Haemolytic Transfusion Reaction: Critical Issues

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INTRODUCTION

Transfusion of blood and its product is generally a safe and effective way of correcting hematological defects but adverse effects do occur during or after transfusion and they are commonly called blood transfusion reactions. These untoward effects vary from being relatively mild to lethal and some of them can be prevented while others cannot. Medical personnel who order and administer transfusions should be able to recognize transfusion reaction so that appropriate actions can be taken promptly.

There are four broad categories of transfusion reactions:
1. Acute immunologic(<24hrs)
2. Acute non immunologic(<24hrs)
3. Delayed immunologic(>24hrs)
4. Delayed non immunologic(>24hrs)

Hemolytic transfusion reactions (HTR) can occur in the first three categories mentioned above. HTR is due to the accelerated clearance or lysis of transfused red cells because of immunologic or non immunologic mechanisms. The great majority of HTRs are a result of Red Blood Cell (RBC) transfusion. However, HTRs may also result from transfusion of plasma-containing blood components, such as Fresh Frozen Plasma or Platelets, which contain red cell antibodies but very few, if any, red cells.

A few signs and symptoms that are typically associated with transfusion reactions can aid in their recognition.

- Fever with or without chills associated with transfusion
- Shaking chills
- Pain at the infusion site or in the chest, abdomen or flanks
- Hypertension or hypotension
- Respiratory distress including dypnea, tachypnea, wheezing or hypoxemia
- Skin changes like urticaria, flushing, angioedema or pruritis.
- Nausea and vomiting.
- Darkened urine or jaundice.
- Bleeding or other manifestations of a consumptive coagulopathy.

IMMUNE TRANSFUSION REACTIONS
Pathophysiology and manifestations

Very severe hemolytic reactions occur when transfused red cells interact with preformed antibodies in the recipient. However the interaction of transfused antibodies with the recipient's red cells rarely causes symptoms. Antigen antibody interaction on the red cell membrane can initiate a sequence of complement activation, cytokine and coagulation effects, and other elements of a systemic inflammatory response that result in clinical manifestations of a severe acute hemolytic transfusion reaction (HTR). Severe symptoms can occur after the infusion of even 10-15ml of ABO incompatible red cells. In anaesthetized patients the initial manifestations of an acute HTR may be hemoglobinuria, hypotension or diffuse bleeding at the surgical site. Severe acute HTRs are usually caused by ABO incompatibility, but rarely may be caused by antibodies with other specificities due to anti-Pk, anti-Vel or rarely anti-Le^a (Lewis), anti-Jk^a, anti-Jk^b (Kidd) or anti-K1 (Kell) antibodies or due to effect of drugs. Eg. cefotetan.
**Complement activation:**
The binding of antibody to blood group antigens activates complements. C3 activation releases the anaphylotoxin C3a; red cells are coated with C3b and are removed by phagocytes. When the complement cascade proceeds to completion a membrane attack complex is formed and intravascular hemolysis results with the production of C5a, a potent anaphylotoxin. Intravascular hemolysis results in hemoglobinemia and hemoglobinuria. Anaphylotoxin causes hypotension, bronchospasm, urticaria, chest and abdominal pain and vomiting.

**Cytokines:**
Some of the effects of alloimmune hemolysis are mediated by inflammatory cytokines like TNF alpha, interleukin 1b and 6(IL 1b,IL 6), and chemokines like IL8 and monocyte chemoattractant protein(MCP). The complete role of cytokines in the consequences of immune hemolysis remains to be defined.

**Coagulation activation:**
Both activated complement components as well as cytokines like TNF alpha and IL1b may increase the expression of tissue factor by leucocytes and endothelial cells. Tissue factor activates the coagulation pathway resulting in disseminated intravascular coagulation. This can result in a hemorrhagic diathesis characterized by generalized oozing or uncontrolled bleeding.

**Shock:**
Shock is mediated by anaphylotoxins, kinins, vasoactive amines and cytokines. Hypotension provokes a compensatory sympathetic system response that produces vasoconstriction in renal, pulmonary, splanchnic and cutaneous capillaries.

