count threshold for prophylactic platelet transfusion to effectively reduce bleeding is 10,000 cells / $\mu$L (four RCTs)
        - Transfusion of platelets at a 10,000 cells / $\mu$L threshold was associated with less platelet usage and fewer transfusion reactions, while transfusion at a 20,000 – 30,000 cells / $\mu$L threshold did not further decrease incidence of bleeding or bleeding-related mortality

# Platelets

- Dosing is ONE single-donor apheresis platelet or ONE apheresis-equivalent pool of platelets.
    - From six RCTs:
    - Two apheresis platelet units does not decrease bleeding risk compared to one apheresis platelet unit
    - One-half of an apheresis platelet unit actually conveys the same prophylactic bleeding protection as one whole apheresis platelet unit
- Evidence supporting prophylactic platelet transfusion for invasive procedures is largely based on observational studies
- Clinical practice guideline on platelet transfusion from the AABB suggests an appropriate platelet count for placement of central venous catheter is 20,000 cells / $\mu$L and for lumbar puncture or for major elective nonneuraxial surgery is 50,000 cells / $\mu$L

# Guidelines for transfusion of platelets

- Platelet count less than 10,000 cells /µL and bone marrow failure
- Platelet count less than 50,000 cells /µL and impending surgery or invasive procedure
- Platelet count less than 100,000 cells /µL and neurosurgical or ophthalmic procedure
- Platelet count less than 50,000 cells /µL with active bleeding
- Platelet count less than 100,000 cells /µL with multiple trauma or cardiopulmonary bypass patient with intraaortic balloon pump

# Plasma

- Plasma is used as a source of clotting factors in bleeding patients or patients requiring an invasive procedure with multiple coagulation factor deficiencies, such as those in liver dysfunction or consumptive or dilutional coagulopathy
- An understanding of the half-life of clotting factors is necessary to help understand the appropriate use of plasma
  - Factor VII, the main clotting factor of the extrinsic pathway of the coagulation cascade, has the shortest half-life, in the range of 2 – 7 hours
    - Most factor VII is therefore depleted from plasma products before their manufacturing is complete, and thus plasma cannot correct a deficiency in factor VII, diagnosed by a prolonged prothrombin time (PT) and normal activated partial thromboplastin time (aPTT)
  - The next factors with the shortest half-lives are factors V and VIII, with 15 – 36 hours and 8 – 12 hours, respectively
    - These factors also decline during plasma processing and storage, but not below the levels required for hemostasis.

# Clotting factors and hemostasis

- Normal hemostasis can be achieved with only 5% – 30% of normal clotting factor activity
- The PT and the aPTT can be used to assess patients for need for plasma transfusion and to follow the efficacy of administered plasma
  - If both PT and aPTT are prolonged : consider decrease in final common pathway clotting factors (prothrombin, fibrinogen, factor V, factor X) or a combined decrease in extrinsic and intrinsic factors, such as in vitamin K antagonists or liver disease
  - If aPTT alone is prolonged, consider a decrease in extrinsic clotting factors (factors VIII, IX, XI, and XII), such as with lupus anticoagulant
  - If PT alone is prolonged, consider factor VII deficiency

# INR is for coumadin patients!

- Clinical practice for the evaluation of bleeding or bleeding risk often deviates from the assessment of PT and aPTT, focusing rather on the international normalized ratio (INR)
  - The INR is a calculated value meant to standardize commercial reagents against international standards, in order for patients on vitamin K antagonists to achieve accurate and standardized results assessing their therapeutic range of treatment, regardless of which laboratory performs the test
  - Some argue that the INR should only be used for this purpose but many in clinical practice use the INR to evaluate bleeding risk or target the INR for "correction" with therapeutic intervention in bleeding patients

