Regulatory Issues

Case 1

Product Retrievals and Lookbacks

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Case History

In November 2015, a transfusion service received a notice of a market withdrawal on a plasma unit donated in October 2013. Investigation into the final disposition of the unit indicated it was issued to a patient in December 2013. The patient in question received the unit without complication and is still followed at the institution. When the same donor attempted to donate in October 2015, he completed an unabridged donor history questionnaire. At this time, the donor, who had not noted any high-risk behaviors on his previous questionnaire, indicated that he had one-time male-male sexual contact in December 2014 and was incarcerated for more than 72 hours in late August 2013.

Case Questions

1. Which infectious disease markers would this donor be at highest risk for?
   a. West Nile virus, Eastern equine encephalitis virus, and Zika virus
   b. Babesiosis, malaria, and *Trypanosoma cruzi*
   c. Creuztfeldt-Jakob disease
   d. Cytomegalovirus and human T-lymphotrophic virus
   e. Hepatitis B, hepatitis C, and human immunodeficiency virus (HIV)
2. What are the serologic and nucleic acid testing window periods for HIV?
   a. 44 days and 30-35 days
   b. 22 days and 10 days
   c. 58 days and 8 days
   d. 51 days and 6 days
3. If this case requires notification, how long does the blood bank medical director have to notify the ordering physician or recipient?
   a. 120 days
   b. 90 days
   c. 60 days
   d. 30 days
   e. 14 days
4. How long must a donor be deferred if they report a male-to-male sexual encounter in the last 12 months?
   a. 3 years
   b. Indefinitely
   c. 8 weeks
   d. 6 months
   e. 1 year
5. Which infectious disease agent has a defined algorithm for donation and recipient notifications in the Code of Federal Regulations?
   a. HIV
   b. Human T-lymphotrophic virus

c. Zika virus
d. *Babesia*
e. Hepatitis B

Case Discussion

Blood components are biological products that are regulated much like drugs. Inherently, blood components will have variability due to human biology. The Food and Drug Administration (FDA) Current Good Manufacturing Practices (cGMPs) strive to minimize controllable variability in the safety, purity, and potency of blood components. But despite the strict application of cGMPs, potential problems with blood components can be recognized after their release to transfusion services. When such problems are recognized, blood collection facilities are obliged to issue product retrievals, informing consignees (the transfusion services who received these products) of the identified risks. These product retrievals are enacted to prevent blood components that do not meet FDA requirements or with potential risk from being transfused, as well as to inform transfusion services so that they may investigate the medical impact upon recipients.

In considering blood product retrievals, two parties are involved:

- The recalling firm: the group that initiates a blood product recall or the group that has primary responsibility for the manufacture and marketing of the product to be recalled
- The consignee: anyone who received, purchased, or used the product being recalled

Broadly, blood product retrievals have a three-fold categorization, as follows.

Lookbacks/Tracebacks

Lookback retrievals (alternately named "tracebacks" by some blood collection facilities) result from a donor having a reactive test for an infectious disease marker on a later donation. Lookbacks will prompt investigation and quarantine of prior donations that have not yet been transfused and possibly the investigation of patients who have received prior donations. The Code of Federal Regulations (CFR) has defined algorithms for managing donations and recipient notification in cases of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) lookbacks.[1,2] For both HIV and HCV lookbacks, recipient notification is required by law within 12 weeks of the consignee receiving notification of the confirmatory positive test results from the blood collection facility. Furthermore, should the recipient be deceased, notification of next-of-kin is also required for HIV lookbacks. Recipient notification for lookbacks from other infectious disease agents is either required or recommended in order to provide testing and counseling of recipients, but for some infectious disease agents, recipient notification may be performed at the discretion of the transfusion service medical director and/or the recipient's physician. The FDA has issued guidance for other infectious disease agents (such as West Nile virus and babesiosis), including recommendations for donor management and recipient notification.[3]

Recalls

The Code of Federal Regulations (21 CFR 7.3) defines a recall as the removal or correction of a marketed product that is in violation of the law. The CFR classifies such recalls by the relative health hazard presented by the recalled product:

- Class I: Reasonable probability that the use of the recalled product will cause serious health consequences or death.
- Class II: Use of the recalled product may cause temporary or medically reversible adverse health consequences, or risk of serious adverse health consequences is remote.
- Class III: Use of the recalled product is not likely to cause adverse health consequences.