**Renal Failure:**
Renal failure in acute HTR is multifactorial contributed by hypotension, renal vasoconstriction, antigen antibody complex deposition formation of thrombi in the renal vasculature and toxicity due to free hemoglobin.

**Frequency**
The most common causes of ABO-incompatible transfusion are clerical and other human errors leading to mistaken identity. A study of reported transfusion errors in New York over a 10-year period in the 1990s estimated the incidence of ABO incompatible red cell transfusions at 1:38,000⁶. A study of 3601 institutions by the College of American Pathologists found 843 acute HTRs reported over a 5-year period, of which 50(6%) were fatal⁴. The Serious Hazards of Transfusion (SHOT) initiative in the United Kingdom and Republic of Ireland reported 161 cases of ABO-incompatible transfusion, with nine fatal cases in 5 years⁵.

**Treatment**
The treatment of an acute HTR depends on its severity⁸. Vigorous treatment of hypotension and promotion of adequate renal blood flow are priority. Renal perfusion should be monitored by measurement of urine output, with a goal of maintaining urine flow rates above 100 mL/hour in adults for at least 18 to 24 hours. The usual first support is intravenous normal saline, but it is important to avoid overhydration especially in patients with pre-existing cardiac or renal disease. Invasive monitoring of pulmonary capillary wedge pressure is recommended in guiding fluid therapy in the face of hemodynamic instability. Diuretics help to improve blood flow to the kidneys and increase urine output. Intravenous furosemide at a dose of 40 to 80 mg for an adult or 1 to 2 mg/kg for a child not only has a diuretic effect but also improves blood flow to the renal cortex. This dose may be repeated once, and the patient should be adequately hydrated. The use of low-dose dopamine(2-5 µg/kg/minute), as an agent to protect renal function, has been recommended in the management of acute HTRs. However, evidence suggests that it is not effective in this role, and it has many toxicities⁹. Consumptive coagulopathy may be the initial presentation in an anesthetized patient. The use of heparin is controversial. Administration of Platelets, Fresh Frozen Plasma (FFP), and Cryoprecipitated AHF, a source of fibrinogen and Factor VIII, may be necessary. Red cell exchange may be considered in patients with a significant load of circulating incompatible red cells. Because medical management of an acute HTR is often complicated and may require aggressive interventions such as hemodialysis, consultation with specialists in critical care medicine may be prudent when treating a patient with a severe acute HTR.

**Prevention**
The best hope for prevention lies in preventing or detecting errors in every phase of the transfusion process. In each institution, there should be systems designed to prevent and detect errors in patient and unit identification at the time of phlebotomy, at all steps in laboratory testing, at the time of issue, and when the transfusions are given. The SHOT reports particularly emphasize the importance of the bedside check at the time of transfusion. All clinical staff should recognize the signs of acute reactions and stop the transfusion before a critical volume of blood has been
administered.

NONIMMUNE-MEDIATED HEMOLYSIS

Causes
- Thermal exposure of transfused red cells
- Mechanically hemolysed red cells
- Chemically effected red cells
- Blood infected with bacteria
- Hyperkalemia

Red cells may undergo in-vitro hemolysis if the unit is exposed to improper temperatures during shipping or storage or is mishandled at the time of administration. Malfunctioning blood warmers, use of microwave ovens or hot waterbaths, or inadvertent freezing can cause temperature-related damage. Mechanical hemolysis may be caused by the use of roller pumps (such as those used in cardiac bypass surgery), pressure infusion pumps, pressure cuffs, or small-bore needles. Osmotic hemolysis in the blood bag or infusion set may result from the addition of drugs or hypotonic solutions. Inadequate deglycerolization of frozen red cells may cause the cells to hemolyze after infusion. Hemolysis may also be a sign of bacterial growth in blood units. Transfusion reactions due to bacterial contamination are commonly caused by endotoxins produced by bacteria capable of growing in cold temperature such as pseudomonos species, Escherichia coli and Y. enterocolitica. They are commonly attributed to platelet transfusion because platelets are stored at 20 - 24°C.