# INR is for coumadin patients!

- An INR prolonged in the mild-moderate range (< 2) is not predictive of bleeding
- Plasma does not "correct" a mild-moderate elevation in INR
  - The actual INR measured on plasma products varies between 1.14 and 1.4
- Twenty-five published studies between 1966 and 1996 show
  - PT / INR does not show any correlation with clinical bleeding in association with invasive procedures unless they are very abnormal
  - Prophylactic plasma does not attenuate bleeding risk
- Appropriate prophylactic utilization of plasma can thus be considered for patients requiring an invasive procedure with an INR in the moderately prolonged range, conservatively between 1.7 and 2.0

# Plasma dosing

- Dosing for plasma for clotting factor replacement is 10 – 20 mL / kg total body weight, which would increase clotting factors approximately 20% immediately post-transfusion
  - Remember that normal hemostasis can be achieved with only 5% – 30% of normal clotting factor activity
- Plasma should be avoided for normalizing an INR < 1.7 in the absence of bleeding, blood volume expansion or nutrition support, coagulopathy that can be corrected with vitamin K administration, and single factor deficiency where commercial factor concentrates are available.

# Guidelines for transfusion of plasma

- International normalized ratio (INR) > 1.7 with an anticipated invasive procedure
- Post massive transfusion to prevent development of coagulopathy
- Treatment of thrombotic thrombocytopenia purpura if plasmapheresis not available
- Single factor deficiency where commercial concentrate is not available
- Warfarin reversal ONLY IF vitamin K and / or 4-factor prothrombinase complex concentrate are not available
- Treatment or prophylaxis of thromboembolism in antithrombin, protein C or protein S deficiency

# Cryoprecipitate

- Each unit of cryoprecipitate contains Factor VIII (minimum of 80 IU), fibrinogen (minimum of 150 mg), von Willebrand factor, factor XII in 5 – 20 mL plasma
  - In adults, cryoprecipitate is often given in a pool of 5 – 10 individual units, resulting in a volume between 50 – 200 mL, dependent on individual blood banks
  - Each unit in the pool will increase the fibrinogen by 5 – 10 mg / dL in an average-sized adult. In children, cryoprecipitate can be given in individual units at a dose of 1 – 2 units / 10 kg, which can increase fibrinogen by up to 100 mg / dL.

- Solid clinical evidence for appropriate utilization and fibrinogen threshold for cryoprecipitate transfusion is lacking

- With technological advances in recombinant factor development, cryoprecipitate is no longer used for its original purpose of factor VIII replacement but is instead used for acquired coagulopathy, such as in clinical settings associated with hemorrhage, or in consumptive disorders of fibrinogen

# Guidelines for transfusion of cryoprecipitate

- Diffuse active bleeding with fibrinogen less than 100 mg/dL
- Von Willebrand disease unresponsive to desmopressin when factor concentrates are unavailable

