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PEARLS OF LABORATORY MEDICINE

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TITLE: Challenges in Blood Group Alloantibody Detection: the Antibody Screen

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Slide 1:
Hello, my name is Chris Tormey and I am an Associate Professor of Laboratory Medicine at the Yale University School of Medicine & the VA Connecticut Healthcare System. Welcome to this Pearl of Laboratory Medicine on "Challenges in Blood Group Alloantibody Detection: the Antibody Screen."

Slide 2:
Non-ABO blood group antibodies are a significant problem for laboratory medicine practitioners. About 1-3% of general transfused patients are known to develop antibodies, with even higher rates (approaching 40% of patients) among chronically transfused groups. While the blood bank and lab medicine communities have traditionally thought of antibodies as being primarily a nuisance because they delay the timely provision of compatible red blood cell (or RBC) units, there is increasing data suggesting that alloimmunization is a cause of significant morbidity and mortality for transfused patients.

Slide 3:
As shown in this slide, which summarizes nearly a decade's worth of data from the Food and Drug Administration (FDA), hemolysis due to non-ABO antibodies is the second leading cause of death associated with transfusion in the United States. And, as noted in the slide, there is great variability in the specificities of antibodies which are associated with mortality. Recent data also suggests that alloimmunization-associated delays in providing compatible RBCs can contribute to morbidity and mortality. Thus, RBC antibodies are a highly important issue for transfusion practice and safety.

Slide 4:
In considering why non-ABO antibodies are associated with such high rates of morbidity and mortality, one of the major causes is the difficulty associated with their detection. Undetected antibodies frequently lead to the inadvertent administration of incompatible RBC units, which can result in delayed hemolytic reactions. Such reactions are responsible for much of the morbidity and mortality associated with non-ABO antibodies.

In this Pearl, we will highlight three principal challenges facing blood banks and transfusion services as they relate to antibody detection, namely: antibody evanescence, transfusion record fragmentation, and missed opportunities for antibody detection. We will discuss how each of these factors contributes to problems with alloimmunization and we will also review what steps blood banks can take to try and overcome such obstacles.

Slide 5:
Perhaps the most challenging aspect of detecting blood group alloantibodies is their tendency to disappear from detection over time, in a process that has been called antibody evanescence. Until recently, there were few large-scale estimates of how frequently antibodies disappeared from detection over time, and how rates of disappearance varied by antibody specificity. A study performed in 2009 helped better elucidate the scope of problems associated with evanescence. This study focused on antibodies developed as a result of transfusion at the study facility; such an approach thereby excluded pre-existing antibodies and alloimmunization that may have resulted from pregnancy.

Slide 6:
As shown on this slide, nearly half of hospital-acquired blood group antibodies became undetectable over time. Moreover, evanescence was dependent on the degree of follow-up testing, such that antibody disappearance rates of nearly 65% were seen among patients with 5 years or more of follow-up testing. The authors also found that disappearance rates varied by antibody specificity, with the highest rates of evanescence (about 80%) being seen with anti-Jk^a alloantibodies.

Slide 7:
While the exact immunologic mechanisms underlying evanescence remain unknown, the methods used to screen for blood group antibodies are highly influential in whether or not an antibody will be detected. Some techniques, such as the tube method pictured here, possess lower sensitivity and could be associated with higher evanescence rates.

Slide 8:
Newer technologies, such as gel (pictured here) and solid phase assays, are associated with higher sensitivity. Nonetheless, evanescence is still observed despite the adoption of these tests. Platforms such as flow cytometry are promising in their potential to offer very high sensitivity for alloantibody detection; however, such testing is not yet widely available. Moreover, work continues to be done in order to ensure that such high sensitivity assays also offer reliable specificity, with avoidance of false-positive reactions.

Slide 9:
Because of the property of evanescence, it is critical that a patient's history of alloimmunization be highly portable – historical antibodies may not be detectable at all the facilities where a patient seeks care over time. Currently, however, there are no robust mechanisms in place for

an antibody history to be communicated, and it is possible that fragmentation of a patient's transfusion record can occur. This is the second major challenge to antibody detection.