Class I recalls, the most serious type, are almost unknown in current blood establishments, with most being class II or III, which have at worst the "risk of a risk." While the FDA considers recalls voluntary, manufacturers are required to conduct recalls. Additionally, the FDA can initiate recalls if the manufacturer fails to take the required action. The FDA has carefully delineated the responsibility of recalling firms regarding conduction of recalls (21 CFR 7.3, 21 CFR 7.40-7.59). On rare occasion, recalls may involve public warnings under serious circumstances. The vast majority of recalls involving blood products are of negligible risk. The FDA publishes recalls in the US FDA Enforcement Reports.[4]

Market Withdrawals

The CFR defines market withdrawals as the removal or correction of a distributed product that involves a minor violation that would not be subject to legal action by the FDA. These are usually secondary to problems that are beyond the control of the manufacturer. The most common source of market withdrawals involving blood components is post-donation information (PDI): information provided by a donor after a donation that, had the blood collecting facility been aware of the information, would have resulted in a donor deferral. Estimates of PDI incidence by the American Red Cross have been as high as 1 in 600 donations, with 1 in 450 distributed products having retrievals issued.[5] Some of the most frequent forms of PDI include donor disclosure of travel to malaria-endemic areas and risk behaviors for transfusion transmitted infection (unacceptable tattoos, intravenous drug use, or men engaging in sexual contact with other men). There is considerable leeway for handling market withdrawals on the part of both the collecting facility and the transfusion service.

Recalls and market withdrawals are both biological product deviations, in which blood product safety, purity, or potency has or may have been compromised. The transfusion service must report these events to the FDA.

Consignees will most often receive notices of recalls or market withdrawals after a component has been transfused to a recipient. In relatively recent guidances on malaria and variant Creutzfeldt-Jakob disease, the FDA has also provided more general guidance on actions that should be taken by blood collectors and, to a lesser extent, consignees.[6-11] However, in many cases of PDI, there is room for medical discretion on the part of both the blood collector and consignee. The AABB Standard 7.1.3 asserts that transfusion services will have a process for identification, quarantine, retrieval, and recall of nonconforming blood and blood components.[12] Similarly, the College of American Pathologists (CAP) Laboratory Accreditation Program 2019 *Transfusion Medicine Checklist* item TRM.42135 states that the transfusion service has a procedure for managing quarantines, recalls, and market withdrawals issued by its blood suppliers.

There is room for interpretation of the above standards for transfusion services regarding how to approach recalls and market withdrawals. Two valuable reviews on recalls and market withdrawals by Dr. Glenn Ramsey offer some helpful advice on managing these product retrievals.[3,13]

- Standard operating procedures (SOPs): CAP and AABB standards require these procedures, which should detail the approach of the transfusion service or blood bank.
- Transfusion staff must take *immediate* action to follow instructions provided by the blood supplier regarding quarantine, discarding, or returning the implicated blood components.
- Ensure reliable chains of communication between the transfusion service and blood supplier at all times.
- Keep records of actions and notifications as required. The 31st edition of the AABB standards require record retention for 10 years.
- Medical director review of the medical implications for transfused units involved in a recall or market withdrawal: Medical directors of transfusion services should review these retrievals for risk of recipient harm and evidence of adverse transfusion-associated events in recipients. Such evaluation should involve consideration of the level of risk and the possibility of risk mitigation. Discussion with the recipient's physician may be useful.

Regarding the above case, the FDA guidance, "Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products," changed the decades-old indefinite blood donor deferral policy regarding men who have had sex with men (MSM) to a 1-year deferral since the last sexual contact with another man. All US blood collection organizations are encouraged to follow this federal recommendation, which was considered and ruled appropriate by the Health and Human Services (HHS) Advisory Committee on Blood and Tissue Safety and Availability in 2015.

Based on several years of research and recent Centers for Disease Control and Prevention data on HIV, the FDA's decision to change the deferral policy for MSM donors better aligns the deferral period with that of other men and women engaging in behaviors that place them at increased risk for HIV infection.[7]

In evaluating market withdrawals for these collective sources of PDI, the most significant risk to the transfused patient is determining if that donor was tested during the window period of detection of infection. A window period is that period of time between a person's exposure to an infectious agent and when such infection is detectable by laboratory methods. Window periods for HIV and viral hepatitis seroconversion using current testing platforms in blood collection facilities can be of relatively short durations. For example, the anti–HIV-1 antibody window period by enzyme-linked immunoassays has been reported at 22 days.[8] Nucleic acid testing for HIV has an even shorter window period, with a 9.5-day window period for pooled testing and an estimated 5.6-day window period for individual testing.[9,10] Awareness of window periods and the donor's dates of previous donation with negative test results may be helpful in ruling out donor infection at the time of donation.