# Risks of allogeneic blood exposure

**Direct causal risks:**

Viral exposure

Bacterial contamination

Citrate exposure:
- acidosis, hypocalcemia

Hyperkalemia

Mistransfusion

Volume overload

Transfusion reactions

**Indirect plausible risks:**

Immunomodulation

Infection

Pneumonia

Slowed wound healing

Prolonged ventilator use

Increased length of stay
Increased cost
Increased morbidity and mortality

*Decreased exposure = increased safety and decreased cost*

# Transfusion-associated fatalities

| Complication | FY12 No. | FY12 % | FY13 No. | FY13 % | FY14 No. | FY14 % | FY15 No. | FY15 % | FY16 No. | FY16 % | Total No. | Total % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anaphylaxis | 2 | 5% | - | 0% | 2 | 7% | 2 | 5% | 5 | 12% | 11 | 6% |
| Contamination | 3 | 8% | 5 | 13% | 1 | 3% | 5 | 14% | 5 | 12% | 19 | 10% |
| HTR (ABO) | 3 | 8% | 1 | 3% | 4 | 13% | 2 | 5% | 4 | 9% | 14 | 8% |
| HTR (non-ABO) | 5 | 13% | 5 | 13% | 4 | 13% | 4 | 11% | 1 | 2% | 19 | 10% |
| Hypotensive Reaction | - | 0% | - | 0% | 1 | 3% | 1 | 3% | 1 | 2% | 3 | 2% |
| TACO | 8 | 21% | 13 | 34% | 5 | 17% | 11 | 30% | 19 | 44% | 56 | 30% |
| TRALI* | 17 | 45% | 14 | 37% | 13 | 43% | 12 | 32% | 8 | 19% | 64 | 34% |
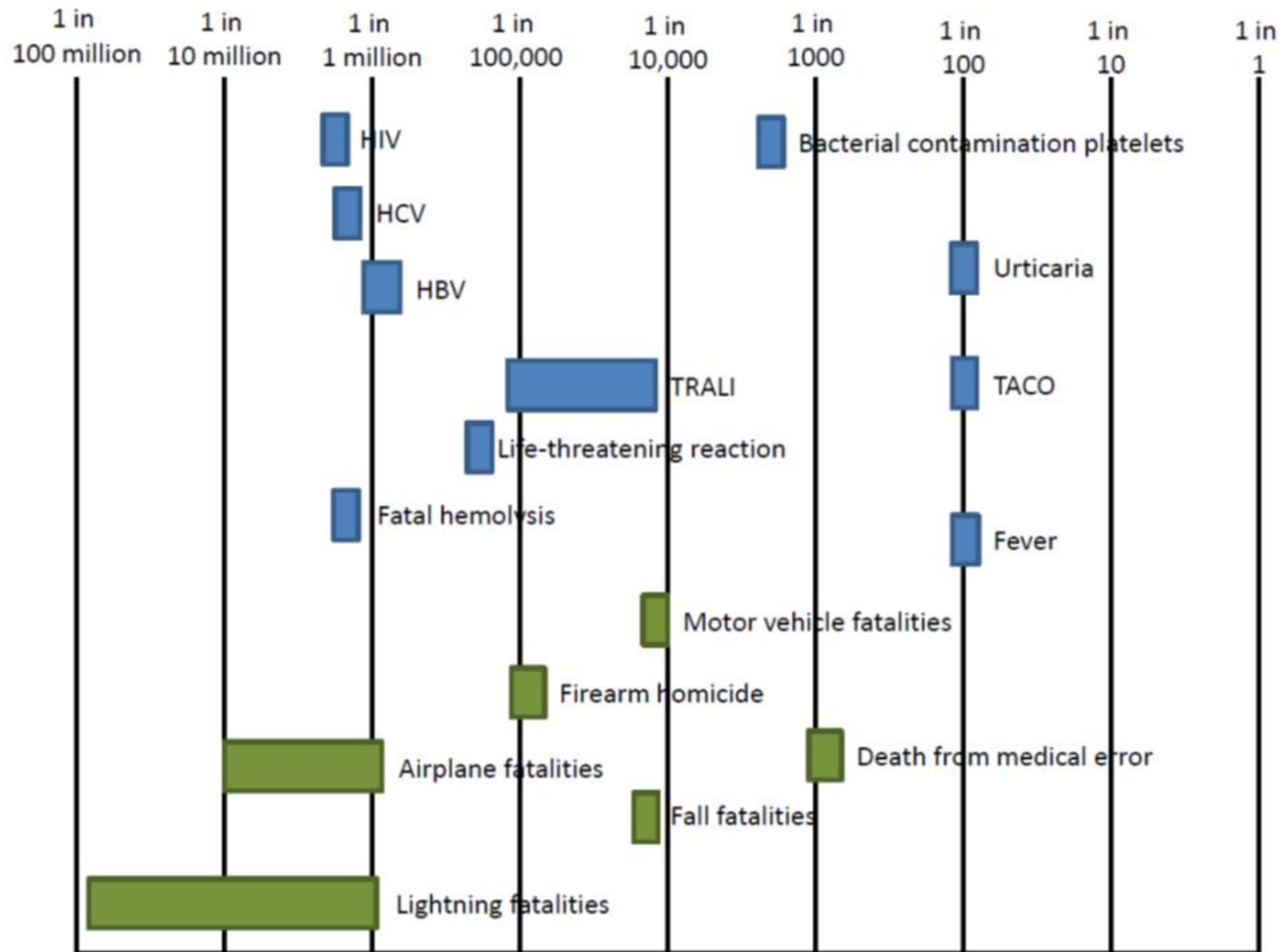
**Adverse effects of transfusion contrasted with other life risks.** Estimates of the current risk per unit of red blood cell transfused (or per platelet transfused, as designated), in blue, are contrasted against risk for fatality per year for various life events, in green. Risk is depicted on a logarithmic scale. HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload. (Adapted from Carson JL, Grossman BJ, Kleinman S, et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. Ann Intern Med, 2012;157:49-58.)

