

## **THE INADEQUACY OF PASSIVE SURVEILLANCE TO DETECT SEPTIC TRANSFUSION REACTIONS FROM PLATELET TRANSFUSION**

Septic transfusion reactions resulting from the transfusion of bacterially contaminated platelet components are a potentially fatal hazard of platelet transfusion. Platelet components are particularly vulnerable to bacterial contamination owing to their storage at room temperature. Although interventions such as culturing platelet components shortly after collection mitigate this risk, serious, life-threatening, and fatal reactions to bacterially contaminated platelets continue to occur regularly. A recent report in *BLOOD* documented that septic reactions resulting from the transfusion of bacterially contaminated platelets are a major hazard of platelet transfusion and that these reactions are often not reported to the hospital transfusion service.<sup>1</sup>

In this report, Hong and colleagues performed active and passive surveillance for bacterially contaminated platelet components from 2007 through 2013 by culture of platelet aliquots at the time of transfusion and reviewing reported transfusion reactions.<sup>1</sup> Each platelet had been cultured 24 hours after collection and released for transfusion as negative. The authors found that 20 of 51,440 platelet units (1 in 2,572) that had been transfused were actually bacterially contaminated by active surveillance. Five of these resulted in septic transfusion reactions one of which was fatal and one of which was life-threatening. Four of the five reactions occurred in outpatients. None of these reactions had been reported to the transfusion service by passive surveillance. During this period, 284 transfusion reactions had been reported by passive surveillance (e.g. non-hemolytic febrile and allergic reactions), although none of these patients had received bacterially contaminated platelets. This study documents the continuing risk of septic transfusion reactions from platelet transfusion despite negative results from early culture and the failure of passive surveillance to detect and report these reactions to the hospital transfusions service.

In an accompanying editorial titled “Transfusion related sepsis: a silent epidemic”, Benjamin noted that the risk of sepsis is compounded by the transfusion of multiple platelets to immunocompromised allogeneic stem cell transplant patients and that outpatients may be at particular risk of under recognition.<sup>2</sup> (The reactions occurred 9-24 hours post-transfusion in the report by Hong et al.) Benjamin concluded that the experience of Hong et al. was likely to be representative of the US as a whole as the authors detected similar rates of bacterial contamination in both apheresis and whole blood-derived platelets and also from 2 different suppliers using the 2 available post-collection bacterial culture screening devices.

The findings by Hong et al. are similar to the authors’ experience at the same institution from 1991 to 2006, where active surveillance detected 32-fold more bacterially contaminated platelet units and 10.6-fold more septic reactions than did passive surveillance. In this large study, a total of 56,883 apheresis platelet units and 182,100 whole blood-derived units in

36,418 pools were transfused during the surveillance period. Fifty-two bacterially contaminated platelet units were detected (50 by active and 2 by passive surveillance).<sup>3</sup>

A retrospective analysis of French active hemovigilance data based upon the surveillance of patients by dedicated hemovigilance personnel (where bacterial screening is not performed) included  $1.94 \times 10^6$  platelet concentrates transfused from 2000 to 2008. The incidence of any platelet component “transfusion transmitted bacterial infection (TTBI)” was 24.7 per million (1:40,486) and incidences of severe (life threatening or death) and fatal TTBI were 13.4 and 5.14 per million, respectively.<sup>4</sup> It must be noted that the definition of a TTBI in this report included temperature above 39°C or an increase in temperature above 2°C occurring within 2 hours after the start of the transfusion. However, as noted above, the five cases of sepsis reported by Hong et al. occurred 9-24 hours post-transfusion. Thus, if this strict time interval was honored to diagnose a TTBI, it is likely that many such reactions were not recorded. Since no bacterial testing was performed, it is not possible to know how many bacterially contaminated units were transfused during the course of the study.

Eder et al. have also documented the failure of the early culture to detect all bacterial contamination of platelets.<sup>5</sup> Between March 1, 2004, and May 31, 2006 they performed bacterial culture testing on 1,004,206 platelet donations from which 1,496,134 components were distributed. During this period, 20 septic transfusion reactions were reported (1:74,807 per distributed component), including 3 fatalities (1:498,711 fatalities per distributed component). The authors concluded that platelet component contamination with bacteria that evade detection by early culture remains “a significant residual transfusion risk”. (It should be noted that a significantly higher rate of confirmed-positive bacterial cultures was seen with products collected utilizing two-arm collection procedures compared to one-arm procedures (22.7 vs. 11.9 per  $10^5$  donations; odds ratio 1.9; 95% confidence interval 1.4-2.7)).

With respect to another adverse event following transfusion in the US, active surveillance for platelet transfusion associated circulatory overload found significant underreporting, with a 36-fold difference in detection between active and passive surveillance: 1:5,997 cases reported by passive surveillance compared to 1:167 by active surveillance.<sup>6</sup>

The aforementioned reports collectively document that early culture fails to identify many pathogenic bacteria in platelet components and that passive surveillance fails to identify many, if not most, septic transfusion reactions resulting from the transfusion of these contaminated components. Furthermore, even active hemovigilance programs have limitations, particularly if patients are not followed for a sufficient time after transfusion for septic reactions to become manifest.

