Article Review: A recent article published in TRANSFUSION reported platelet septic transfusion reaction rates before and after the introduction of primary culture at a US Academic Medical Center 1991 through 2017

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Bacterial sepsis following platelet transfusion is a continuing threat, principally due to the room temperature storage of platelet concentrates. 58 deaths in the United States attributable to the transfusion of bacterially contaminated platelets were reported to the FDA from 2001 to 2018 including 37 deaths since testing for contamination was required by the AABB in March 2004 through September 2018.[1,2,3] To address this threat, FDA issued a Final Guidance on September 30 2019 in which several strategies were recommended that could be implemented to mitigate risk.[4] The need for additional measures was underscored by an FDA literature review that demonstrated the sensitivity of the primary bacterial culture that to date has been routinely performed in the US on platelets collected by apheresis has been only between 11 and 47%.[5]

Dr. Michael Jacobs at University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine has been the leader of a longstanding clinical research program addressing platelet bacterial contamination and septic transfusion reactions caused by contaminated platelet transfusions. He and his colleagues have recently published a comprehensive review of their scholarship and experience from 1991 through 2017 at their medical center.[1] This publication serves as a capstone to his important body of work and is summarized here. In the report, the authors compare bacterial contamination of platelets and rates of sepsis from platelet transfusion before and after the introduction of testing of pooled and apheresis platelets by primary culture from June 1991 through December 2017.

At the authors' institution, pooled platelets were prepared from whole blood–derived units prepared just prior to issue before the introduction of primary culture whereas whole blood-derived prestorage pools were used after the introduction of primary culture. Primary culture of platelets was initiated for apheresis platelets in 2004 and for pre-storage pools in 2007. In an effort to define better the risks to patients, platelets were also cultured at the time of issue for transfusion. (The authors define this as "active surveillance.") These at-issue cultures were performed on each unit issued from July 1991 through February 1993 and from March 2004 through December 2017. Cultures were performed only on Day 4 or Day 5 units from March 1993 through February 2000. (These surveillance cultures were discontinued in February 2000 but reinitiated in March 2004.) Gram stains were also performed on units on the day of issue from July 1991 through February 2000. Components with positive Gram stains were not released for transfusion.

The authors report the at-issue bacterial contamination rates they detected. Prior to the introduction of primary culture, 28,457 units were cultured: 12,720 apheresis platelets and 15,737 at issue pools. After the introduction of primary culture 97,595 units were cultured at

release: 77,438 apheresis platelets and 20,157 pre-storage pools. Seventy-seven units were culture positive: 43 in the pre–primary culture era and 34 after primary culture was introduced. The storage age of bacterially contaminated platelets at time of issue ranged from 2 to 5 days prior to introduction of primary culture era and from 4 to 5 days after primary culture was introduced. Overall, the rate of bacterial contamination was significantly higher in the pre–primary culture period compared to after primary culture (1511 vs. 348/million; $p < 0.0001$). The contamination rates in apheresis platelets during both periods were very similar (393 vs. 387/million; $p = 0.97$), while the rate in prestorage pools during the post-culture era was significantly lower than the rate of at-issue pooled platelets in the pre–primary culture period (198 vs. 2415/million; $p < 0.0001$).

Sixty-seven of the 77 contaminated units detected were transfused, 36 prior to the implementation of primary culture period and 31 in the post–primary culture period. Transfusion of these 67 contaminated products resulted in 22 septic reactions.

The septic transfusion rate was significantly higher in the pre– versus post–primary culture period (492 vs. 82/million; $p < 0.0001$). Additionally, there were significantly more severe, life-threatening, or fatal septic reactions among all septic reactions in the post– vs. pre–primary culture period (75.0% vs. 21.4%; $p = 0.026$). There was also a higher rate of late onset (>4 hours after transfusion completion) septic transfusion reactions in the post– versus pre–primary culture period (62.5% vs. 14.3%; $p = 0.05$).

Overall contamination and septic rates decreased significantly in post–primary culture period ($p < 0.0001$ for both comparisons). These decreases between the two time periods were significantly associated with pooled platelets (contamination rates 2415 vs. 198 $p=0.0001$; septic transfusions, 826 vs. 50/million $p=0.0006$), while rates for apheresis platelets in both time periods were similar (contamination rates, 393 vs. 387 $p=0.97$; septic transfusions 79 vs. 90/million $p=0.98$).

