Editorial Commentary

Retrograde bacterial contamination as an artifact of platelet contamination investigations

Shailaja Hegde[1,2], Jose A. Cancelas[1,2]

[1]Hoxworth Blood Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [2]Division of Experimental Hematology, Cincinnati Children's Research Foundation, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Correspondence to: Jose A. Cancelas. Hoxworth Blood Center, University of Cincinnati College of Medicine, 3130 Highland Avenue, Cincinnati, OH 45267, USA; Division of Experimental Hematology, Cincinnati Children's Research Foundation, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA. Email: Jose.Cancelas@cchmc.org.

Comment on: Drews SJ, Lesley P, Detsky ME, *et al.* A suspected septic transfusion reaction associated with posttransfusion contamination of a platelet pool by vancomycin-resistant Enterococcus faecium. Transfusion 2020;60:430-5.

Received: 22 June 2020. Accepted: 19 July 2020; Published: 30 December 2020.
doi: 10.21037/aob-20-45
View this article at: http://dx.doi.org/10.21037/aob-20-45

Platelet transfusion in thrombocytopenic or thrombocytopathic patients remains a cornerstone of the prophylaxis or therapeutic support of patients with cancer, trauma or undergoing major surgery. Universal storage of platelet products at room temperature favors the growth of skin flora contaminants in platelet products. Diversion pouches for collection or insensitive bacterial detection with automatic culture systems have been implemented and resulted in decreased frequency of transfusion-transmitted bacterial infections (1-4). AABB Standards (5) require the use of enhanced methods to detect bacteria in platelet components; these methods are either based on cultures or in immunoassays and in USA, they have to be FDA-approved or validated to provide equivalent sensitivity [reviewed in (6)]. However, transfusion-transmitted bacterial infection and septic transfusion reactions remain major sources of morbidity and mortality following platelet transfusion. The reported frequency of bacterial contamination of platelets ranges from 1 in 1,000 to 1 in 2,500 units (7) and the risk for symptomatic bacterial sepsis per platelet dose transfused as around 1 in 100,000 (8). Longer time of storage (9) and type of processing (10) associate with higher frequency of bacterial contamination of clinical platelet products and the most recent 2019 FDA Guidance from the Blood Product Advisory Committee meeting will require by March 2021 the implementation of bacterial mitigation strategies will include pathogen inactivation, large volume delayed culture, and primary culture with additional immunoassay safety measure testing; or, alternatively cold storage of platelet products, approved for storage for up to 14 days (11,12). RT stored platelet contaminations remain mostly being due to *Staphylococcus aureus*, coagulase-negative staphylococci, aerobic and anaerobic diphtheroid bacilli, streptococci, and gram-positive bacilli and may be dependent on the processing method.

Vancomycin resistant enterococci (VRE) are bacteria that are normally present in the human intestine and in the female genital tract and these can cause serious infections. In 2017, VRE caused an estimated 54,500 infections among hospitalized patients and 5,400 estimated deaths in the United States (2019 AR Threats Report). People who have been previously treated with antibiotics, are immunodeficient, hospitalized for longer term, have catheters or have been diagnosed and treated for cancer are at high risk (13,14). VRE can spread from one person to another through contact with contaminated surfaces or equipment or through person to person spread, often via contaminated hands. Drews *et al.* present an interesting case report of on the investigation of a suspected septic transfusion reaction in relation with a contamination of a platelet pool by vancomycin-resistant VRE (15). A 27-year-old male with relapsed leukemia and bleeding thrombocytopenia was transfused with a 5-day-old buffy coat platelet concentrate (PC) pool and developed an immediate, acute febrile transfusion reaction fever.

