**Transfusion Reactions:** Transfusion reactions are divided into those which are usually febrile and those which are usually non-febrile; also into those which are acute (within the first 24 hours) and those which are delayed. In all cases of suspected transfusion reaction, the first thing to do is to **stop the flow** of transfused blood, but keep the IV line open with saline. The blood product bag must be returned to the Blood Bank, along with freshly drawn phlebotomy samples, to be used in determination of the type of transfusion reaction.

### Febrile Acute Transfusion Reactions:

### Acute Hemolytic Transfusion Reaction (AHTR):

The incidence of AHTR is approximately one per 25,000 units, with 10% mortality. Most often AHTR is due to RBCs incompatible with antibodies in the recipient's plasma, but may also be caused by donor antibodies in the plasma component incompatible with recipient red blood cells during Platelet or Plasma transfusions. AHTR is caused by acute immune-mediated destruction of transfused RBCs, due to alloantibodies directed against ABO, Rh, Kell, or other RBC antigen(s). The chief determinant for severity of AHTR, both of morbidity and mortality, is the volume of transfused incompatible blood. Most frequent symptoms are: Fever and Chills. Other symptoms may be pain at the infusion site, flank pain, hypotension or shock, and/or disseminated intravascular coagulation. In an anesthetized patient, increased intraoperative bleeding (due to DIC) or hypotension or hemoglobinuria may be the only symptoms of AHTR. Occasionally the initial symptom of AHTR may be limited to a generalized sense of discomfort ("I'm feeling bad.")

Initial response: Stop the flow of transfused blood, but keep IV line open with saline. Keep urine output greater than 1 mL/Kg/hr. Consider mannitol to maintain urine output, or low dose dopamine if hypotension. Consider immediate exchange transfusion if a large volume of incompatible blood has been transfused.

#### Transfusion-related Acute Lung Injury (TRALI):

The incidence of TRALI is approximately one per 1,000 units, with 10% mortality. Most often TRALI is due to Plasma or Platelet transfusions, due to the relatively greater volume of plasma, but TRALI may also be due to transfusion of RBCs or Cryoprecipitate. TRALI is due to anti-neutrophil or anti-HLA antibodies of the donor causing pulmonary microvascular injury. TRALI is defined as acute respiratory distress syndrome (ARDS) within 6 hours of transfusion, with clinical symptoms of hypoxemia (dyspnea) and bilateral pulmonary infiltrates by chest X-ray, and is usually accompanied by fever. The differential diagnosis includes transfusion-associated circulatory overload (TACO), also acute lung injury and other non-transfusion-related causes of acute pulmonary edema. Many blood donation centers are attempting to reduce the incidence of TRALI by not supplying Plasma obtained from females, the demographic group most likely to

have anti-neutrophil or anti-HLA antibodies, resulting from exposure during pregnancy.

Initial response: Treatment includes supplemental oxygen and ventilatory support, possibly intubation. Unlike TACO, TRALI does <u>not</u> respond to diuretics, because TRALI is due to damage of pulmonary microvasculature, with leakage, causing pulmonary edema. TRALI usually resolves in 1 to 2 days.

# Septic Transfusion Reaction (Transfusion-related Sepsis):

The incidence of transfusion-related sepsis is approximately one per 100,000 Platelet units and one per 500,000 RBC units, with 50% mortality. Most often TR-Sepsis is due to bacterially contaminated platelets (most frequently Staphylococci or Streptococci), less frequently due to contaminated RBC's [most often Yersinia enterocolitica (60%), occasionally Pseudomonas sp. or other Gram negatives]. TR-sepsis presents with rapid onset of high fever, rigors, chills, abdominal cramps, hypotension or shock, and disseminated intravascular coagulation. Symptoms usually begin <u>early</u> during the transfusion.

Initial response: Stat IV antibiotics. Consider vasopressors for shock and/or heparin for DIC.

## Febrile Non-hemolytic Transfusion Reaction (FNHTR):

The incidence of FNHTR is 1% of transfusions, essentially due only to RBC or Platelet transfusions. The incidence is reduced to 0.1% by leukoreduced blood products, preferably by pre-storage leukoreduction. FNHTR is defined as 1°C rise in temperature within 2 hours of transfusion, occasionally with chills or rigors. The fever tends to begin <u>later</u> during, or after, the transfusion (unlike septic transfusion).

Initial response: Antipyretic medication. If history of previous FNHTR, may pre-medicate with antipyretic.

