



Advancing Transfusion and
Cellular Therapies Worldwide

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To: AABB Members

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Re: Recommendations to Address Residual Risk of Bacterial Contamination of Platelets

Summary

Since the introduction of AABB Standard 5.1.5.1, multiple interventions have been implemented to decrease the risk of transmission of bacteria from apheresis platelet transfusions.¹ These interventions include improved arm disinfection, diversion of an initial volume of the collected apheresis unit, and use of automated cultures inoculated early in the shelf life of the apheresis platelet component. Automated bacterial cultures also have been used for testing of prepooled and stored whole-blood-derived (WBD) platelets. When Standard 5.1.5.1.1 became effective in January 2011, a point-of-issue rapid assay generally began to be used for WBD platelets, including those that are transfused singly or pooled immediately before transfusion.²

Recently, increased concern has been focused on the residual risk of bacterial contamination of apheresis platelets. Subsequent to an AABB-sponsored public conference on secondary bacterial screening of platelet components on July 17, 2012, and an Food and Drug Administration (FDA) Blood Products Advisory Committee (BPAC) meeting on September 21, 2012, AABB is publishing this Association Bulletin to provide updated information about bacterial contamination in apheresis platelet components and to make several recommendations.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains recommendations for all blood establishments that distribute and/or issue platelet components for transfusion.



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Recommendations

AABB recommends that blood collecting organizations and transfusion services 1) develop a policy or policies to further reduce the residual risk of bacterial contamination of apheresis platelets, 2) improve the recognition and monitoring of septic transfusion reactions (STRs) of all platelet components, and 3) optimize appropriate transfusion practice for all platelet components.

Background

Since 2003, multiple interventions including improved arm disinfection, the diversion of an initial volume of the collected apheresis unit, and the use of automated cultures inoculated early in the shelf life of the apheresis unit (usually at 24 hours) have been implemented to decrease the risk of transmission of bacteria from apheresis platelet transfusion.

Data on STRs gathered by the American Red Cross (ARC) and data on sepsis-related fatalities reported to the FDA indicate that since these interventions have been implemented, there has been a 50% to 75% decrease in both of these adverse outcomes.³⁻⁵ Of particular note is the effectiveness of early culture testing in addressing gram-negative bacterial contamination, which historically had accounted for approximately two-thirds of transfusion fatalities associated with platelet units contaminated by bacteria.⁵⁻⁸

Despite these results, several studies have established that apheresis platelets contaminated with bacteria continue to be transfused and that these sometimes result in STRs in recipients. A large multicenter US study [Post Approval Surveillance Study of Platelet Outcomes – Release Tested (PASSPORT)] found that at platelet outdate (which was day 7 of storage), 1 in 1500 units were contaminated with bacteria that were not detected by early automated culturing.⁹ Studies conducted in Ireland and Wales found the bacterial contamination rate at product outdate (5 days) to be between 1 in 1000 and 1 in 1200 for a mixed inventory of apheresis and buffy-coat pooled platelets.^{10,11} Based on clinical data reported to the ARC from hospitals that it supplies, the STR rate following transfusion of apheresis platelets screened for bacteria by early automated culture from 2007-2011 was estimated to be 1 in 107,000 (95% CI: 1 in 77,000 to 1 in 143,000).^{12,13} It has been well established that the majority of STRs are caused by aerobic gram-positive species.^{6,7}