In a patient with transfusion-associated hemolysis for which both immune and nonimmune causes have been eliminated, an intrinsic red cell defect, such as glucose-6-phosphatase dehydrogenase deficiency in either patient or donor causing coincidental hemolysis should be considered.

Treatment
Treatment depends on the severity of the reaction. If the patient develops a severe reaction with hypotension, shock, and renal dysfunction, intensive clinical management is indicated even before the cause of the mishap is investigated. If the patient exhibits only hemoglobinemia and hemoglobinuria, supportive therapy might be sufficient.

Prevention
There should be written procedures for all aspects of procuring, processing, and issuing blood, and administering transfusions. All staff should be trained in the proper use of equipment, intravenous solutions, and drugs used during the administration of blood and blood components. Equipment must be properly maintained and records kept of how and when items are used. Care must be exercised in the selection and use of intravenous access devices.

EVALUATION OF A SUSPECTED ACUTE TRANSFUSION REACTION

The Role of Clinical Personnel Attending the Patient
Medical personnel attending the patient are generally the first to suspect that a transfusion reaction has occurred and the first to take action. The appropriate actions should be specified in the institution’s patient care procedures manual, and transfusion service personnel should be prepared to act as consultants.

1. The transfusion should be stopped to limit the volume of blood infused.
2. All labels, forms, and patient identification should be checked to determine whether the transfused component was intended for the recipient.
3. An intravenous line should be maintained with normal saline.
4. The transfusion service and the patient’s physician should be notified immediately. A responsible physician should evaluate the patient to determine whether a transfusion reaction is a possibility, what kind it might be, and what immediate actions should be undertaken.
5. If there is any possibility of acute HTR a post reaction blood sample(s) should be sent to the laboratory for evaluation. The specimen(s) must be carefully drawn to avoid mechanical hemolysis and must be properly labeled. In addition, the transfusion container with whatever contents remain, the administration set (without the needle), and the attached intravenous solutions should be sent to the laboratory, following standard precautions. In some cases, a post reaction urine sample will be useful.

The Role of the Laboratory
Whenever hemolysis is a possibility, the laboratory should perform the following three steps:

1. Check for Identification Errors:
The identification of each patient’s sample and the blood component(s) must be checked for errors. If an error is discovered, the patient’s physician or other responsible health-care professional must be notified immediately, and a search of appropriate records should be initiated to determine whether misidentification or incorrect issue of other specimens or components has put other patients at risk. Once the acute crisis has passed, each step of the
transfusion process should be reviewed to find the source of error.

2. **Visual Check for Hemolysis:**
The serum or plasma in a postreaction blood specimen must be inspected for evidence of hemolysis and compared with a pre reaction sample. Pink or red discoloration after, but not before, the reaction suggests destruction of red cells and release of free hemoglobin. Intravascular hemolysis of as little as 2.5 mL of red cells may produce visible hemoglobinemia \(^ \text{12}\). Hemolysis resulting from poor collection technique or other medical interventions can cause hemoglobinemia; if faulty sampling is suspected, examination of a second specimen will resolve the question. Myoglobin, released from injured muscle, may also cause pink or red plasma and might be suspected if a patient has suffered severe trauma or muscle injury \(^ \text{13}\). In examining a postreaction urine specimen, it is important to differentiate among hematuria, hemoglobinuria and myoglobinuria. In acute HTRs hemoglobinuria would be expected.

3. **Serologic Check for Incompatibility:**
A Direct Coomb’s test (DCT) must be performed on a postreaction specimen, preferably one anticoagulated with EDTA to avoid in-vitro coating of red cells by complement proteins. If the postreaction DCT is positive, a DCT should be performed on red cells from the pretransfusion specimen and compared. If the transfused cells have been rapidly destroyed, the postreaction DCT may be negative. If both the pre- and postreaction DCTs are positive, further workup is required to rule out incompatibility. Comparison of the graded strength of these two tests is not a reliable method to rule this out. Nonimmune hemolysis causes hemoglobinemia but not a positive DCT. The recipient’s ABO type must also be confirmed on the postreaction specimen.