# Non-febrile Acute Transfusion Reactions:

## Transfusion-related Circulatory Overload (TACO):

The incidence of TACO is uncertain due to ambiguities of pre-existing conditions. The chief determinants of severity are volume and rapidity of transfusion, as well as patient pre-existing conditions. Patients at risk for TACO include those with congestive heart failure, liver failure, renal failure, chronic anemia (due to the pre-existing compensatory increase in plasma volume), and also premature newborns, though less likely with term newborns. Symptoms are similar to TRALI, with rapid onset of pulmonary edema and bilateral pulmonary infiltrates by chest X-ray. Unlike TRALI, TACO usually does not cause a fever. Also unlike TRALI, TACO has symptoms of systemic circulatory overload, including jugular venous distension, systolic hypertension, tachycardia, increased pulmonary wedge pressure, and often elevated BNP.

Initial response: Sit up patient or put in reverse Trendelenburg. Diuretics. Supplemental oxygen as needed. Prophylaxis for patients with known risks includes reduction of infusion rate to 1 mL/Kg/hr, and one may also ask the Blood Bank to split units into aliquots, or for volume-reduced units. (See **Special Attributes**). One may also consider CPD-RBCs (less volume), rather than AS-1 or AS-3 RBCs (see **RBCs**).

## Allergic/Urticarial Transfusion Reaction:

Incidence is approximately 1% of transfusions. A/UTR is usually due to hypersensitivity to medication, food metabolite, or other antigen in donor blood product. A/UTR is usually limited to localized urticaria, but occasionally may have pulmonary wheezing, or rarely laryngeal edema.

Initial response: IV antihistamine, i.e. diphenhydramine. Consider SQ epinephrine if wheezing. Consider IV epinephrine if laryngeal edema. If history of previous allergic/urticarial reaction, may premedicate with antihistamine.

#### Anaphylactic/Anaphylactoid Transfusion Reaction:

Incidence is approximately one per 20,000 units, with 2% mortality. Defined as anaphylactic shock during transfusion, and usually occurs <u>early</u> in the transfusion. Most often anaphylactic reactions occur in IgA deficient recipients (approximately 0.1% of the population), usually in recipients pre-sensitized by previous transfusion. Rarely may be caused by hypersensitivity to medication, food metabolite, or other antigen in donor blood product.

Initial response: IV epinephrine.

### Hyperkalemia:

RBC transfusion poses possible risk for hypekalemia in premature, and to a lesser degree, term newborns. The risk is lessened with 'fresh' CPD RBCs (6 days or less since collection). Symptoms are vague, so EKG monitoring is recommended. Consider washed RBCs for prophylaxis.

Initial response: If potassium exceeds 6.5 mmol/L, consider IV insulin ± glucose, or IV bicarbonate.

## Hypocalcemia (Citrate toxicity):

There is risk of transient hypocalcemia due to citrate (anticoagulant) binding of calcium, especially during rapid infusion of blood product(s) or during apheresis (plasma exchange). Because citrate is metabolized in the liver, patients with hepatic failure or in hypotensive shock with reduced hepatic bloodflow are at greater risk, especially if rapid transfusion is given via a deep central intravenous line. The earliest symptom is usually paresthesia, most often perioral tingling.

Initial response: Oral calcium carbonate (Tums tablets), or rarely IV calcium chloride, if tetany or electrocardiographic signs.

#### **Transient Hypotensive Reaction:**

Patients on angiotensin-converting enzyme (ACE) inhibitors may experience sudden onset of hypotension and flushing when receiving RBCs or platelets via bedside-filter leukoreduction, or during apheresis (plasma exchange), due to bradykinin released by white cells in contact with the filter.

## Hypothermia:

In general, blood warming devices are not recommended because of the risk of heat-related hemolysis of transfused RBCs; however, rapid transfusion of large volumes of blood can lower core body temperature with attendant risk for cardiac arrhythmia. Only FDA-approved blood warming devices should be used.

## Febrile Delayed Transfusion Reactions:

#### **Delayed Hemolytic Transfusion Reaction (DHTR):**

The incidence of DHTR is approximately one per 5000 units. DHTR is usually due to an anamnestic (rarely primary) antibody response to an RBC antigen, by immune memory cells inciting the re-production of an antibody not detectable during the pre-transfusion antibody screen done by the Blood Bank. Most often the antibody is directed at Kidd, Duffy, or Kell antigens. DHTR may present as anemia without other symptoms, but often has fever (50%) and 'flu' symptoms, occasionally also jaundice (10%) with elevated bilirubin and elevated lactate dehydrogenase (LDH). DHTR usually occurs within 1 to 3 weeks of transfusion.

