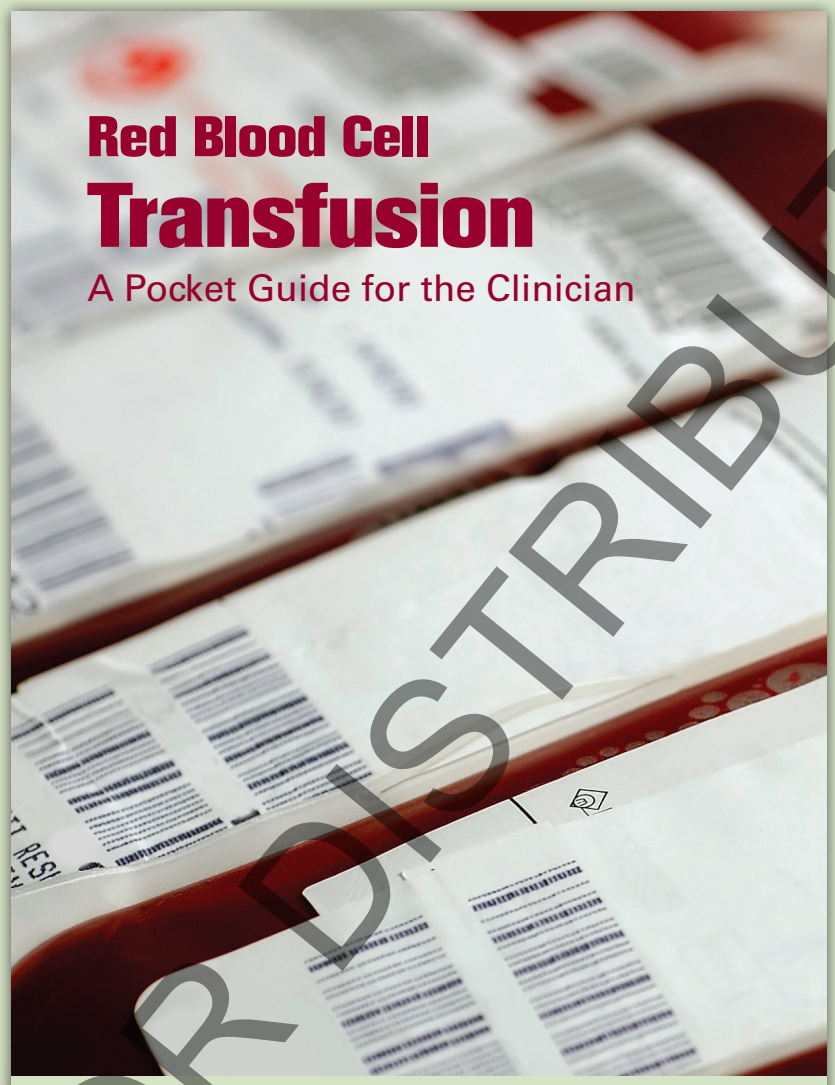

Red Blood Cell Transfusion

A Pocket Guide for the Clinician

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Adapted from *Red Blood Cell Transfusion: A clinical practice guideline from the AABB, Clinical Practice Guidelines from the AABB: Red blood cell transfusion thresholds and storage,* and additional sources

Red Blood Cells as a Therapeutic Product

Appropriate uses of red blood cell (RBC) transfusion

- Treatment of symptomatic anemia
- Prophylaxis in life-threatening anemia
- Restoration of oxygen-carrying capacity in case of hemorrhage
- RBCs are also indicated for exchange transfusion
  - Sickle cell disease
  - Severe parasitic infection (malaria, babesiosis)
  - Severe methemoglobinemia
  - Severe hyperbilirubinemia of newborn

RBC transfusion is not routinely indicated for pharmacologically treatable anemia such as:

- Iron deficiency anemia
- Vitamin B_{12} or folate deficiency anemia

Dosage and administration

- One unit of RBC will raise the hemoglobin of an average-size adult by ~1 g/dL (or raise HCT ~3%)
- ABO group of RBC products must be compatible with ABO group of recipient
- RBC product must be serologically compatible with the recipient (see Pretransfusion Testing). Exceptions can be made in emergencies (see Emergency Release of Blood Products).
- Rate of transfusion
  - Transfuse slowly for first 15 minutes
  - Complete transfusion within 4 hours (per FDA)

Major Red Cell Products for Transfusion

Most RBC products are derived by collection of 450-500 (±10%) mL of whole blood from volunteer donors and removal of the plasma by centrifugation (see Table 1). After removal of the plasma, the resulting product is red blood cells (referred to informally as "packed red blood cells").

The most commonly available US RBC product has a 42-day blood bank shelf life and HCT 55-65%.

