Platelet Bacterial Safety – What's Next?

In accordance with AABB Standards, all platelet units are collected using steps to limit the potential for bacterial contamination and are tested to detect bacteria prior to their release or issue. While any test has the potential for false negativity and failing to detect the target agent, culturing platelet units has yielded less safety than anticipated. Currently, there are multiple discussions ongoing by regulatory agencies and accrediting bodies whether additional detection steps should be implemented.

When culturing of apheresis platelets first began to be implemented in the US in 2003 and 2004, there was hope that this would provide sufficient safety and even allow the reintroduction of storage for 7 days rather than 5. (The reduction in allowed storage time had occurred with the recognition that contaminating bacteria were more likely to grow to dangerously high concentrations with longer storage. The five-day storage period was a compromise between concerns about shortages from outdating with a short storage limit and safety concerns.) The FDA indicated that demonstration of a residual risk of contamination below 1 per 10,000 units would be necessary to approve 7-day platelet storage. Repeat cultures of 6,039 outdated, culture-negative apheresis units found 4 positives that had been missed by Day 1 culturing, a rate of 662/million or 1 per 1,500 (Dumont LJ *et al. Transfusion* 2010;589-99.) thus missing the target by a considerable amount. Since that time, several augmentations to culturing protocols have been widely adopted, including culturing a greater volume of each unit. However a study reported in December 2011 (Jacobs MR *et al. Transfusion* 2011;51:2573-82.) demonstrated that the apparent rate of missed contamination had not decreased markedly. Nine contaminated units out of 27,620 apheresis platelet units had been missed by Day 1 culturing, meaning that the residual risk of contamination was still 1 in 3,100. This is similar to reports from other countries where surveillance (repeat) cultures of apheresis platelet units indicated that culture detects, at most, about half of contaminated units and that the residual risk is in the range of 1 per 1,000 units.

Conversely, culture does appear to have reduced the risk of mortality associated with bacterial contamination of platelets. Data reported by the FDA suggests a downward trend in the number of reported deaths. The number of reported septic reactions also appears to have declined by about two-thirds (Brecher ME. *Transfusion* online.) This success is probably attributable to culture's greater ability to detect contamination by rapidly growing organisms. These contaminants are primarily gram-negative bacteria that have greater pathogenicity at all concentrations. Nevertheless, as most platelet recipients are immunosuppressed, and infection with more slowly growing organisms is frequently not detected as a consequence of transfusion, many remain concerned that additional steps need to be taken to reduce this risk.

Several approaches have been suggested. One is to re-culture units on Day 3, a time at which even the more slowly growing organisms would have had a chance to multiply to the point where an aliquot would likely contain bacteria. This protocol would be logistically challenging, however, and would likely lead to a dramatic increase in outdating. Further increasing the volume cultured has also been suggested. A modeling of this approach published previously (Wagner SJ, Eder AF. Transfusion 207;47:430-3.) suggested that this

would increase sensitivity but only to a limited extent. Another model, using a lower (more realistic) initial inoculum size (Tomasulo PA, Wagner SJ. Transfusion, in press.) suggests that increasing the volume to 3.8% of the unit volume would reduce the number of falsely negative cultures by half. This has been implemented in Ireland, Wales and Germany; the only report to date, from Germany, did not indicate reduced residual risk, however. An entirely different approach would be to use a rapid detection test shortly before issue of the unit to a patient for transfusion. Today, two such tests are approved by the FDA and both detect common surface antigens on bacteria. While they are "less sensitive" than culture (generally requiring 10,000 – 100,000 bacteria/mL before turning positive), the time at which they are applied makes this a clinically relevant sensitivity threshold. These tests take 30-60 minutes for completion, and thus some laboratories in various parts of the country are considering using them periodically (for example, once each 24 hours) in order to detect any contamination that may have reached detectable levels after having been missed by a Day 1 culture.

The FDA is paying close attention to this issue, as is the AABB. A July 2012 workshop considered the recent data and the possibility of the imposition of a requirement to perform some additional detection testing beyond Day 1 culture for apheresis platelets. The matter will be discussed at the September 2012 FDA Blood Products Advisory committee, as well. Puget Sound Blood Center is closely monitoring the situation and preparing to ensure its ability to fulfill all regulatory and accreditation requirements as well as hospital requests. We believe there will be a requirement to perform some augmentation of current culturing, and this may include a rapid detection test close to issue for apheresis platelets (in addition to the culture based test performed at the blood center). Within our centralized Transfusion Service, we would likely use the same rapid detection test currently in use for whole blood platelets.

We will continue to keep all hospitals informed with any updates. We anticipate that our Transfusion Services will perform rapid detection testing of apheresis units for the hospitals served by the Transfusion Services if this becomes regarded as the most appropriate way of further reducing bacterial risk, and we will assist regional hospitals in implementing this testing if and when requested.

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