complement. They most commonly stem from an error in patient identification or tube labeling that allows a patient to receive an ABO incompatible unit of blood. Pre-existing high affinity "natural" IgM antibodies, usually against polysaccharide blood group antigens A or B, bind to red cells and rapidly induce complement mediated lysis, intravascular hemolysis, and hemoglobinuria. Fever, shaking chills, and flank pain appear rapidly. The direct Coombs test is typically positive, unless all of the donor red cells have lysed. The signs and symptoms are due to complement activation rather than intravascular hemolysis *per se*, as osmotic lysis of red cells (e.g., by mistakenly infusing red cells and 5% dextrose in water simultaneously) produces hemoglobinuria without any of the other symptoms of a hemolytic reaction. In severe cases the process may rapidly progress to DIC, shock, acute renal failure, and occasionally death.

***Delayed hemolytic reactions* are caused by antibodies that recognize red cell antigens that the recipient was sensitized to previously, for example, through a prior blood transfusion.** These are typically caused by IgG antibodies to foreign protein antigens and are associated with a positive direct Coombs test and laboratory features of hemolysis (e.g., low haptoglobin and elevated LDH). Antibodies to antigens such as Rh, Kell, and Kidd often induce sufficient complement activation to cause severe and potentially fatal reactions identical to those resulting from ABO mismatches. Other antibodies that do not fix complement typically result in red cell opsonization, extravascular hemolysis, and spherocytosis, and are associated with relatively minor signs and symptoms.

Transfusion-Related Acute Lung Injury

TRALI is a severe, frequently fatal complication in which factors in a transfused blood product trigger the activation of neutrophils in the lung microvasculature. The incidence of TRALI is low, probably less than 1 per 10,000 transfusions, but it may occur more frequently in patients with preexisting lung disease. Though its pathogenesis is incompletely understood, current models favor a "two hit" hypothesis. The first is a priming event that leads to increased sequestration and sensitization of neutrophils in the microvasculature of the lung. It is postulated that this event may involve endothelial activation, for example by inflammatory mediators. The primed neutrophils are then activated by a factor present in the transfused blood product, which constitutes the second hit.

A variety of factors have been implicated as "second hits", but the leading candidates are antibodies in the transfused blood product that recognize antigens expressed on neutrophils. By far the most common antibodies associated with TRALI are those that bind major histocompatibility complex (MHC) antigens, particularly MHC class I antigens. These antibodies are often found in multiparous women, who generate such antibodies in response to foreign MHC antigens expressed by the fetus. Rarely, donor antibodies to neutrophil-specific antigens trigger TRALI. Although TRALI has been associated with virtually all plasma-containing blood products, it is more likely to occur following transfusion of products containing high levels of donor antibodies, such as fresh frozen plasma and platelets. The presentation is dramatic, sudden onset respiratory failure, during or soon after a transfusion. Diffuse bilateral pulmonary infiltrates that do not respond to diuretics are seen on chest imaging. Other associated findings include fever, hypotension and hypoxemia. The treatment is largely supportive and the outcome is guarded; mortality is 5% in uncomplicated cases and up to 67% in those who were severely ill. TRALI is important to recognize, because donor products that induce the complication in one patient are much more likely to do so in a second. Indeed, recent measures to exclude multiparous women from plasma donation have resulted in the incidence of TRALI being cut in half.

Infectious Complications

Virtually any infectious agent can be transmitted through blood products, but bacterial and viral infections are most likely to be so. Most *bacterial infections* are caused by skin flora, indicating that the contamination occurred at the time that the product is taken from the donor. Significant bacterial contamination (sufficient to produce symptoms) is much more common in platelet preparations than red cell preparations, due in large part to the fact that platelets (unlike red cells) must be stored at room temperature, conditions that are favorable for bacterial growth. Rates of bacterial infection secondary to platelet transfusion can be as high as 1 in 5000, with infections secondary to red cell transfusions being several orders of magnitude less frequent. Many of the symptoms (fever, chills, hypotension) resemble those of hemolytic and non-hemolytic transfusion reactions, and it may be necessary to start broad-spectrum antibiotics prospectively in symptomatic patients while awaiting laboratory results.

Advances in donor selection, donor screening, and infectious disease testing have dramatically decreased the incidence of viral transmission by blood products. However on rare occasions when the donor is acutely infected but the virus is not yet detectable with current nucleic acid testing technology, there can be transfusion-related transmission of viruses such as HIV, hepatitis C, and hepatitis B. Rates of transmission of HIV, hepatitis C, and hepatitis B are estimated to be 1 in 2 million, 1 in 1 million, and 1 in 500,000, respectively. There also remains a low risk of "exotic" infectious agents such as West Nile virus, trypanosomiasis, and babesiosis.

SUGGESTED READINGS

Red Cell Disorders

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