Slide 10:
As shown on this slide, a recently published study examined how often patients sought transfusion-related care at more than one facility. The authors found that about a quarter of total patients undergoing type and screen testing at their facility reported being transfused elsewhere. And, such transfusions occurred at a number of locations, including facilities bordering the state of the study site, as well as facilities much more remotely located.

Slide 11:
The authors of this same study then wanted to examine how often alloimmunized patients seeking transfusion-related care at more than one facility had a discrepancy in their antibody records. To accomplish this, they investigated whether any of the 200 alloimmunized patients in their database had an antibody on file at a neighboring hospital and, if so, whether the documented antibodies matched. They found that about 1 in 5 alloimmunized patients did have a transfusion record at the neighboring facility and, disturbingly, nearly two-thirds of the time, there was a discrepancy in the record files between the two institutions. The most common discrepancy was lack of the second hospital having an antibody on file.

As such, this study indicates that not only do 20-25% of patients seek transfusion-related care at more than one facility, but that the resulting fragmentation of their transfusion records leads to frequent discrepancies in documented alloantibodies, thereby raising risks for hemolytic reactions.

Slide 12:
The final challenge to antibody detection that we will discuss today is a concept we will call missed alloimmunization. Prospective studies have shown that it takes about 30 days after RBC transfusion for an alloantibody to be detectable by standard blood bank techniques. Given this delay between transfusion exposure and antibody development, it is important to determine whether appropriately-timed antibody screen testing is being performed. In other words, if testing is not done, or is done too soon after transfusion, then antibodies will be missed because of the time frame needed for their development.

Slide 13:
In a small pilot study at our facility, we examined greater than 550 consecutive, but randomly-selected, RBC transfusions and determined whether follow-up antibody screen testing was done. We found that about a quarter of RBC transfusions had no associated follow-up test, while for another quarter, follow-up testing was performed fewer than 30 days after transfusion. As such, these data suggest that it is impossible to assess whether an antibody has developed in essentially half of RBC transfusions due to lack of adequate follow-up testing.

Slide 14:
To summarize, we have discussed three fundamental challenges to antibody detection in the preceding slides. Antibody evanescence, or disappearance, is a frequent problem, with nearly 65% of antibodies becoming undetectable at 5 years after their initial development. Moreover, as patients seek care at more than one facility, antibody evanescence and lack of a system for communicating antibody history creates fragmentation of the transfusion record, leading to increased risks for incompatible transfusions. Finally, because there is often no routine approach to screen for alloantibodies post-RBC transfusion, large percentages of transfused patients do not undergo adequate surveillance for RBC alloimmunization. These are all very serious obstacles to providing safe and compatible RBCs for transfusion. Fortunately, there are some steps that the blood bank and medical communities can take to overcome these challenges.

Slide 15:
As demonstrated on this slide, one strategy to combat the phenomena of evanescence and record fragmentation is to increase the portability of alloantibody history and records. Devices such as wallet cards and alert bracelets can raise the profile of historical antibodies. Moreover, enrolling in (or creating) local or regional antibody registries can also help combat the problems of antibody evanescence and record fragmentation. In addition, as higher sensitivity tests are developed and implemented, our ability to detect very low titer antibodies should also be enhanced. Finally, the implementation of routine follow-up testing after RBC transfusion can help overcome the problem of missed alloimmunization. Ultimately, virtually all of the above problems can also be overcome by preventing the alloimmunization event in the first place. This can be accomplished by providing RBCs that are pheno- or genotypically-matched for the most clinically-significant non-ABO antigens. Such strategies are commonly employed for individuals who are chronically transfusion-dependent, such as those with sickle cell disease.

Slide 16: References
The references used in this Pearl are shown on this slide; please see these pieces of literature to seek further information about the topics discussed today.

Slide 17: Disclosures

Slide 18: Thank You from www.TraineeCouncil.org
Thank you for joining me on this Pearl of Laboratory Medicine on “Challenges in Blood Group Alloantibody Detection: the Antibody Screen.”