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A recent study using point-of-issue, non-culture-based bacterial screening of apheresis platelets previously tested by early culture has also corroborated the rate of undetected bacterial contamination.¹⁴ Testing using the Pan Genera Detection (PGD) assay (Verax, Worcester, MA) of 27,620 apheresis platelet units that tested negative on early culturing [BacT/ALERT (bioMerieux, Marcy l'Etoile, France) or Enhanced Bacteria Detection System (eBDS; Pall Corporation, Port Washington, NY)] was performed within 24 hours of transfusion (or shortly after transfusion) in 18 hospitals. Nine repeat-reactive units were confirmed by culture to be bacterially contaminated (PGD true-positive rate: 326/million or 1 in 3068) and 149 were PGD repeat reactive but culture negative (PGD false-positive rate: 5390/million or 1 in 185). In a substudy that (re)cultured 10,344 PGD-negative units at time of issue, two were culture positive and PGD false negative (residual risk = 193/million or 1/5172). Additionally, one reported STR was detected by routine surveillance from a PGD-negative unit that was not part of the culture substudy. Notably, only gram-positive organisms were detected by the PGD assay with the implication being that the majority of (if not all) gram-negative organisms were detected by early screening culture or, that if there were false-negative early-culture results for gram-negative organisms, the PGD assay was not able to detect them.

From these data, the authors projected that implementation of PGD screening at the point of issue for apheresis platelets that tested negative by early culturing had the potential to prevent over 300 STRs per year.¹⁴ The study did not evaluate whether point-of-issue screening could replace early culture testing. As discussed above, no clinical data exist to suggest that replacement of early culturing by point-of-issue screening would provide equivalent safety to current early culturing protocols.

Information pertinent to Recommendation 1: Develop a policy or policies to further reduce the residual risk of bacterial contamination of apheresis platelets

AABB sponsored a public conference, "Secondary Bacterial Screening of Platelet Components," held in Bethesda, MD on July 17, 2012 to review current practices and potential options for transfusion services and blood donor centers to address the residual risk of bacterial contamination of apheresis platelets. Data were presented by a number of invited speakers. In an open session, presentations were made by a variety of stakeholders including patient advocates, manufacturers of testing devices, blood collecting organizations, and hospital transfusion



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services. Subsequently, an FDA BPAC meeting on September 21, 2012, provided a further forum for the presentation and discussion of similar subject matter. At the BPAC meeting, the 18-member committee voted unanimously that "additional measures are necessary to decrease the current risk of transfusion of bacterially-contaminated platelet products."

Pertinent information from the talks and discussions at both of these meetings, which should be helpful in implementing AABB's first recommendation, is summarized below. Although the risk of death due to STRs from gram-negative organisms has markedly decreased, the fatality risk attributable to gram-positive species appears unchanged despite widespread implementation of early automated culturing. Coagulase-negative *Staphylococcus* species remain an important residual pathogen, accounting for 58% of platelet-related STRs reported to ARC.¹² Strategies to address residual gram-positive contamination are needed.

There is evidence showing enhanced yield of early bacterial culturing when a larger platelet volume (8 mL vs 4 mL) is inoculated in the BacT/ALERT system.^{3,15} However, at present, there is no standard regarding the optimal inoculum and a recent AABB survey indicated that some centers inoculate 4 mL. Extending this line of reasoning further, one large blood collection system reported on its plans to further increase culture volume beyond 8 mL for split apheresis products (doubles or triples) and presented a mathematical model indicating that this would increase the yield of positive cultures.¹⁶ Studies are needed to assess the impact of increased inoculum volume with the goal of developing a standard inoculum volume.

Culturing soon after collection (usually 24 hours) is the current prevailing practice for bacteria detection in apheresis products. The sensitivity of the approach is limited by the low concentration of bacteria and the delayed and/or slow growth rate of certain organisms early in storage.^{10,17} One approach to enhancing culture sensitivity could be to inoculate the culture at a later time in platelet storage (e.g., 36-48 hours rather than 24 hours). However, before adopting this approach, the impact of this change on platelet availability would need to be evaluated and inventory management practices (e.g., time of release of the unit by the blood center) might need to be modified to prevent platelet shortages.

It appears from recent ARC hemovigilance data that fresher units pose a lower risk for STRs than units stored for 4 or 5 days,¹³ although the recently published PGD clinical trial data did not



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demonstrate such a definitive distinction for detection of bacterial contamination between day 3 vs day 4-5 platelets.¹⁴ Data from two large centralized transfusion services reported at the AABB July 17, 2012 conference and the BPAC September 21, 2012 meeting indicated that the majority of their bacterial yield (6 of 7 positives) from PGD screening of WBD platelets was for products stored for 4 or 5 days.