Initial response: Most often no treatment is indicated, but if significant hemolysis, then is treated similarly to AHTR.

Hyperhemolysis syndrome is a rare type of DHTR, almost only seen in patients with sickle cell disease, with life-threatening hemolysis initiated by an anamnestic (rarely primary) antibody response, resulting in immune-mediated destruction of both transfused RBCs **and** the recipient's **own** RBCs, which may also include destruction of RBC precursor cells in the bone marrow. In the work-up, the direct antiglobulin test (DAT) may be negative and no new RBC antibody may be found.

Initial response: Treatment of hyperhemolysis syndrome includes IVIG and steroids in addition to the standard treatment for AHTR. Avoid transfusion of RBCs if possible, as that may exacerbate the acute hemolysis, even when phenotypically-matched RBCs are administered.

# Transfusion-associated Graft Versus Host Disease (TA-GVHD):

TA-GVHD almost always causes death within 1 to 2 months, and is caused by engraftment of donor T lymphocytes, which attack recipient tissues. TA-GVHD usually presents with fever one week after transfusion, then skin rashes and diarrhea, followed by pancytopenia and death. Patients at risk for TA-GVHD include preterm newborns and fetuses receiving intrauterine transfusion, patients with aplastic anemia, bone marrow transplant patients, patients with hematological malignancies (especially Hodgkins disease), patients receiving high dose chemotherapy (especially purine analogs) and/or whole body radiation, patients receiving granulocyte transfusions, and patients with congenital T cell immunodeficiencies (i.e. Wiskott-Aldrich syndrome, Di George syndrome, and subacute combined immunodeficiency). Many neonatologists also consider term newborns to be at some risk. Also at risk for TA-GVHD are patients receiving HLA-matched platelets and patients receiving blood donated by a first degree relative, because in these instances, there is risk that donor T cells will not be recognized as "non-self", and thus not destroyed by the recipient's immune system.

Initial Response: TA-GVHD has a uniformly dismal prognosis of death within several months. If the clinical circumstances indicate any risk factors, then **all** RBC and Platelet products **must** be irradiated prior to transfusion, which causes all transfused T lymphocytes to become incapable of proliferation. Leukoreduction does NOT prevent TA-GVHD.

### Non-febrile Delayed Transfusion Reactions:

#### **Post-transfusion Purpura (PTP):**

The incidence of PTP is approximately one per 500,000 units, with less than 1% mortality when treated. PTP is due to an anamnestic (rarely primary) antibody response, resulting in immune-mediated destruction of both transfused platelets **and** the recipient's **own** platelets (The pathophysiology has similarities to hyperhemolysis syndrome, where there is destruction of both transfused and recipient RBCs.) Onset of severe thrombocytopenia occurs 1 to 2 weeks after transfusion with symptoms of cutaneous petechiae (usually on legs), occasionally ecchymoses (usually on forearms), bleeding from nose or gums, menorrhagia, or blood in urine or stool.

PTP is most often caused by platelet transfusions, but may also be caused by RBCs (which contain nonfunctional 'passenger' platelets), and may also rarely be caused by maternal alloimmunization (sensitization) during pregnancy to paternal platelet-specific or HLA antigens on fetal platelets.

There are two different types of PTP: Most frequently (about <sup>3</sup>/<sub>4</sub>) PTP is due to an anamnestic antibody response by an alloantibody to a high incidence platelet-specific antigen (usually HPA-1a, which is present on the platelets of 99% of the population). Previous sensitization to HPA-1a is by exposure during pregnancy or previous transfusion, and female:male ration is 5:1. PTP is less frequently due to an anamnestic antibody response directed against high frequency class 1 HLA antigen(s) on transfused platelets.

Initial response: PTP usually responds to IVIG, but may require plasma exchange by aferesis. Avoid platelet transfusion if possible, as that may exacerbate the acute thrombocytopenia, but if necessary, PTP may require transfusion of HPA-1a negative platelets, or HLA-matched platelets, depending on reference laboratory's determination of causative antibody(s).

# Iron Overload:

Patients with chronic anemia (i.e. thalassemia major, aplastic anemia, Diamond-Blackfan syndrome, sickle cell disease and other hemoglobinopathies, etc.) who receive more than about 100 transfusions will incur permanent tissue damage to the heart, liver, and endocrine organs unless given iron chelation medication. Treatment is deferoxamine.

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