After active culture surveillance was initiated, there were 14 septic reactions in the pre-primary culture era. Of these, 7 were recognized by the clinical team and transfusion reactions were reported to the transfusion service, 4 were recognized but not reported, and 3 were not recognized as transfusion reactions. There were 8 septic reactions during the post–primary culture period, of which only 1 was recognized by the clinical team and reported to the transfusion service, while 6 were recognized but were not reported, and 1 was not recognized as a transfusion reaction. The recognition of septic transfusion reactions associated with a failure to report these in the primary culture era was associated with reactions occurring more than 4 hours after transfusion. This may have been because the age of units transfused in this period was older (2-5 days vs. 4-5 days) owing to the hold periods associated with primary culture. These older components may have had a greater proportion of the slower growing Gram-positive organisms that can contaminate platelets and which are more likely to be associated with delayed septic reactions.

The authors analyzed bacterial concentrations in relation to the likelihood of a septic reaction. Transfusion of units contaminated with bacterial concentrations >10^5 CFU/mL resulted in significantly more septic reactions than platelets with bacterial loads ≤10^5 CFU/mL in both pre– and post–primary culture periods (p = 0.001 and 0.01, respectively). Not surprisingly, the severity of reaction was also correlated with the bacteria concentration of the transfused component. In the pre-primary culture period 13/17 transfusions with >10^5 CFU/ml resulted in a septic reaction compared to 4/22 below this concentration. In the post-primary culture era, 8/18 transfusions with >10^5 CFU/mL resulted in a septic reaction compared to 0/12 below this concentration. However, among all contaminated units detected by active surveillance culture or passive surveillance (defined as the detection of bacterial contamination of a platelet component by investigation of a reported transfusion reaction), there was no difference in the rate of septic transfusion reactions in either the pre- or post-primary culture periods regardless of bacterial concentration. Interestingly, there were no significant differences in the severity of septic reactions, the early onset of reactions, and mean bacterial loads (1.04×10^{10} vs. 1.82×10^7 CFU/mL; p = 0.17) between units contaminated with less versus more virulent organisms.

Of 40,144 platelet components tested by BacT/ALERT (bioMérieux) using 8- to 10-mL samples and 43,266 by eBDS (Haemonetics) using 3- to 4-mL samples, a total of 26 units were found to be contaminated with bacteria at the time of issue. 12 had been cultured with BacT/ALERT and 14 with eBDS. The contamination rates were similar: 299 and 279/million, respectively (p = 0.84). There was no significant difference in contamination rates between apheresis platelets and post-storage pools. This is of interest since the eBDS used approximately half the volume of BacT/ALERT (3-4mL; 8-10mL) reflecting no increase in detection with a doubling of sample volume.

The authors document that the introduction of primary culture of platelets in 2004 significantly reduced bacterial contamination and septic transfusion rates with pooled platelets whereas primary culture did not significantly reduce the rate of bacterial contamination (393 vs. 387/million) or the rate of septic reaction with apheresis platelets (79 vs. 90/million). The authors state “These findings highlight the continued need to further reduce these rates by performing secondary testing near time of use or application of pathogen reduction technologies.” Pointedly, they do not include large volume delayed sampling (LVDS) in their recommendation.

From a literature review of six published studies the authors calculated a mean contamination rate of apheresis platelets found negative by primary culture of 358/million (excluding an outlier value of 823/million). They pointed out this translates to approximately 700 bacterially contaminated apheresis platelets annually in the US which would result in more than 170 STRs, with more than 130 likely to be severe, life-threatening, or fatal based on the rates they report They restated, “Implementation of measures such as secondary testing or pathogen reduction is needed to prevent these septic transfusion reactions.”