One approach to decreasing STRs could be to transfuse platelets as early as possible in their shelf life. Alternatively, facilities performing an additional point-of-issue rapid assay on apheresis platelets (see below) could do so only later in the storage interval (e.g., day 4 or day 5) due to the lower relative risk earlier in storage. Facilities using such an approach should review available literature in determining a storage interval for testing under this option. When considering this issue, the BPAC voted 16 yes, 1 no, 1 abstain to the question "For platelets limited to 5 days of storage do the available data support a strategy to culture platelets after the first 24 hours of storage and then retest day 4 and day 5 platelets just once with a rapid test on day of transfusion?" When the committee was asked a further question: "Should the same strategy apply to testing of day 3 platelets?" the vote was 5 yes, 5 no, 7 abstain.

Previously published extensive surveillance data from one hospital shows that platelet units with bacteria concentrations of CFU $<10^5$ /mL are much less likely to cause severe STRs than are units with higher bacteria concentrations.¹⁸ Nevertheless, it remains possible that a unit with a lower concentration could cause an STR if transfused to a susceptible recipient. Furthermore, only limited data exist on the possible risk of delayed septic complications attributable to platelet units with low bacterial titers that were not intercepted by available methods.¹⁹⁻²² Further study will be needed to clarify this issue. Process errors still account for a small number of platelet-related STRs. Quality improvement steps to minimize process-related failures should be implemented. Developing robust electronic control processes similar to those employed in viral disease testing might help.

Another approach to decreasing risk is the implementation of point-of-issue testing. Currently, only one assay (PGD, Verax) has been approved for secondary screening of apheresis platelets. Data from a web-based AABB survey conducted in 2012 indicate that very few hospitals are performing PGD point-of-issue screening of apheresis platelets. The PGD assay is also approved for detecting bacteria in leukocyte-reduced or non-leukocyte-reduced pools of WBD platelets



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that are pooled within 4 hours of transfusion. A second manufacturer's assay (BacTx, Immunetics, Boston, MA) has recently been approved by FDA for detecting bacteria in leukocyte-reduced WBD platelets that are pooled within 4 hours of transfusion, but is not FDA-cleared for secondary screening of apheresis platelets.²³ Additional studies of this system with apheresis platelets are currently under way.

The Verax clinical trial demonstrated a substantial yield of bacteria-contaminated units when PGD was used as a secondary bacteria detection assay. However, there are limited published data with regard to the performance of the PGD assay. Routine operational data for secondary screening of apheresis platelets were reported at the conference by two institutions that reported no yield. Specific data from one of the institutions was 0 confirmed positives in 3505 4-day-old apheresis platelet units.^{24,25}

Independent laboratory evaluation indicates that PGD performance for gram-positive organisms was similar to package insert claims ($\sim 10^4$ to 10^5 for most evaluated species) but detection of some strains of gram-negative organisms (e.g., *Escherichia coli* and *Klebsiella pneumoniae*) was not as good.²⁶ Significant inter-operator variability was also reported and the subjective interpretation required for determining weak-positive reactions was cited as a concern.²⁷

With regard to logistics of point-of-issue screening, multiple institutions stated that logistics were not a barrier to implementation of the PGD assay. However, implementation requires revision of the laboratory's workflow and may require additional staff commitment to testing and/or unit management. Assessment of turn-around time needs to include time for assay performance as well as time for additional process steps (computer entry, labeling, and quality checks). Automation of results generation and management would improve testing capability. Screening can be performed either in batch mode or "on demand." Batch screening is likely to be the preferred approach to maximize the efficiency of providing a screened inventory. If the need for platelet support is not urgent or frequent, performing on-demand screening may be manageable. PGD false-positive rates are substantially higher if determined by initial reactivity as compared to repeat reactivity, the latter being permitted by the package insert. Using the repeat-reactive approach, the false-positive and product discard rates range from 0.3% to 0.5%.^{14,28} The false-positive rate poses a particular concern in the risk/benefit analysis of special platelet products; e.g., HLA-matched or HPA-1-negative platelets.