Table 1. Special Processing of RBC for Transfusion

Process	Indications	Technical Considerations
Leukocyte Reduction	Decrease risk of recurrent febrile, nonhemolytic transfusion reactions Decrease risk of cytomegalovirus (CMV) transmission (marrow transplant) Decrease risk of HLA-alloimmunization Does not prevent transfusion-associated graft-versus-host disease (TA-GVHD)	Most commonly achieved by filtration Usually soon after collection (prestorage) May be performed at bedside <$5x10^6$ leukocytes per product (per FDA)
Washing (removes residual plasma)	Decrease risk of anaphylaxis in IgA-deficient patient with anti-IgA antibodies Decrease reactions in patients with history of recurrent, severe allergic or anaphylactoid reactions to blood product transfusion	Wash fluid is 0.9% NaCl ± dextrose Shelf life of washed RBCs 24 hours at 1-6°C 4 hours at 20-24°C May lose 20% of red cells in washing process
Irradiation	Prevention of TA-GVHD in certain circumstances Donor categories Product donated by family member Product from HLA-selected donor Products from directed donors whose relationship to recipient's family has not been established Pediatric practice Intrauterine transfusion (IUT) Exchange or simple transfusion in neonates if prior IUT Congenital immune deficiency states Acute leukemia: HLA-matched or family-donated products Allogeneic hemopoietic progenitor cell (HPC) transplant recipient Allogeneic HPC donor 7 days prior to, or during, HPC harvest Autologous HPC recipient Hodgkin disease History of treatment with purine analogues and related drugs Fludarabine 2CDA (Cladribine®) Deoxycoformycin (Pentostatin®) Clofarabine (Clolar®) Bendamustine (Treanda®) Nelarabine (Arranon®) History of treatment with alemtuzumab (anti-CD52) Aplastic anemia on rabbit anti-thymocyte globulin	Radiation dose: 2500 cGy to center of product Gamma or X-irradiation Shelf life of irradiated product: up to 28 days unless original expiration date is sooner NB: Supernatant K+ may be higher than usual Allogeneic HPC transplant recipient: Start with initiation of conditioning regimen Continue throughout period of GVHD prophylaxis Usually for at least 6 months Until lymphocytes are > 1 x 10^9/L Indefinitely if treated for chronic GVHD Autologous HPC recipient 7 days prior to, and during, harvest Initiation of conditioning through 3 months post transplant (6 months if TBI was used)

Pretransfusion Testing

Prevents incompatible red cell transfusion

- Compatibility of donor red cells and recipient plasma
- Avoid immune hemolytic transfusion reactions in the recipient

Pretransfusion blood sample from the intended recipient

- Usually EDTA tube (plasma and red cells)
- Proper labeling of the sample
  - 2 independent patient identifiers
  - Identity of the phlebotomist
  - Date and time of sample collection
  - Sample rejected without these
- Age of the sample
  - Up to 3 days if hospital inpatient or, in past 3 months, recipient
    - Has been pregnant
    - Has been transfused
    - Has uncertain history of either
  - Longer (often 1–2 weeks, according to hospital policy) for outpatient
    pre-op testing if negative history within 3 months

Table 2. Pretransfusion Testing

Test	Purpose	Reagents	Time
ABO Group & Rh Type	Determine if recipient's blood group Rho(D) is positive or negative	Test recipient's red cells with anti-A, anti-B, anti-D; test recipient's plasma with A_1* and B cells	~25 min
Antibody Screen	Detect unexpected, clinically significant (non-ABO) anti-RBC antibodies in recipient's plasma	Test recipient's plasma with phenotyped "reagent" RBCs	~50 min
Antibody Identification	Identify specificity of anti-RBC antibody if antibody screen is pos	Test recipient's plasma with many "reagent" RBCs	Varies: Hours to days
Immediate Spin Crossmatch (when antibody screen is negative)	Ensure ABO compatibility between recipient's plasma and RBC product chosen for transfusion	Test recipient's plasma with sample of red cells from product chosen for transfusion	~10 min
Full Serological Crossmatch (when antibody screen is positive)	Ensure full serological compatibility between recipient's plasma and RBC product chosen for transfusion	Test recipient's plasma with sample of red cells from product chosen for transfusion. Includes extra incubations (e.g. at 37°C and with Coombs reagent).	Up to an hour
Electronic Crossmatch (not universally available)	Match ABO/Rh compatible RBC from inventory with patient whose ABO/Rh status has been confirmed and who has no history of, and negative testing for, RBC alloantibodies	Validated blood bank computer system.	~10-15 min

*A_1 is the most common subgroup of Group A

Emergency Release of Blood Products

An emergency release of blood products is warranted when the clinical setting precludes waiting for completion of pretransfusion and compatibility testing. Examples include:

