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Hemolytic Transfusion Reactions: Immune and Non-Immune-Mediated Hemolysis Associated with Transfusion

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INTRODUCTION

Hemolysis (or shortened red blood cell survival) in a patient receiving, or having recently received, a blood transfusion usually reflects an immune-mediated phenomenon properly referred to as an acute hemolytic transfusion reaction (AHTR). A reaction days to weeks following a transfusion, characterized by mild anemia and/or hyperbilirubinemia, is a delayed HTR. DHTRs are the result of anamnestic immune response, with the recipient generating antibodies that coat donor red blood cells (RBCs), causing extravascular hemolysis.

A number of non-immune-mediated causes of RBC destruction are associated with transfusion. These phenomena (sometimes referred to as "pseudo-hemolytic transfusion reactions") include RBC lysis caused by: thermal injury, osmotic injury, mechanical injury, infection, congenital hemolytic anemia, acquired hemolytic anemia, or drugs. This brief review will highlight both hemolytic and "pseudo-hemolytic" transfusion reactions, with emphasis on the mechanism of RBC destruction in each situation.

IMMUNE-MEDIATED HEMOLYSIS

AHTR: This medical emergency results from the rapid destruction of donor RBCs by preformed recipient antibodies, usually anti-A or anti-B (but occasionally anti-Rh or Kidd system antibodies) capable of fixing complement. The rapid intravascular hemolysis may lead to disseminated intravascular coagulation (DIC), shock, and acute renal failure. The classic presenting triad of fever, flank pain, and red or brown urine (i.e., hemoglobinuria) is rarely seen; fever and chills may be the only manifestation in conscious patients. For patients under anesthesia, or in coma, DIC may be the initial clue of an AHTR. When an AHTR is suspected, the transfusion must be stopped immediately, the patient hydrated with normal saline, and vigorous supportive care (to the patient's airway, blood pressure, urine output, and heart rate) applied while clerical and serologic investigation and notification of the blood provider is carried out.

DHTR: DHTRs most often are due to an anamnestic antibody response occurring after re-exposure to a foreign RBC antigen (often of the Kidd or Rh system) previously encountered via transfusion, transplantation, or pregnancy. Occurring anywhere from 3-21 days after transfusion, they are characterized by extravascular hemolysis (sequestration and removal of antibody-coated RBCs by macrophages in the spleen) that usually is gradual and less severe than with AHTRs. A falling hematocrit, slight fever, mild increase in serum unconjugated bilirubin, and spherocytosis on the blood smear may be found in association with a new positive direct antiglobulin test (DAT) and a change in antibody test results. In the absence of brisk hemolysis, no treatment is required (other than replacement RBCs, if indicated).

TABLE 1. Hemolysis Associated with Transfusion

- **Immune-Mediated**
  - **Acute Hemolytic Transfusion Reaction (AHTR)**
  - **Delayed Hemolytic Transfusion Reaction (DHTR)**
- **Non-Immune-Mediated**
  - **Thermal Injury**
    - **Heat**
    - **Cold**
  - **Osmotic Injury**
  - **Mechanical Injury**
  - **Infection**
  - **Congenital Hemolytic Anemia**
  - **Acquired Hemolytic Anemia**
  - **Drugs**

NON-IMMUNE-MEDIATED HEMOLYSIS

Thermal Injury: Thermal injury occurs when transfused blood is too hot or too cold.

Heat: RBCs cannot tolerate temperatures above 40°C. The RBC membranes become damaged, leading to changes in viscosity, fluidity, deformability, permeability, and osmotic fragility. These RBCs lyse or are rapidly cleared from the circulation by the spleen.

In-line blood warming devices must be standardized to prevent warming the blood above 38°C. Other methods of warming blood, such as the use of microwaves or phototherapy units, or simply holding the unit under uncontrolled hot water, should be avoided.

Cold: RBCs exposed to below freezing temperatures without a cryoprotective agent (such as glycerol) can sustain either a dehydration injury, if the freezing rate is slow (less than 10°C/min), or membrane damage caused by intracellular ice crystal formation, if the freezing rate is rapid (more than 10°C/min). In either situation, RBC hemolysis occurs prior to transfusion and occasionally can be detected by observing purplish discoloration of the contents of the blood bag. Additionally, inadequately deglycerolized RBCs can undergo

intravascular osmotic lysis when transfused; one such death of a 1,000g infant.