# Transfusion reactions, acute (<24 hours) - Immunologic

| Type | Presentation | Treatment |
|------|--------------|-----------|
| Hemolytic | Chills, fever, hypotension, renal failure, back pain, hemoglobinuria, pain along infusion vein, anxiety, DIC (oozing from IV sites) | Keep urine output > 1 mL / kg / hr with fluids and IV diuretic (furosemide); analgesics; pressors (low-dose dopamine) |
| Febrile, nonhemolytic | Temperature elevation > 1°C from baseline, chills and/or rigors, headache, vomiting | Antipyretics (acetaminophen) |
| Urticarial | Pruritus, urticaria, flushing | Antihistamine |
| Anaphylactic | Hypotension, urticaria, bronchospasm, respiratory distress, wheezing, local edema, anxiety | Trendelenburg position; fluids; epinephrine; antihistamines; corticosteroids, beta-2 agonists |
| Transfusion-associated acute lung injury | Hypoxemia, respiratory failure, hypotension, fever, bilateral pulmonary edema | Supportive care |

# Transfusion reactions, acute (<24 hours) - Nonimmunologic

| Type | Presentation | Treatment |
|---|---|---|
| Transfusion-associated sepsis | Fever, chills, hypotension | Broad spectrum antibiotics; treat complications (e.g. shock) |
| Hypotension (associated with angiotensin-converting enzyme (ACE) inhibition) | Flushing, hypotension | Discontinue ACE inhibition; avoid albumin volume replacement for plasmapheresis; avoid bedside leukocyte filtration |
| Circulatory overload | Dyspnea, orthopnea, cough, tachycardia, hypertension, headache | Upright posture; oxygen; IV diuretic (furosemide); phlebotomy (250-mL increments) |
| Nonimmune hemolysis (e.g. physical or chemical destruction of blood such as heating, freezing, drug or solution transfused in conjunction) | Hemoglobinuria, hemoglobinemia | Identify and eliminate cause |
| Air embolus | Sudden dyspnea, acute cyanosis, pain, cough, hypotension, cardiac arrhythmia | Place patient on left side with legs elevated above chest and head |

# Transfusion reactions, delayed (>24 hours) - Immunologic

| Type | Presentation | Treatment |
|---|---|---|
| Hemolytic | Fever, decreasing hemoglobin, new positive antibody screening test, mild jaundice | Transfuse compatible PRBC as needed |
| Graft *versus* host disease | Erythroderma, maculopapular rash, anorexia, nausea, vomiting, diarrhea, hepatitis, pancytopenia, fever | Corticosteroids, cytotoxic agents |
| Posttransfusion purpura | Thrombocytopenic purpura, bleeding 8 – 10 days after transfusion | IVIG, plasmapheresis |
| Alloimmunization, human leukocyte antigens | Platelet refractoriness | Avoid unnecessary transfusions |
| Alloimmunization, red cell antigens | Positive blood group antibody screening test, delayed hemolytic reaction, hemolytic disease of the fetus / newborn | Avoid unnecessary transfusions |