- Severe, ongoing life-threatening hemorrhage
- Life-threatening anemia

What you should do:

- Notify blood bank of need for emergency release of RBCs
- Complete hospital's "emergency release" form
  - Documents your declaration of a transfusion emergency
  - U.S. federal regulations require 2 specific items on the form
    - Statement of the nature of the emergency (e.g. "massive GI hemorrhage")
    - Signature of MD or "equivalent"; (PA, NP, RN, etc. cannot sign)
- Send patient blood sample to blood bank ASAP (before emergency transfusion begins, if possible)

What you'll get from the blood bank (depending on how much testing has already been performed):

- Uncrossmatched RBCs (ABO group-specific if determined on a current blood specimen)
- Group O RBCs if blood bank has not documented patient's ABO group on a fresh blood sample
  - Rh neg depending on availability and hospital policy, if patient's Rh status is unknown

Blood bank will retrospectively crossmatch all emergently issued units when it receives the patient's testing sample

Blood bank will begin issuing type specific and crossmatched products when testing is complete

Transfusion of Incompatible RBCs

Clinical scenario: severe warm (or cold) autoimmune hemolytic anemia

- Patient's plasma autoantibody reacts with all of the blood bank's reagent red cells
- Blood bank unable to determine presence or absence of underlying alloantibodies
- All RBC units are crossmatch-incompatible

Balance of risks

- Severe anemia requiring transfusion support
- Possibility of hemolytic transfusion reaction due to undiagnosed underlying alloantibodies

Principles of approach to this situation

- Communication between bedside clinician and transfusion service physician is essential
  - Obtain careful history of prior transfusion or pregnancy
    - If history negative, probably safe to transfuse ABO-compatible RBCs
    - If history positive or uncertain, assess risk:benefit of delaying transfusion to complete testing
  - Assess how long it may take for blood bank or reference lab to complete pretransfusion testing
  - Agree on best approach to choosing among incompatible RBC units (transfusion physician will advise)
- Attempt to mitigate need for immediate transfusion: bed rest, oxygen

Ultimately, do not deprive a patient with autoimmune hemolytic anemia of a needed, lifesaving transfusion

- Autoantibody will shorten survival of transfused RBCs and patient's endogenous RBCs to a similar extent
- Most undetected alloantibodies will cause delayed hemolytic transfusion reactions
  - May be misdiagnosed as worsening of autoimmune hemolysis
  - Not usually life-threatening
- Bedside team must be hypervigilant for acute intravascular hemolytic reaction during transfusion (see Adverse Effects of Transfusion)

Red Blood Cell Transfusion

Table 3. RBC Transfusion Recommendations* for Hospitalized, Hemodynamically Stable Patients in Specific Clinical Situations

Clinical Situation	Potential Transfusion Threshold	Strength of Recommendation	Quality of Supporting Evidence
Adult Inpatients, Hemodynamically Stable	Hgb** ≤ 7 gm/dL	Strong	Moderate
ICU Patients, Hemodynamically Stable (adult or pediatric)	Hgb ≤ 7 gm/dL	Strong	High
Postoperative Orthopedic or Cardiac Surgery Patients	Hgb ≤ 8 gm/dL§ or for symptoms†	Strong	Moderate
Cardiovascular Disease	Hgb ≤ 8 gm/dL‡ or for symptoms†	Strong	Moderate
Acute Coronary Syndrome	AABB does not recommend for or against a liberal or restrictive RBC transfusion strategy	Uncertain	Very Low
All Patients	Guided by symptoms as well as by Hgb level	Weak	Low

*Table adapted from: Red Blood Cell Transfusion: A clinical practice guideline from the AABB. *Ann Intern Med* 2012;157:49-58 and Clinical practice guidelines from the AABB: Red blood cell transfusion thresholds and storage. *JAMA*. doi:10.1001/jama.2016.9185.
**Hgb=Hemoglobin level
§Cannot be generalized to the preoperative setting, where expected surgical blood loss must be taken into account in transfusion decision making.
† Chest pain, orthostatic hypotension or tachycardia unresponsive to fluids, or congestive heart failure.
‡There remains some uncertainty regarding the risk of perioperative myocardial infarction with a restrictive transfusion strategy.

Adverse Effects of Transfusion

The most clinically important adverse effects of transfusion in medical patients are infectious or immunological phenomena. The most significant infectious risks are addressed during the donor screening process, and most blood centers employ bacteriological surveillance measures on certain blood products.