Osmotic Injury: RBCs are sensitive to osmotic pressures and will hemolyze rapidly when admixed with hypotonic solutions. To prevent this, only isotonic solutions are mixed with RBCs, *e.g.*, 0.9% ("normal") saline, ABO-compatible plasma and 5% albumin. RBCs must not be mixed with any drug, any hypotonic solution (such as 5% dextrose, 5% dextrose in 0.225% saline, 3.3% dextrose in 0.3% saline, or 0.45% saline). Lactated Ringer's solution should not be added to red blood cells because the calcium in this solution can chelate the citrate in the anticoagulant/preservative and lead to clot formation in the unit. Finally, attention must be directed towards the occasional (inadvertent) administration of a hypotonic solution, *e.g.*, distilled water accidentally substituted for normal saline as a diluent either directly into the patient's circulation leading to intravascular hemolysis, or indirectly, when a hypotonic solution has been used for bladder irrigation after prostate surgery.

Mechanical Injury: Donor RBCs can be damaged during transfusion by mechanical forces created during their passage through fine needles, narrow openings, kinked or twisted intravenous lines, mechanical pumps or forced expression. Both donor and recipient RBCs are susceptible to lysing by artificial cardiac valves or by transit through extracorporeal circulation devices used in cardiac surgery, hemodialysis, plasmapheresis, or cytapheresis.

Microbial Contamination: An estimated 0.1 - 0.3% of blood is contaminated at collection. Given differing storage conditions, and the ability of microorganisms to grow under such conditions, the risk of sepsis after RBC transfusion is estimated at one in 1.5 million. In the absence of a definitive culture, bacterial contamination of RBC units can be suspected if the unit is observed to contain particulate matter or clots, gross hemolysis, a change in color and/or the presence of gas. Patients transfused with bacterially-contaminated blood can manifest all of the symptoms of an AHTR, including fever, chills, hypotension, tachycardia, shock and even hemoglobinemia and hemoglobinuria. Although much less frequent, transfusion of a unit contaminated by a malarial protozoan could manifest as unexplained fevers several days to weeks after transfusion, thereby mimicking a DHTR. Any suspicion that a contaminated unit is being infused should be met by immediate discontinuation of the transfusion, attention to the patient's clinical status, careful evaluation of the blood bag for contaminating microorganisms, and notification of the blood provider.

Congenital Hemolytic Anemia: RBCs from donors with certain forms of congenital hemolytic anemia can hemolyze in the recipient, mimicking an acute or delayed HTR. The most common such hemolytic anemia is glucose-6-phosphate dehydrogenase (G6PD) deficiency. RBCs with this enzyme deficiency are susceptible to lysis when exposed to oxidant stress, *e.g.,* when exposed to certain drugs (vitamin K, primaquine, and others), the ingestion of fava beans, or alterations in plasma pH. G6PD-deficient RBCs will survive almost normally in recipients not subjected to oxidant stress, with the exception of premature infants, in whom hemolysis has been reported without oxidant stress. Finally, RBCs from donors with sickle cell trait, while able to survive normally in most recipients, have been shown to have shortened survival in recipients subjected to hypoxic conditions.

circumstance was reported to have caused the

Acquired Hemolytic Anemia: At least two forms of acquired hemolytic anemia can contribute to hemolysis in conjunction with a transfusion: paroxysmal nocturnal hemoglobinuria (PNH) and autoimmune hemolytic anemia (AIHA). Since the RBCs of patients with PNH have enhanced sensitivity to the action of complement, any antigen-antibody reaction capable of activating complement (donor RBC-recipient antibody; donor white blood cell-recipient antibody; recipient RBC-donor antibody, etc.) can trigger hemolysis in a recently transfused patient with PNH. In patients with AIHA, autoantibody induced lysis of transfused RBCs can either mimic or mask alloantibody induced hemolysis. A thorough search for underlying alloantibodies in patients with AIHA is essential prior to transfusion.

Drugs: A number of drugs and chemical agents can cause either immune or non-immune hemolysis and, in the appropriate patient population, mimic an HTR. The list of drugs includes those contributing to an oxidant stress, high dose cyclophosphamide, ribavirin, pegylated interferon, Rho (D) immune globulin, and penicillin, quinidine, and cephalosporins. Lead and copper have been reported to cause hemolysis following acute, toxic exposure or as a result of inherited metabolic disorders such as Wilson's disease. Hemolysis caused by exposure to a toxic chemical or drug must be ruled out when available evidence does not irrefutably establish transfusion as the cause of hemolysis.

General References

Beauregard P and Blajchman MA. Transfusion Med Rev 1994; 8:184-99.

Ismeno G et al. Int J Cardiol 1999; 69:179-83

Capon SM and Goldfinger D. Transfusion 1995;35:513-20.

Andreu G *et al*. Transfusion 2002;42:1356-64.

Williamson LM. Transfusion 2002;42:1249-52.

Pineda AA *et al*. Transfusion 1999;39:1097-103.

Hillmen P *et al*. N Engl J Med 2004;350:552-9.

Davenport, RD *et al*.. Transfusion 1993;33:19-24.

Kowdley KV.. J Clin Gastroenterol 2005;39(1 Suppl):S3-8.

Gertz MA.. Clin Lymphoma 2005;5:290-3.

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