

Pathogen Reduction in Platelets: A Review of the Proposed Draft Guidance

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LEARNING OBJECTIVES

1. Discuss the methodologies currently available to reduce bacterial contamination of platelets.
2. Compare and contrast the advantages of bacterial and rapid bacterial detection methods verses pathogen reduction technology.
3. List the two FDA approved tests for rapid bacterial detection and benefits to the use of these tests.

ABSTRACT

In an effort to reduce the incidence of transfusion-transmitted infections (TTI) and septic transfusion reactions (STR) from bacterially-contaminated platelet products, the Center for Biologics Evaluation and Research (CBER) department of the Food and Drug Administration (FDA) recently published draft guidance in March of 2016. Entitled, "Bacterial Risk Control Strategies for Blood Collections Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion," the new guidance recommends either the use of rapid bacterial testing at point-of-issue on days four or five of stored platelets or the use of pathogen reduction technology (PRT) at the time of platelet collection. A literature review demonstrates that both methodologies effectively reduce the incidence of TTI and STR without compromising the efficacy of the platelet product. However, the use of PRT has further-reaching implications. Utilizing amotosalen in the presence of ultraviolet (UV) light, PRT intercalates with nucleic acids. Not only does this render bacteria inactive, it also inactivates viruses and protozoa. This effectively eliminates the need for some viral testing, and reduces the risk of TTIs due to new and emerging pathogens. The use of PRT, therefore, proves to be the superior option for both transfusion services and blood collection centers, with implications for future use with additional blood products such as whole blood.

ABBREVIATIONS: TTI - transfusion-transmitted

infections, STR - septic transfusion reactions, CBER - Center for Biologics Evaluation and Research, FDA - Food and Drug Administration, AABB - organization formerly, the American Association of Blood Banks, TS - transfusion services, PRT - Pathogen-Reduction Technology, PGD - Pan Genera Detection, CMV - cytomegalovirus

INDEX TERMS: Septic Transfusion Reactions, Biological Products, Transfusion Reaction, Pathogen Inactivation, Platelet transfusion

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INTRODUCTION

The increase in surgical procedures and patients receiving treatment for cancer, have led to an increased usage of platelet concentrates.^{1,2} Platelet transfusions are indicated for the treatment of many disorders, but especially for patients with thrombocytopenia and platelet dysfunction who are more prone to bleeding.² Despite recent advances in donor screening and infectious disease testing, there is still a large risk for adverse transfusion reactions associated with platelets, such as bacterial contamination, transfusion-transmitted infections (TTIs), and sepsis. This paper evaluates the literature associated with the current Draft Guidance submitted by the Center for Biologics and Research (CBER) division of the Food and Drug Administration (FDA).³ It is an overview of methodologies available to reduce the contamination of platelets by bacteria in particular and an analysis of the safety and efficacy of pathogen-inactivated platelets. The review suggests that pathogen-

inactivated platelets are a safer alternative to leukoreduced apheresis platelets and leukoreduced whole blood-derived platelets currently in use.

Current Recommendations for Platelets

The AABB (formerly, the American Association of Blood Banks) recommends prophylactic transfusion to reduce the risk for spontaneous bleeding in patients who have a platelet count of 10×10^9 cell/L or less.⁴ Other indications include decreased platelet function due to drug therapy, myeloproliferative disease, or active hemorrhage. As platelet usage increases, medical directors, physicians, and transfusion services personnel struggle to maintain a safe and adequate inventory of platelets. Confounding this struggle are the complications that arise due to the current storage requirement of platelets. Current standards require platelet products to be stored at room temperature,⁴ which increases the likelihood of bacterial proliferation in platelet products.⁵ To prevent bacterial proliferation in these units, donor centers are required to hold platelets for bacterial testing for a minimum of two days before they are released to transfusion services (TS). Once the platelets arrive at the TS, they typically expire in three days or less. The short expiration time challenges hospitals and transfusion services that try to maintain adequate inventories of platelets.