# Transfusion-transmitted infection

- Pathogens of well-documented importance in blood safety:

| Bacterial | Viral | Parasitic | Other |
|-----------|-------|-----------|-------|
| Escherichia coli | Cytomegalovirus (CMV) | Babesiosis (Babesia spp.) | Creutzfeldt-Jakob |
| Klebsiella oxytoca | Enterovirus | ★Chagas disease | Disease, Variant |
| Klebsiella pneumoniae | Epstein Barr (EBV) | (Trypanosoma cruzi) | (vCJD) |
| Pseudomonas | Hepatitis A | Malaria (Plasmodium spp.) | |
| aeruginosa | ★Hepatitis B | | |
| Serratia marcescens | ★Hepatitis C | | |
| Staphylococcus aureus | ★Human Immunodeficiency Virus | | |
| Staphylococcus | 1 (HIV-1) | | |
| epidermidis | ★Human Immunodeficiency Virus | | |
| Staphylococcus | 2 (HIV-2) | | |
| lugdunensis | Human Parvovirus B-19 | | |
| ★Syphilis (Treponema | ★Human T-Cell Lymphotropic (or, | | |
| pallidum) | leukemia) Virus-1 (HTLV-1) | | |
| Yersinia enterocolitica | ★Human T-Cell Lymphotropic (or, | | |
| | leukemia) Virus-2 (HTLV-2) | ★ Denotes infectious disease testing | |
| | ★West Nile Virus (Flaviviridae) | performed on blood components | |

# Plausible risks of transfusion

- Beyond the direct risks of transfusion-transmitted infection and transfusion reaction
  - increased mortality (both short- and long-term)
  - increased hospital and/or ICU length of stay
  - higher incidence of various morbidities, including serious infections, prolonged ventilator time, renal failure, cardiac ischemia, atrial fibrillation, and / or systemic inflammatory response syndrome
- Slow strength of evidence: cohort studies either retrospective or observational
- The majority of RCTs evaluating restrictive *versus* liberal transfusion practices show no difference in these types of outcomes, rather than an increased incidence of mortality or complications in patients receiving more RBC

# Minimizing transfusion

- Given the known risks and the costs associated with blood transfusions, efforts should be made to minimize the use of transfusion whenever possible
- Comprehensive strategy of Patient Blood Management should be followed
  - A multidisciplinary, patient-focused effort defined as "the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcomes"
- In patients with anemia:
  - The need to correct anemia should be assessed (with emphasis on type and etiology of anemia)
  - Sources of ongoing blood loss should be controlled
  - Measures to enhance erythropoiesis should be entertained

# Minimizing blood loss

- Repeated phlebotomy in hospitalized patients can result in up to 40 mL blood loss daily from a single patient
  - Particularly significant in children with smaller blood volumes
- To avoid iatrogenic anemia
  - Carefully consider the need for frequent phlebotomy in hospitalized patients
  - Obtain laboratory results only when the result will affect care
  - Consider eliminating standing laboratory orders
  - Use microsampling techniques including bedside point-of-care testing
  - Limit the practice of drawing the 'rainbow' collection of specimen tubes without purposeful ordering

# Optimization of red cell production

- Erythropoiesis is dependent on both iron and erythropoietin
- If iron deficiency anemia is confirmed, treatment must consist of addressing chronic or acute bleeding and may also consist of iron replacement
- Oral iron therapy
  - Can take weeks to months to replete iron, has a number of adverse side effects, and is therefore not appropriate in the acute care setting
  - Hospitalized patients commonly demonstrate chronic inflammatory states, which may impede iron absorption that is inherently already low
  - Persistent blood loss can exceed the dosing of oral iron or gastrointestinal absorption rates
- Intravenous iron therapy
  - Faster, takes days to weeks to replete iron
  - Some associations of intravenous iron with hypersensitivity reactions, particularly in the high molecular weight formulations that have fallen out of common use
  - Some association with increased infections, which has not been confirmed in clinical trials

