Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Delayed Hemolytic Transfusion Reactions

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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 Associate Professor of Pathology and Medicine at Boston University School of Medicine. The subject today is delayed hemolytic transfusion reaction.

Slide 2:
About 5% of transfusion recipients develop antibodies against foreign red blood cell antigens after exposure. Certain patient populations who are heavily transfused over time, such as those with sickle cell disease, have much higher rates of alloimmunization. Development of one red blood cell alloantibody predisposes an individual to subsequent production of additional alloantibodies. Pre-transfusion compatibility testing is time-consuming and costly in alloimmunized individuals.

Slide 3:
RBC antibodies may become undetectable in the individual's blood at the time of subsequent transfusion months or years from the initial sensitizing transfusion. At the time of pre-transfusion compatibility testing, if the antibody screen is negative, selection of blood based solely on ABO and Rh(D) – unmatched for the unknown offending antigen - may cause anamnestic antibody production, similar to a vaccine booster effect.

Slide 4:
Typical presentation of a delayed hemolytic transfusion reaction occurs 5-21 days after the offending transfusion. The patient presents with unexplained anemia, low grade fever, jaundice, or worsening renal function. Temporal association with transfusion is not always appreciated. The appropriate lab tests for investigation include bilirubin, LDH, reticulocyte count, and direct antiglobulin test (DAT). Spherocytes may be noted on the peripheral blood smear. Management consists of serial monitoring of blood counts, adequate hydration, and transfusion of antigen-negative blood for all subsequent transfusions.

Slide 5:
The reported incidence of delayed hemolytic transfusion reactions varies widely. A prospective study is more accurate because all patients are tested within 7 days of each transfusion (with an antibody screen and DAT). One prospective study found the incidence to be 1:2000 patients transfused. Many more patients – as many as 2.5% - may have a delayed serologic transfusion reaction, where the patient has a positive antibody screen or DAT without biochemical evidence of hemolysis.

Slide 6:
Hemovigilance data from the United Kingdom from 1996-2004 found that delayed hemolytic transfusion reactions account for 10% of all reported transfusion hazards. Mortality and major morbidity of these reactions exceed those from acute hemolytic transfusion reactions.

Slide 7:
Transfusion fatality reporting to the United States Food and Drug Administration 2008-2011 demonstrates that non-ABO hemolysis accounts for twice the number of transfusion fatalities as ABO hemolysis.

Slide 8:
As an illustrative case, a 65-year-old man presented to my hospital for preoperative evaluation. A blood bank specimen was received, and no previous transfusion history was noted in our laboratory information system. Preop hemoglobin was 10.1 g/dL.

Slide 9:
Antibody screen was positive, with a panel that demonstrates anti-E as shown on this slide.

Slide 10:
He was phenotyped for Rh antigens and found to be negative for big E, little c, positive for little e and big C.

Slide 11:
The blood bank resident noticed that the preop note mentions prior abdominal and cardiac surgeries. After some detective work, we discovered that he had been transfused 8 units of blood over the past 5 years, with anti-E, c, K identified at various times at 3 outside hospitals. Our transfusion recommendation was to provide blood negative for E, c, K.

Slide 12:
He received 7 units of blood on the day of surgery and postoperative day 1. A week later, his hematocrit and hemoglobin started dropping to a nadir of 21 and 6.8 g/dL respectively on postop day 14. A new blood bank sample was received.

Slide 13:
Antibody screen on the new sample showed new reactivity with Cell II, and a DAT that was positive for IgG and C3.

Slide 14:
New antibody identification panels were performed, as shown on this slide and the next, showing anti-E, c, K reactivity that we knew about…

Slide 15:
…in addition to a new anti-S. The patient's plasma agglutinated Cells 3, 5, and 7 on this panel which are positive for big S, and negative for big E, little c, and K.

Slide 16:
An eluate confirmed the presence of anti-S on transfused donor cells. The patient's pre-transfusion specimen typed as S negative. Transfusion recommendation was updated to crossmatch blood negative for E, c, K, and S. He had hyperbilirubinemia that was improving by this time, consistent with a delayed hemolytic transfusion reaction, although the event was not reported as a reaction by the clinical team.

Slide 17:
According to a Dutch study in 2000, 25% of all RBC antibodies become undetectable over time. Antibodies detected with a more sensitive technique (such as LISS instead of albumin) may be less persistent. Kidd antibodies are notoriously evanescent, and a culprit in many delayed hemolytic reactions for this reason. In another study of U.S. military veteran men, the prevalence of RBC alloantibodies was 2.2%. Among a subset of these alloimmunized men who underwent serial blood bank testing (a median of 6 times over 16 months), 20% of pre-existing antibodies disappeared, and half of newly-identified antibodies disappeared.

Slide 18:
Patients receiving care and transfusions at multiple hospitals compound the problem of antibody evanescence. 4% of commercially insured patients under age 65 in Kansas City receive care at more than one hospital. The prevalence of this problem is likely much higher in larger metropolitan areas. Outside the United States, a single payer health care system does not necessarily mean a single electronic medical record.

Slide 19:
Potential strategies to reduce the risk of delayed hemolytic transfusion reactions include a thorough transfusion history, and the transfusion of antigen-negative blood regardless of current antibody detection. Regional or national RBC alloantibody registries such as those in place in Kansas City, Quebec, and the Netherlands are invaluable. Routine post-transfusion or postpartum antibody screens have been proposed but are unlikely to be adopted because of cost.

Slide 20:

Future strategies to prevent red blood cell alloimmunization would ideally target primary prevention of initial antibody production. Genetic studies have identified certain HLA alleles that are markers of immune "responders." Murine models of alloimmunization suggest that it may be possible to screen for biomarkers such as inflammatory cytokines which signal an increased risk of alloimmunization. Immunomodulatory therapy such as anti-inflammatory drugs could be considered as a preventive strategy. For transfusion recipients who are identified to be at high risk of alloimmunization, blood centers could offer prophylactic matching for Rh, Kell, and Kidd antigens, for instance, from a database of blood donors who have been genotyped for red blood cell antigens.

Slide 21: Disclosures

Slide 22: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "Delayed Hemolytic Transfusion Reactions." I am Karen Quillen.