Despite these bacterial testing requirements, the FDA reports 13 fatalities from 2009 to 2013 as a result of bacterial contamination of platelet products.⁶ According to a recent study conducted by Hong, Xiao, Lazares et al.,² this number may be underestimated by as much as 10-fold. Some recognition criteria of septic transfusion reactions (STRs) overlap with criteria for noninfectious febrile/febrile-like transfusion reactions,² which can lead to possible misdiagnoses. The authors assert that more measures should be taken to address this problem.

Proposed Recommendations for Platelets

Cold temperature (4 °C) storage has been proposed to reduce pathogens in platelet products.^{7,8} While some studies have shown that platelet function can be preserved at cold temperatures (4 °C),^{7,8} there is currently no globally accepted test to demonstrate platelet function in vivo.¹ Unfortunately, von Willenbrand factor receptors can aggregate at cold temperatures leading to the phagocytosis of platelets by liver macrophages in vivo.¹ Therefore, an alternative

method is required to reduce TTIs of platelet products. In an effort to reduce TTIs due to platelet products, CBER released its Draft Guidance for industry entitled, “Bacterial Risk Control Strategies for Blood Collections Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion,” in March 2016. To supplement initial bacterial detection and culture as previously described³, the FDA now recommends additional measures to reduce bacterial contamination of platelet products. The first method described in the CBER draft guidance is a rapid bacterial detection test performed on day four- or day five-stored platelets, prior to transfusion. This rapid detection test is recommended even when there is no growth of bacteria in the platelet cultures that were performed on day one after collection. Rapid bacterial detection tests should be conducted within 24 hours prior to transfusion. According to the Blood Products Advisory Committee in 2012, transfusion of platelets that have been stored for 4 or 5 days have been the source of all fatalities due to bacterial sepsis and most (95%) of platelet transfusion-related septic reactions.⁹ To minimize TTIs, then, it would seem that shortening the duration of platelet storage to 3 or 4 days maximum would be the logical choice, but that would result in significantly decreased platelet availability, and is therefore not considered to be a feasible strategy.

An alternative recommendation by the FDA is the use of Pathogen-Reduction Technology (PRT). While solvent-detergent methods are currently in place for the use of pathogen reduction in plasma and non-cellular blood products,¹ PRT in platelets inactivates viruses, fungi, bacteria, and parasites within blood components that contain cells using a photochemical process.¹⁰ The photochemical treatment prevents the replication of virtually all microorganisms, while preserving cellular function and minimizing toxicity of the treated platelets.

Technologies for Rapid Bacterial Detection

Currently, there are two rapid bacterial detection tests cleared by the FDA for bacterial detection in platelet products. The BacTx (Immunitics, Inc., Boston, MA), detects peptidoglycan that is found exclusively in bacterial cell walls.¹⁰ Bacterial contamination triggers a melanization reaction, triggering an enzyme cascade and resulting in melanin formation. After 30 minutes, a photometric change in color represents a positive

bacterial detection.¹¹ A study conducted by Heaton, Good, Galloway-Haskins et al.,¹² demonstrated sensitivity ranging from 6.3×10^2 CFUs/mL for *Staphylococcus epidermidis* to 7.6×10^4 CFUs/mL for *Escherichia coli*. The sensitivity for remaining organisms was less than 7.6×10^4 , all of which are below the clinically significant level of 10^5 CFUs/mL.

The platelet Pan Genera Detection (PGD) test (Verax Biomedical, Inc., Worcester, MA) uses an enzyme-linked immunoabsorbent assay to detect the lipoteichoic acid of gram-positive bacteria and polysaccharide antigens specific to gram-negative bacteria.¹³ It is the only rapid bacterial detection test cleared for use as a “safety measure” by the FDA. A test can be labeled for use as a safety measure when “clinical studies have shown benefit for detection of contamination not revealed by previous bacterial testing and where clinical specificity was determined.”³ According to the draft guidance, these two approved tests act as a safety measure and can extend the shelf life of platelet products by an additional 24 hours, not to exceed 7 days.