The authors address what would be required to assure that LVDS would provide safety in addition to the primary culture already performed. They conclude 25,000 to 50,000 components would need to be cultured to demonstrate with statistical significance that rates would be reduced to less than 50 per million. They point out that detection of one contaminated component out of 25,000 is a rate of 40/million, with 95% CI of 10-223/million and detection of 1 contaminated component out of 50,000 is a rate of 20/million, with 95% CI of 5-111/million. Jacobs had previously called for such a study in his comments to the Blood Products Advisory Committee in November 2017.[6]

The authors compare their results with those reported by the US National Healthcare Safety Network Hemovigilance Module for 2010 to 2016 obtained from 82 to 277 hospitals reporting annually. During this period, 30 septic reactions were passively reported from 1,536,115 platelet transfusions (19.5/million)—26 from apheresis platelets (24/million) and 4 from pooled platelets (8.6/million). The rates reported by Jacobs and colleagues with active surveillance (90/million for AP and 50/million for PSPPs) were considerably higher. Passive reporting of septic reactions in the period reviewed by Jacobs and colleagues was about 10/million. These data underscore the inadequacy of passive reporting as previously published by Hong et al.[7]

The authors specifically address the LVDS report from the United Kingdom. They state it does not provide evidence that the method is better than the standard primary culture method in use in the United States. They note reporting is passive which results in the very low septic transfusion reactions and by the fact that insufficient at-issue or outdate cultures have been reported to determine the real rate of contamination. They note the contrast between the septic transfusion rate by passive surveillance rates in the UK study (3/million) and the septic transfusion rate by active surveillance in the post–primary culture period in their study (82/million) is “striking.” They note only one of eight septic reactions at their institution during this period was recognized and reported to the transfusion service, six of eight were recognized but not reported and one was unrecognized as a transfusion reaction.[7] Dr. Art Bracey called attention to the many concerns with the UK LVDS reports in his comments to the FDA Docket on this issue.[8]

The authors offered the following conclusions which we annotate here.

1) “Introduction of primary culture significantly reduced bacterial contamination and septic transfusion rates associated with pooled but not apheresis platelets.” Delayed release due to early culture and subsequet quarantine resulted in an aging of the inventory with increased transfusion of day 4-5 platelets. This would likely result in higher rates of units with clincically significant levels of bacteria and thereby explain why culture did not reduce contamination rates in apheresis platelets. Furthermore, primary culture detects many Gram-negatve contaminants but misses most of the more common Gram-positive bacteria. These latter organisms are associated with a delayed onset of sepsis. This likely explains the higher rate of delyed onset of septic reactions (>4 hours after transfusion was completed) after primary culture was implemented.

2) “Reporting of transfusion reactions by caregivers to the transfusion service is suboptimal, limiting the value of findings from passive surveillance programs.”

3) “Enhanced primary culture methods have not been shown to be better than standard methods.” On May 20, 2020 FDA cleared the BACT/ALERT® BPA Culture Bottle and BACT/ALERT® BPN Culture Bottle for use as safety measures in accord with the Final Guidance for LVDS of platelets no sooner than 48 hours after collection to extend permissible storage up to seven days (BK200472).[8] LVDS would delay release and transfusion of platelets due to sampling no sooner than 48 hours with the attendant risk of bacterial growth in a greater proprotion of units than with earlier sampling and transfusion. There is no assurance these contaminated units would be detected by a 48-hour culture.

4) “There is a need for further reduction of bacterial contamination rates by performing secondary testing near the time of use by rapid tests or secondary culture, or by application of pathogen reduction technologies.”

Overall, this powerful manuscript documents the prodigious and tenacious efforts of Dr. Michael Jacobs and his colleagues during a 27-year period at a single institution to understand and prevent the continuing threat to vulnerable patients posed by the bacterial contamination of platelet components and meaningfully informs clinical practice.

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2. Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2017 Available at https://www.fda.gov/media/124796/download#:~:text=2%2C3%20During%20FY2013%2C%20there,2016%2C%20and%2044%20in%202017. (Accessed 03 August 2020)

3. Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2018 Available at https://www.fda.gov/media/136907/download#:~:text=2%2C3%20During%20FY2014%20there,2017%2C%20and%2043%20in%202018. (Accessed 03 August 2020)

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5. US Food and Drug Administration. Bacterial risk control strategies for blood collection establishments and transfusion services to enhance the safety and availability of platelets for transfusion; draft guidance for industry. FDA. March 2016. p 27.Available at: https://www.fda.gov/media/90370/download (Accessed 03 August 2020)

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7. Hong H, Xiao W, Lazarus HM, et al. Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance. Blood 2016;127:496-502

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