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The optimal period for product shelf life following PGD batch screening needs to be defined. The package insert states that results are valid for 24 hours after testing for leukocyte reduced apheresis platelets, but this claim is not supported by data. A requirement to track screened product in order to identify those units requiring retesting after the validity period has lapsed would be needed to avoid release of product without valid PGD results. Creation of a blood product controlling attribute that is time-limited and different from the expiration date of the platelet product (e.g., a 24-hour limit for actionable PGD test results) would be desirable to aid inventory management. Careful attention to clinical ordering patterns is needed to limit retesting to a small fraction of the inventory.

Workflow issues and budgetary considerations have led two of the institutions that previously performed PGD testing on apheresis platelets to either discontinue or consider discontinuation of this testing. Several speakers at the AABB conference stated that, in the current cost containment environment in hospitals, budgetary constraints preclude hospitals from adding new testing in the absence of a regulatory requirement.

Although not discussed in detail at the AABB July 17, 2012 conference, it should be noted that additional steps to detect bacteria in apheresis platelets should not be needed in facilities located in countries that treat platelets with a regulatory-approved pathogen inactivation (PI) system.²⁹ The PI bacterial sepsis mitigation option is the most definitive approach – but remains unavailable in the United States at this time. Ongoing experience from those countries adopting pathogen inactivation may eventually influence decisions by US policy makers regarding PI.

Information pertinent to Recommendation 2: Improve the recognition and monitoring of septic transfusion reactions of all platelet components

Improved capture of platelet-related STRs is needed. Clinicians should be made aware of the possibility of STRs following platelet transfusion. The transfusion service should develop a policy regarding clinical findings suggestive of a STR and educate clinical staff to ensure an effective process for reporting possible STRs. To this end, institutions should review their policies for reporting of transfusion reactions characterized by fever and chills, as well as their procedures for evaluating whether an STR has occurred in such platelet recipients.



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Following apheresis platelet transfusion, if an STR is strongly suspected based on clinical symptoms (temperature criteria, shock) and/or any laboratory finding indicative of bacterial contamination of the transfused unit, the reaction should be reported immediately by the transfusion service to the blood supplier to allow prompt retrieval of "sister" platelet apheresis units (or other co-components from the same apheresis collection) that may also be contaminated. The need for immediate reporting to the blood supplier is a safety issue and is distinct from biovigilance reporting, which would be performed after final culture results were available. Background information concerning the criteria for reporting a suspected STR to the US biovigilance system is available

at <http://www.aabb.org/programs/biovigilance/us/Pages/default.aspx>.

Information pertinent to Recommendation 3: Optimize appropriate transfusion practice for all platelet components

Well-designed clinical studies of platelet transfusion outside the setting of myelosuppressive therapy are extremely limited. Additional challenges in understanding platelet therapy exist due to the growing application of platelet inhibitor drugs for a variety of disorders. Patients treated with these drugs are known to be at greater bleeding risk. Strategies to address bleeding in these patients are needed. Focus on the clinical outcomes of platelet transfusion will be essential in optimizing platelet therapy. AABB members should actively monitor platelet use in their facilities and encourage clinical colleagues to develop trials to answer unaddressed questions of platelet therapy. AABB is currently developing guidelines for platelet transfusion therapy.

Conclusion

Adoption of rapid point-of-issue bacterial screening of apheresis platelets as an additional safety measure requires careful risk/benefit assessment in a broad context to ensure application of the most effective strategy for improving transfusion safety. AABB will work to ensure that information useful for developing policy is available to its membership. In the absence of regulatory guidance from the FDA, assessment of the role of point-of-issue bacterial screening should be performed at the local facility with medical staff involvement because detailed information regarding case mix and platelet logistics requires an in-depth understanding of local operations.



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