Benefits of both rapid bacterial methods are clear. Both detection methods can detect clinically significant levels of bacterial contamination of platelets, serving as an additional safety measure to reduce TTIs and STRs. Neither methodology has been shown to alter or interfere with the efficacy of the platelet product. In addition, the PGD test allows for an extension of platelet shelf life, aiding in inventory management and reducing platelet wastage. However, the PGD test is not currently cleared for use on platelets suspended in platelet-additive solutions (PAS). Neither test detects viral or protozoan activity in platelet products. In addition, neither bacterial detection test is cleared for reduction of any additional adverse platelet transfusion events.

Pathogen Reductions Technology

Pathogen reduction technology (PRT) is currently cleared to control bacterial contamination risk. The Intercept® system utilizes amotosalen in the presence of UV light.¹⁰ Amotosalen is a psoralen that selectively binds to nucleic acids cross-linking them upon photoactivation, rendering pathogens inactive, and unable to replicate.¹⁰ The Intercept brand includes a compound absorption device to recover residual amotosalen to reduce toxicity of the treated platelet product.

Although the Intercept® system package insert notes that there is about a 10% loss of platelet product when undergoing amotosalen-UV treatment,¹¹ efficacy of the platelet product is not compromised. In one study, PRT treatment did not affect the mean 1-hour Corrected Count Increment, representing an adequate response to transfusion.¹⁴ In addition, Amato, Schennach, Astl et al.,¹⁵ demonstrated that among patient subpopulations, there were no differences in the platelet concentrate use per patient, number of platelet concentrate units transfused, or amount of time between platelet transfusions between the control and test patients.

As previously stated, bacterial culture and rapid bacterial detection methods do not detect viral or protozoan contamination. In a world of new and emerging pathogens such as Chikungunya Virus, *Babesia*, Dengue Virus,¹⁶ and most recently, Zika Virus,¹⁷ rapid bacterial detection is at a disadvantage to PRT. Since PRT interferes with nucleic acids, even emerging pathogens (for which the FDA may not have a detection test) will be rendered inactive. This also eliminates the need for cytomegalovirus (CMV) testing.¹⁸

In addition to demonstrating clinical effectiveness of PRT, the PREPAREs trial¹⁹ describes several additional benefits of PRT. Not only did residual white blood cells not proliferate but they also could not present antigens at a normal level. The result was a decreased incidence of Graft-vs-Host disease, and decreased potential HLA alloimmunization. Chi, Zhi, and Vostal²⁰ even demonstrated a reduction in acute lung injury.

Conclusions/Future Trends

Based on the FDA Draft Guidelines for bacterial risk control strategies, it is clear that additional measures will be required in the coming years to reduce TTIs and STRs as a result of bacterial contamination of platelet products. According to the current literature, both pathogen reduction technology and point-of-issue rapid bacterial detection prove to be safe and effective measures to reduce the transfusion of bacterially-contaminated platelet products. However, PRT has far-reaching applications, including reducing the need for viral testing, reducing the incidence of graft-vs-host disease, and reducing the incidence of transfusion-related acute lung injury. Intercept® brand is in the process of submitting evidence that demonstrates the efficacy of

their pathogen-inactivated platelets up to 7 days old, which could extend platelet shelf life an additional 24 hours. Its efficacy on other blood components such as whole blood is being tested as well. Further studies should focus its attention on performing cost-comparison studies. These are needed to demonstrate the monetary effects on blood collection and testing facilities as well as transfusion services, since cost now plays a large role in today's healthcare decision-making processes. Nevertheless, it is encouraging to see these measures implemented to provide a safer platelet transfusion for the millions of individuals in the United States currently in need.

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