**Additional Laboratory Evaluation:**
If any of the three initial checks and tests gives positive results, the diagnosis of an acute HTR should be actively pursued. Even if no error or apparent incompatibility is found, the possibility of an acute HTR should still be considered if the patient’s clinical presentation is consistent with such a reaction. The tests listed below help characterize the cause of the HTR.

1. If ABO and Rh typing on the prereaction and postreaction samples do not agree, there has been an error in patient or sample identification, or in testing. It is important to check the records of all specimens received at approximately the same time.
2. Perform ABO and Rh testing on blood from the unit or an attached segment. If blood in the bag is not of the ABO type noted on the bag label, there has been an error in unit labeling.
3. Perform antibody detection tests on the prereaction and postreaction samples and on the donor blood. If a previously undetected antibody is discovered, it should be identified. Once the antibody has been identified, retained samples from transfused donor units should be tested for the corresponding antigen.
4. Repeat crossmatch tests, with prereaction and postreaction samples in parallel using the antiglobulin technique. A positive crossmatch in the face of a negative antibody screening test may indicate the presence of an antibody directed against a low incidence blood group antigen.
5. Perform DAT and antibody detection tests on additional specimens obtained at intervals after the transfusion reaction even if a first postreaction sample has serologically undetectable levels of a significant alloantibody.
6. Perform frequent checks of the patient’s hemoglobin values, to see whether the transfused cells produce the expected therapeutic rise, or whether a decline occurs after an initial increase. In complex cases, phenotypic differences between autologous and transfused cells quantitated by flow cytometry have been used to follow survival \(^ \text{14}\).
7. In-vivo red cell survival studies have been used to demonstrate the rare occurrence of an acute HTR in the absence of detectable alloantibody \(^ \text{15}\). If an antigen is present on the donor’s red cells and absent from those of the patient, its presence or absence in postreaction samples indicates whether the transfused cells have survived and remained in the circulation.
8. Markers of hemolysis, including lactate dehydrogenase, unconjugated bilirubin, and haptoglobin levels, may be useful.
9. Examine the blood remaining in the unit and the administration tubing for evidence of hemolysis, especially if no immune explanation for hemolysis can be demonstrated.

**DELAYED CONSEQUENCES OF TRANSFUSION**

**Alloimmunization to Red Cell Antigens & Delayed Reactions**

**Pathophysiology:**
Primary alloimmunization, evidenced by the appearance of newly formed antibodies to red cell antigens, becomes
apparent weeks or months after transfusion. If red cells that express the antigen are subsequently transfused, an anamnestic response may cause the appearance of IgG antibodies that react with the transfused red cells. If the clinical laboratory discovers an anamnestic response, both the transfusion service director and the patient’s clinician should be notified and the possibility of a delayed HTR (DHTR) should be investigated. The most common presentation of a DHTR is a declining hemoglobin and a newly positive antibody screen, but fever, leukocytosis, and mild jaundice may be present. Some DHTRs present as the absence of the anticipated increase in hemoglobin after transfusion. DHTRs may be particularly problematic in patients with sickle cell disease, where hemolysis may include autologous red cells, a phenomenon termed sickle cell hemolytic transfusion reaction syndrome. If a DHTR is suspected, a freshly obtained blood sample may be tested for unexpected alloantibodies, both in the serum and, by DCT, on the red cells.

**Treatment**

Specific treatment is rarely necessary. If transfusion is still necessary, donor red cells should lack the antigen corresponding to the newly discovered antibody.

**Prevention**

Future transfusions for the patient should lack the antigen(s) responsible for the anamnestic response. Standards for Blood Banks and Transfusion Services mandates permanent preservation of records of clinically significant antibodies, and review of previous records before red cells are issued for transfusion. Prospective antigen matching may prevent DHTRs in selected patients, particularly those with sickle cell disease.

**REFERENCES**