# Optimization of red cell production

- Studies and clinical trials have shown that the administration of erythropoiesis-stimulating agents (ESAs) can reduce need for blood transfusion and increase hemoglobin
  - ESAs are synthetic versions of the human hormone erythropoietin
  - Approved for the treatment of anemia secondary to chronic kidney disease, chemotherapy, and certain human immunodeficiency virus therapies, as well as to reduce the number of blood transfusions pre- and post-surgery
- A number of trials has shown adverse outcomes including thromboembolic events and decreased overall survival, which has resulted in an FDA black-box label for ESAs
- Nonetheless, ESAs can be used safely in appropriate patient populations with appropriate dosing and as part of an overall treatment strategy, often incorporating intravenous iron

# Transfusion alternatives

- Research and developmental investigations for a substance mimicking red blood cells that can transport oxygen from the lungs to the tissues have spanned seven decades
  - First-generation substances (perfluorocarbons and stroma-free hemoglobin) abandoned due to problems with manufacturing, ease of use, and adverse effects
- Current investigation is now focused on the hemoglobin-based oxygen carriers (HBOCs)
  - Hemoglobin molecules in these products come from outdated human blood, animal blood, or recombinant DNA technology
  - Offer benefits that are superior to donor blood products : pathogen-free, extended storage stability at room temperature, lack antigenicity (do not require type and screen prior to infusion)
- Currently two HBOC products
  - Hemopure®[hemoglobin glutamer – 250 (bovine)] available through the FDA expanded access program to qualifying patients for whom blood transfusion is not an option, and who have exhausted all other treatments; also under investigation for perfusing organs pre-transplantation
  - SANGUINATE® [PEGylated Bovine Carboxyhemoglobin] has an Orphan Drug Designation from the U.S. FDA for the treatment of SCD comorbidities

# Refusal of blood products

- Patient-centered decision making is paramount
- All patients admitted to the critical care setting should have treatment preferences (including blood transfusion and related products) discussed as soon as possible
  - Include detailed explanation of each blood product, as the origin and technical aspects of these products may affect their acceptance
- One retrospective cohort study evaluated morbidity and mortality in 300 patients who declined transfusion despite postoperative hemoglobin levels ≤ 8 g / dL
  - Odds of death increased 2.5 times for each gram decrease in hemoglobin below 8 g / dL, with sharper rise in morbidity and mortality with hemoglobin level 5 - 6 g / dL
- Use Patient Blood Management strategies, as well as iron and erythropoietin in the management of these patients

# Guideline for Management of Anemia in Bloodless Patients

- Iron sucrose 200 mg IV daily for 5 days
- Folic acid 1 mg IV daily
- Vitamin C 500 mg q 12hr enteral
- Vitamin B12 1000 mcg IM one dose
- EPO
  - Hemoglobin > 7 g/dL = give 40,000 U subcutaneously weekly (IV if sq contraindicated)
  - Hemoglobin 5 - 7 g/dL = give 20,000 U subcutaneously daily for 5 days (IV if subcutaneous contraindicated); if weekly corrected reticulocyte count < 6% redose EPO 40,000 U subcutaneously daily for 4 days
  - Hemoglobin < 5 g/dL = give 20,000 U subcutaneously every 12 hours for 5 days (IV if subcutaneous contraindicated); if weekly corrected reticulocyte count < 6% redose EPO 40,000 U subcutaneously every 12 hours for 5 days

# Key points

- Anemia is common and bad.
  - Iron deficiency is common and easy to fix.
- Transfusions seem to be more bad than good.
- Some low hemoglobins should be tolerated.
  - If you have to transfuse, give one.
- Do not use INR to gauge bleeding risk.
- Do not use plasma to "reverse" mid-range INR.
- Use strategies for less bleeding, more oxygen delivery, and more red blood cell production.