The need to take additional measures to address the problem of bacterial contamination of platelets has been addressed recently by the FDA in draft guidance<sup>7</sup> and the AABB in bulletins

issued in 2012 and 2014.<sup>8,9</sup> In the 2012 Bulletin, the AABB recommended 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 of all platelet components, and 3) optimize appropriate transfusion practice for all platelet components.”<sup>8</sup> The 2014 Bulletin provided “transfusion service medical directors with guidance on the recognition of suspected reactions to bacterially contaminated platelets and the steps recommended to minimize patient harm”.<sup>9</sup>

Jacobs and colleagues reported a landmark study conducted in eighteen US hospitals in which active surveillance with the PGD test was performed on the day of issue on apheresis platelets released by collection centers as culture negative.<sup>10</sup> Confirmatory bacterial culture was performed when PGD tests were repeatedly reactive. The PGD test detected confirmed positive bacterial contamination in 1:3,069 (9 of 27,620) doses released as negative by prestorage culture. The ages of these contaminated doses were Day 3 (n = 4), Day 4 (n = 2), and Day 5 (n = 3). Application of this test within 24 hours of issue can interdict contaminated units and prevent septic transfusion reactions. If the data were extrapolated to the entire US apheresis platelet supply, it would be expected that approximately 650 contaminated apheresis units are being transfused per year in the United States, and that the use of the PGD test on the day of issue has the potential to prevent a large number of septic transfusion reactions and many fatalities each year.

### Summary of Recent Surveillance Studies

Study	Surveillance Methodology	Dates	Number of units	Contaminated Doses Identified	Deaths
Hong et al. <sup>1</sup>	Active Culture at Issue and Passive	2007-2013	51,440	1:2,572	1A (1:51440), zero P
Jacobs et al. <sup>3</sup>	Active Culture at Issue and Passive	1991-2006	102,998 A 135,985 P	1:2,060 1:67,992	1A (1:102,998) 1P (1:135,985)
Lafeuillade et al. <sup>4</sup>	Hemovigilance*	2000-2008	1,940,000**	1:40,486	10 (1:194,000)
Eder et al. <sup>5</sup>	Passive	2004-2006	1,496,134***	1:74,807	3 (1:498,711)
Jacobs et al. <sup>10</sup>	Active PGD Testing and Passive	2008-2010	27,613****	1:3,069	0

STR=Septic transfusion reactions. A=Active. P=Passive. \*"Compulsory reporting for all health care providers" \*\*No bacterial detection performed \*\*\*Distributed components\*\*\*\*excludes seven units not transfused owing to positive PGD test

The Platelet PGD® test offers a means for the detection of aerobic and anaerobic Gram-positive and Gram-negative bacteria in:

- leukocyte reduced apheresis platelets (LRAP) suspended in plasma, LRAP suspended in Platelet Additive Solution C (PAS-C) and plasma, and pre-storage pools of up to six leukocyte reduced whole blood derived platelets suspended in plasma, within 24 hours prior to platelet transfusion as a safety measure following testing with a growth-based quality control test cleared by the FDA for platelet components and

- pools of up to six units of leukocyte reduced and non-leukocyte reduced whole blood derived platelets suspended in plasma that are pooled within four hours of transfusion.

1. 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.
2. Benjamin R. Transfusion-related sepsis: a silent epidemic. *Blood* 2016;127:380-381.
3. Jacobs MR, Good CE, Lazarus HM, Yomtovian RA. Relationship between bacterial load, species virulence, and transfusion reaction with transfusion of bacterially contaminated platelets. *Clin Infect Dis*. 2008;46(8): 1214-1220.
4. Lafeuillade B, Eb F, Ounnoughene N, et al Residual risk and retrospective analysis of transfusion-transmitted bacterial infection reported by the French National Hemovigilance Network from 2000 to 2008. *Transfusion*. 2015; 55(3):636-646.
5. Eder AF1, Kennedy JM, Dy BA, Notari EP, Weiss JW, Fang CT, Wagner S, Dodd RY, Benjamin RJ. A Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: the American Red Cross experience (2004-2006). *Transfusion*. 2007;47:1134-42.
6. Raval JS, Mazepa MA, Russell SL, Immel CC, Whinna HC, Park YA. Passive reporting greatly underestimates the rate of transfusion-associated circulatory overload after platelet transfusion. *Vox Sang*. 2015;108(4):387-392.
7. US Food and Drug Administration. Bacterial Detection Testing by Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion.  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf>

8. AABB Association Bulletin #12-04. Recommendations to Address Residual Risk of Bacterial Contamination of Platelets <http://www.aabb.org/programs/publications/bulletins/Pages/ab12-04.aspx>
9. AABB. AABB Association Bulletin #14-04. Clinical Recognition and Investigation of Suspected Bacterial Contamination of Platelets. <http://www.aabb.org/programs/publications/bulletins/documents/ab14-04.pdf>
10. Jacobs MR, Smith D, Heaton WA et al. Detection of bacterial contamination in prestorage culture-negative apheresis platelets on day of issue with the Pan Genera Detection test. *Transfusion* 2011;51:2573–2582