Transfusion was halted and the patient symptomatically treated. Two blood cultures identified rapid growth of a VRE and the implicated PC bag was also found to lodge, albeit at a much lower level, growth of a VRE and a coagulase-negative Staphylococcus. As presented, most transfusion services in the world would have just reported to their hemovigilance systems the presence of a sepsis likely related to the transfusion of a 5-day stored PC. However, the investigators did something frequently neglected in these studies, i.e., identity analysis of bacterial presence in orifices, a normal protocol in patients undergoing intensification chemotherapy for leukemia therapy or stem cell transplantation to detect dysbiosis (16). Given the rarity of VRE as a platelet product contaminant, the investigators hypothesized that the VRE identified may not be of exogenous origin but to be part of the patient's flora. SmaI pulsed-field electrophoretic analysis of pre-admission rectal and nasal swabs testing from this patient indicated nasal-rectal colonization by the same VRE strain prior to transfusion, a frequent consequence of long-term broad-spectrum prophylactic antibiotic therapy (17). While this data cannot rule out a true contamination of the PC by VRE and a coagulase negative Staphylococcus, it strongly suggested that the VRE identified in the PC resulted from retrograde contamination of the platelet bag. This is interesting because the investigators explain that the implicated PC bag was sent to the hospital transfusion service in a plastic bag with the infusion set attached, and stored flat for 24 hours in the refrigerator before being sent to the microbiology laboratory. To prevent passage of fluid from the infusion tubing back to the bag, the roller clamp was closed during the process of removal of the infusion set at the microbiology laboratory and then separated at 4 cm from the port using a sealer. The most likely source of retrograde contamination happened shortly after the infusion was halted or during the 24 hour-period of storage. After reading this manuscript, we wonder how many of the reported bacterial contaminations merely artifacts of preparation are. This report highlights how complicated can be to establish relatedness in the context of septic transfusion reactions. Traditionally, culture-based methods including pulsed-field gel electrophoresis and, more recently, whole-genome sequencing have been the central diagnostic tools for well-performed septic transfusion investigations. More recently, culture-independent metagenomics sequencing has been shown to extend the utility of these methods by directly detecting pathogens from clinical samples to assess genetic relatedness, obtain precise strain information, and interrogate levels of pathogen in a patient's bloodstream throughout the course of a septic transfusion event. However, culture dependent systems guarantee that only viable micro-organisms are identified and not just non-viable sacs of nucleic acids. Although not directly related, early results derived from RNA analysis of blood products from asymptomatic individuals in the ongoing COVID-19 pandemics raised a concern (18) that was not supported by any elemental support of transmissibility (19). During the last few years, we have seen a large effort devoted to the reduction of the risk of bacterial contamination in platelet products by using rapid tests of detection or pathogen inactivation systems, which are adding a significant cost to the therapeutic product. Since a test for bacterial contamination needs to be sufficiently sensitive and robust to detect the widest range of potential bacterial contaminants, yet sufficiently rapid to achieve results within the reasonable use life of the platelets, issues of sensitivity/specificity remain.

Large-volume delayed sampling and secondary bacterial cultures seem to be effective and competitive when compared their cost-effectiveness with other alternatives (20,21). These other alternatives include technologies for rapid detection of bacterial contamination at point of issue (POI) and pathogen inactivation systems. The goal of the POIs is to detect clinically relevant bacterial loads rapidly, in less than one hour, so that testing might be closer to time of transfusion. These methods may not be as sensitive as culture, but they are rapid and generally capable of measuring bacterial loads below 10 (22). One technology for platelet product pathogen inactivation was first approved in Europe in 2002 and has received FDA approval in 2014 for apheresis platelets. This method uses a combination of UVA illumination and the photosensitive psoralen compound amotosalen to achieve broad-spectrum pathogen inactivation (23). The process is typically performed at a blood collection facility within 24 h of platelet donation.

Tremendous efforts have been made to reduce bacterial contamination risks in platelet products. However, nothing can replace thorough hemovigilance data reporting, recording and analysis. Hemovigilance is the key tool to provide the blood community and regulators with a vehicle to monitor the incidence and prevalence of transfusion transmitted diseases. In the current era of pandemics of blood-transmitted diseases and other viral diseases with potential to threaten the blood supply, hemovigilance data would serve as an early warning system for policy failure or emerging infectious diseases and along with outcome

data can highlight continued challenges related to blood safety, which can help identify areas that would benefit from further innovation. One way to maximize efficiencies and minimize burdens is to leverage and coordinate any new data system with existing platforms, data systems and programs in enforceable systems that improve the data reporting and accessibility and use of informed policies and clinical practices that impact blood safety, blood availability and patient outcomes.

In summary, this report highlights the importance of a strong hospital hemovigilance system with appropriate molecular approaches towards establishing genetic relatedness, obtain strain information, and interrogate levels of a pathogen in different tissues and specimens in the course of a septic transfusion reaction.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Blood*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob-20-45). JAC reports grants from National Institutes of Health, Grants from US Department of Defense, Grants from HHS Barda/Cerus Co., grants from Cerus Co., Grants and personal fees from Hemanext INC, grants and personal fees from Terumo BCT, grants from Fresenius-KABI, grants from Cytosorbents, outside the submitted work. In addition, JAC has a patent US10028503B2 issued. Both authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aob-20-45
Cite this article as: Hegde S, Cancelas JA. Retrograde bacterial contamination as an artifact of platelet contamination investigations. Ann Blood 2020;5:36.