Table 4. Some Infectious Risks of Blood Transfusion (all products)

Transfusion-Transmitted Infection	Residual Risk Per Transfused Component
HIV	1 in 1,467,000
Hepatitis C	1 in 1,149,000
Hepatitis B	1 in 282,000
West Nile Virus	Uncommon
Cytomegalovirus	50-85% of donors are carriers. Leukocyte reduction is protective.
Bacterial Infection	1 in 2-3,000 (mostly platelets)
Parasitic Diseases Babesiosis, Chagas, Malaria	Relatively uncommon

Other Important Adverse Effects of Blood Transfusion

For any of the following, except allergic (uticarial) reactions, stop transfusion and return remaining product to blood bank with transfusion reaction report:

Acute hemolytic transfusion reaction (AHTR): Preformed antibodies to incompatible product (1:76,000). ABO incompatibility (1:40,000). Sometimes fatal ($1:1.8x10^6$). Presents with chills, fever, hypotension, hemoglobinuria, renal failure, back pain, DIC. Keep IV open with normal saline. Keep urine output >1 mL/kg/hour. Pressors PRN. Treat DIC.

Delayed HTR: Anamnestic immune response to incompatible red cell antigen. May present with fever, jaundice, falling hemoglobin, newly positive antibody screen in blood bank. Occurs 1-2 weeks after transfusion. Identify offending antibody in blood bank. Transfuse PRN with compatible RBCs.

Febrile non-HTR: 0.1-1.0%. Due to preformed anti-WBC antibodies in recipient. Risk minimized with leukocyte-reduced products. ≥1°C (2°F) rise in temperature within 2 hours of start of transfusion with no other explanation for fever. Acetaminophen premedication if reactions are recurrent.

Allergic (urticarial) reactions: 1-3%. Antibody to donor plasma proteins. Presents with urticaria, pruritus, flushing, mild wheezing. Pause transfusion, administer antihistamines; may resume transfusion if reaction resolves, but still report reaction to blood bank.

Anaphylactoid/anaphylactic: 1:20,000-50,000. Caused by antibody to donor plasma proteins (IgA, haptoglobin, C4). Hypotension, urticaria, bronchospasm, angioedema, anxiety. Rule out hemolysis. Administer epinephrine 1:1000 0.2-0.5 ml SC, antihistamines, corticosteroids.

Transfusion-related acute lung injury (TRALI): ~1:10,000. Preformed HLA or neutrophil antibodies in donor product. Hypoxemia, hypotension, bilateral pulmonary edema, transient leucopenia, and fever within 6 hours of transfusion. 10-20% fatal. Supportive care. Defer implicated donors.

Transfusion-associated graft-versus-host disease: Rare but almost always fatal. Immunosuppressed recipient receives transfusion from HLA-similar donor (usually a family member). Pancytopenia, maculopapular rash, diarrhea, hepatitis presenting 1-4 weeks after transfusion. Prevented by irradiating blood products.

Transfusion-associated circulatory overload (TACO): Approximately 1% of transfusions. New onset or exacerbation of acute respiratory distress (dyspnea, orthopnea, count) 3-6 hours after transfusion. May be associated with elevated BNP, elevated central venous pressure, left heart failure, positive fluid balance, pulmonary edema on chest x-ray. Risk factors include cardiac or renal dysfunction, female gender, age > 60 years, severe anemia with volume expansion, positive fluid balance, transfusion of multiple products. Mortality rate 1.4-8.3%. Management includes stopping transfusion and other fluids, sit patient up, supplemental oxygen, diuretic therapy.

Rating System and Implications of Recommendations

As indicated in this guide, evidence-based recommendations from the AABB guidelines are separately rated according to the strength of the recommendation (strong, moderate, or weak) and the quality of the supporting evidence (high, moderate, low, or very low). These ratings are intended to have the following implications (adapted from GRADE):

	High-quality evidence ←···→	Low-quality evidence
Strong recommendation ↕	Recommendation can apply to most patients in most circumstances.	Recommendation may change when higher quality evidence becomes available.
Weak recommendation	The best action may differ depending on circumstances or patient or societal values.	Other alternatives may be equally reasonable.

References

This pocket guide is 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 and Carson, JL, Guyatt G, Heddle NM, et al., Clinical Practice Guidelines from the AABB: Red blood cell transfusion thresholds and storage, *JAMA*, published online October 12, 2016. It also presents selected information from: Roback JD, Grossman, BJ, Harris T, Hillyer CD eds. Technical Manual, 17th Edition. Bethesda, MD: AABB Press 2011 and Circular of Information for the Use of Human Blood and Blood Components. AABB, ABC, ARC, ASBP. Revised December, 2009. GRADE adaptation based on Schünemann HJ et al., An official ATS statement: grading the quality of evidence and strength of recommendation in ATS guidelines and recommendations, *Am J Respir Crit Care Med* 2006;174(5):605–14.

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Dr. Weinstein declares no competing financial interests.

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