Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Transfusion in Sickle Cell Disease

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Slide 1:
Hello, my name is Karen Quillen. I'm Medical Director of the Blood Bank at Boston Medical Center, and Professor of Pathology and Medicine at Boston University School of Medicine. Welcome to this Pearl of Laboratory Medicine on "Transfusion in Sickle Cell Disease."

Slide 2:
In sickle cell anemia, a single base substitution (T to A) in the beta-globin gene replaces glutamic acid with valine, which results in a hydrophobic interaction between hemoglobin S molecules to form insoluble polymers when deoxygenated. Polymerization induces membrane damage which leads to dehydration, and ultimately, irreversibly sickled red blood cells. These rigid sickled red blood cells adhere abnormally to vascular endothelium, causing characteristic vaso-occlusive episodes. Sickle cell disease encompasses several mutations, with hemoglobin SS, SC, and S-beta thalassemia being the most common.

Slide 3:
This diagram shows how the sickle polymer injures the erythrocyte and eventually produces irreversible membrane damage. These cells have a shortened life span which constitutes hemolysis; some hemolysis occurs in the intravascular compartment consuming nitric oxide (NO). Sickle erythrocytes also lead to vaso-occlusion leading to tissue ischemia.

Slide 4:
The clinical features of sickle cell disease are protean and involve all organ systems. Chronic hemolytic anemia, hyposplenism resulting in susceptibility to infections, and pigment gallstones are almost universal. Individuals differ in the severity and frequency of pain crises, avascular necrosis of bones, and acute chest syndrome. One of the most devastating manifestations is stroke, typically in children under age 10. As patients are surviving longer, they are developing renal disease, pulmonary hypertension, and high-output heart failure.

Slide 5:
Simple transfusion provides normal red blood cells that increase oxygen delivery to tissues. Exchange transfusion removes the patient's hemoglobin S at the same time as infusing normal red blood cells in an isovolemic fashion, *avoiding the risk of increased viscosity which can occur with simple transfusion* beyond a threshold hematocrit (typically around 30%). Exchange transfusion can be performed manually or with an automated cell separator. The latter procedure is also called red cell apheresis.

Slide 6:
Indications for transfusion include symptomatic anemia, which can occur in aplastic crisis caused by parvovirus or in children with splenic sequestration. Other indications include preoperative preparation, and early acute chest syndrome. Exchange transfusion is reserved for progressive acute chest syndrome or stroke, and in patients with hemoglobin SC whose high baseline hematocrit precludes simple transfusion for acute chest syndrome.

Slide 7:
A landmark study called the “STOP” trial (for stroke prevention trial in sickle cell anemia) demonstrated that transcranial doppler screening of children can identify those at high risk of stroke by virtue of elevated cerebral blood flow, and chronic transfusion in these high-risk children can reduce the risk of stroke ten-fold. Practical problems encountered implementing this strategy include venous access difficulties in children, iron overload (made easier by the availability of oral iron chelators), infectious disease transmission (still a significant problem in many countries), and parental acceptance.

Slide 8:
The immunologic problems of repeated transfusions, most notably the formation of red blood cell allo- and auto-antibodies, are more severe in sickle cell disease compared to thalassemia, where chronic transfusions begin much earlier in life during a period of relative immune tolerance. Non-immunologic problems of chronic transfusions include iron overload and infectious disease transmission.

Slide 9:
The prevalence of red blood cell alloimmunization in transfused sickle cell patients in the United States is 30%, somewhat lower in other countries where populations are more homogeneous. Common phenotypes in African-Americans such as R0 (cDe) and Fy (a-b-) are rare in Caucasian whites who comprise the blood donor pool in many regions of the United States. Although prophylactic phenotype matching for C, E, and K antigens has been recommended for many years, it has been recognized recently that Rh immunization still occurs despite this strategy, due to the presence of Rh variants that are relatively common in blacks. Unnecessary transfusions (such as during vaso-occlusive crises) should be avoided to minimize donor red blood cell exposures which can lead to alloimmunization.

Slide 10:
The table shows a small series of children with sickle cell disease who had delayed hemolytic transfusion reactions 5-14 days after the index transfusion, all with post-reaction hematocrits that were lower than the pre-transfusion level, as low as 10.5% in one patient. New alloantibodies were not detectable in the majority of patients despite a positive a direct antiglobulin test (DAT). These features are characteristic of the hyperhemolysis syndrome. The DAT can be positive or negative; a positive DAT accompanied by a panreactive eluate would be consistent with an autoantibody, as is seen with the first case on this table.

Slide 11:
Hyperhemolysis is a syndrome that occurs in a subset of patients with sickle cell disease and delayed hemolytic transfusion reactions. The hallmark is the development of anemia after transfusion that is more severe than before transfusion, typically accompanied by relative reticulocytopenia. Hemolysis of donor AND autologous red blood cells is inferred on hemoglobin electrophoresis by expected proportions of hemoglobin A and hemoglobin S. The symptoms are non-specific, and may suggest a pain crisis. The pathogenesis is unknown, although suppressed erythropoiesis (from infection and recent transfusion) and macrophage activity are thought to play a role.

Slide 12:
The serologic findings range from multiple alloantibodies and/or autoantibodies, to a negative DAT and negative antibody screen. Crossmatch-compatible, antigen-matched donor red blood cells are hemolyzed upon transfusion, as are autologous red blood cells. Management is to withhold further transfusion, which can worsen the anemia. Corticosteroids and intravenous immunoglobulin have been used empirically with anecdotal success. After recovery, future transfusions may be well tolerated, although caution is needed.

Slide 13:
In conclusion, sickle cell anemia is characterized by protean clinical manifestations, some of which can be ameliorated with transfusion therapy. However, transfusion in sickle cell disease poses unique immunologic challenges, specifically alloimmunization and hyperhemolysis.

Slide 14: Disclosures

Slide 15: Thank You from www.TraineeCouncil.org
Thank you for joining me on this Pearl of Laboratory Medicine on “Transfusion in Sickle Cell Disease.” My name is Karen Quillen.