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Case 2

Electronic Crossmatching and Computer Validation

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Case History

A 75-year-old man with acute necrotizing pancreatitis presented to the emergency department with severe abdominal pain. General surgery was consulted, and an emergent pancreatectomy was scheduled for the morning. He reports no known prior history of red blood cell (RBC) transfusion but has previous surgical history of left hip replacement in 1998. Routine type and screen performed in preparation for surgery found him to be blood type A positive, and his antibody screening result was positive for an anti-Le^a antibody. All initial testing was performed using gel column agglutination techniques, and subsequent tube testing showed the anti-Le^a was only demonstrable in tube at immediate spin.

Case Questions

1. Which of the following is a required condition that must be met for an electronic crossmatch to be used in this patient?
   a. The patient's ABO/Rh type must be done once at the institution.
   b. The laboratory information system (LIS) will alert the technologist to ABO and Rh discrepancies between the donor unit and recipient testing prior to issuing.
   c. At least one immediate-spin crossmatch must be performed before moving to electronic crossmatch.
   d. The LIS is the only element required to ensure correct data entry and interpretation.
2. Under what conditions can electronic crossmatch still be considered in patients with a positive antibody screening result?
   a. The patient has a history of an anti-P1 reactive with anti-human globulin (AHG) antisera.
   b. The current type and screen identifies any alloantibody.
   c. If a "prewarm" antibody screen, in which the reagents are individually warmed to 37°C before performing tube testing, provides negative results.
   d. A previous AHG crossmatch has been performed with a negative type and screen result.
3. What are the situations in which electronic crossmatch may not be appropriate?
   a. The patient has only one ABO/Rh type on record.
   b. The patient has a history of clinically insignificant antibodies.
   c. A type A patient has a typing discrepancy resolved with A1-lectin testing.
   d. Direct antiglobulin test with positive results with polyspecific and C3 antisera.

4. Which of the following is a strength or a weakness of electronic crossmatch compared to immediate-spin crossmatch?
   a. Simplicity of working with the system during downtime procedures
   b. The omission of the requirement of repeat ABO/Rh typing of the patient
   c. Increased risk for human error in ABO incompatibility
   d. Reduced turnaround time

Case Discussion

The electronic crossmatch (EXM) provides an alternative means of assuring donor unit–patient compatibility. Widespread use of EXM became possible when AABB first sanctioned its use in AABB standards in 1993. EXM is a set of rules defined within the laboratory information system (LIS) that selects ABO-compatible products in lieu of performing an immediate-spin crossmatch. Since the 1990s, requirements for the effectiveness, reproducibility, and safety of this alternative method have been developed and refined. EXM helps to minimize analytic error in the laboratory and preanalytic errors from clinical areas, reduce costs, and decrease turnaround times at busy hospital transfusion services.[1,2]

When we perform an EXM we are using the LIS to assign a unit of RBCs. The sole purpose of EXM is to confirm the ABO compatibility between the patient and the donor. It will not entirely prevent transfusion reactions that could result from patient misidentification or precipitated by antibodies missed by an antibody screen.[3]

Transfusion services are tasked with developing eligibility criteria at their institution for patients who may be eligible for EXM. The CAP, in its transfusion medicine accreditation checklist, defines an EXM and provides parameters for patients that may be evaluated by this method.

Transfusion service LISs must develop procedures for an EXM to replace the immediate-spin crossmatch. In order for a donor RBC unit to be selected by these means, the requirements for the patient and the LIS that must be met are:

- The LIS contains a logic system to prevent the assignment and release of ABO-incompatible blood.
- No clinically significant antibodies are detected in the recipient's serum/plasma, and there is no record of previous detection of such antibodies.
- There are concordant results of at least two determinations of the recipient's ABO type on record, one of which is from a current sample.
- Critical elements of the LIS performing these functions have been validated on site.
- There are mechanisms to verify the correct entry of data prior to release of blood.[4]

To be in compliance with the CAP, a transfusion service must supply procedures for defining their method of EXM verification. Work records of test results and the verification of correct data entry must be provided, with a policy to define what elements must be stored in the LIS. The transfusion service must also provide a written description of the alerts that prevent the ability of laboratory staff to issue products if a discrepancy is identified.[5]

Patients ineligible for EXM include:

- Patients with a history of or currently identified clinically significant antibodies
- Patients with unresolved ABO discrepancies
- Patients without a current sample in the laboratory

References

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Case Answers

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