

### III. Experience with Monitoring of Bacterial Contamination of Platlets

**Issue Summary**  
**Blood Products Advisory Committee**  
**July 23, 2004**

**Update: Experience with Monitoring of Bacterial Contamination of Platelets**

**Issue: Bacterial contamination of platelets remains a significant risk for transfusion. This update will summarize recent actions by FDA and industry to monitor and decrease bacterial contamination, and will identify current, unresolved issues.**

**Background:**

Bacterial contamination of platelet transfusion products occurs in about 1/2000 products collected. Approximately 1/20,000-1/85,000 transfusions of platelet products lead to a mortality due to bacterial contamination (1). These rates are orders of magnitude greater than that currently estimated for viral pathogens, and this makes bacterial contamination of transfusion products one of the highest transfusion risks today.

The FDA has taken steps to heighten public awareness of this problem by holding 3 workshops and 2 BPAC sessions on the subject since 1995. The message has been that there is a need for a method or a device that detects bacteria in the platelets that could be used as a release test. The FDA proposed that such test would need to be validated by in vitro tests (ability to detect spiked bacteria in a product) and by a field study that defines the specificity and sensitivity of the test under clinical use conditions. Due to the low contamination rate, the study size would need to sample 30-50, 000 units. In the last 2 years two manufacturers have submitted 510K applications for their automatic culture based devices (Pall Corp and BioMerieux) however they only supplied in vitro data and thus were cleared for Quality control use only. QC is done by collection centers to assure that the collection process is in control and is not used to release products for transfusion. The sponsors have so far not initiated or funded any type of a field trial to validate their devices for a release test, nor have requests for public funding been made to federal agencies.

On March 1, 2004 AABB introduced a new standard that requires blood establishments to test all platelet products with a device that can detect presence of bacteria. Devices recommended by AABB range from automatic culture devices from Pall Corp. and BioMerieux Corp., to Gram stain, to pH and glucose measurements made by use of laboratory dipsticks.

FDA has previously approved the automatic culture devices for detection of bacteria in platelet products for Quality Control purposes. Use of these culture systems to screen all platelet collections could be regarded as equivalent to performing 100% quality control testing (i.e. within the label indication), however, the product approvals do not include any performance data on predictive value of positive or negative test results. As such,

any overt or implicit claims that released units are expected to be culture-negative at their time of use are unsubstantiated. Conversely, there is no doubt that interdiction pre-release or via recall of culture-positive units may provide a safety benefit.

The other recommended methods and devices (gram stain, dipsticks) have not been cleared by the FDA for this purpose and clearly are being used off-label. Absent validation of these methods, their use is likely to lead to failed detection of contaminated units (i.e. a wrongful implicit safety claim) and to a high discard rate due to false positive results. The non-approved methods are also more likely to be used for whole blood derived platelets (as opposed to apheresis platelets) because they can be performed by transfusion services prior to issue of units. Whole blood derived platelet transfusion products are made up of a "pool" of 5-6 single units and since culture devices are not approved for testing the pooled product or for pooling samples from individual units each single unit has to be tested and this becomes cost prohibitive. Since it will cost much more to test the random donor pools the centers will either stop providing these products or test them with the other non-approved and non-validated methods. Whole blood platelets have been used as a lower cost alternative to apheresis platelets and this standard may drive them out of use, which could lead to platelet product shortages. Another issue is the possible development of a two-tiered platelet product inventory in the transfusion services, with apheresis products being screened with a validated automated device and pooled whole blood derived platelet product screened with a non validated system.

The FDA and its partners in DHHS are concerned about the potentially disruptive effects that this standard may have on the platelet supply, the absence of validated methods to assure culture negativity of platelet products at point of use, and the absence of any plan to insure that surveillance data are collected on positive units (i.e. speciation of organisms and aggregated public health reporting.)

The major obstacle to approval of automatic bacterial detection devices has been the design of the field studies that would collect data on performance of the devices in actual clinical use. The data that FDA has been seeking is sensitivity, specificity and predictive value of the device when applied to routinely collected platelet transfusion products. The initial study design proposed by the FDA was presented at December 2002 BPAC. It was aimed at sampling of 5 day platelet products early in the storage period (5 days) and then again at outdate or at release of the product. The second culture is used as the reference method since, due to bacterial proliferation during storage, detection of contaminated units is easier to achieve at the end of storage.

There are two additional issues that are closely tied to the issue of bacterial detection. One is extension of platelet storage to 7 days and the other is pre-storage pooling of random donor units. There are potential advantages to blood centers in utilizing both approaches. Platelet storage had been extended to 7 days in the mid-eighties but was reduced to 5 days by a 1986 BPAC over concerns of increased frequency of transfusion-associated sepsis with the older products. Extension of platelet storage could be allowed if there was a bacterial detection device that was approved for detection of contaminated units and if the current platelet storage conditions were validated out to 7 days. The

validation of storage conditions is necessary to assure that the platelet bags provide sufficient gas exchange, and plasma to platelet ratios, so that platelet efficacy would be preserved out to 7 days. Two bags have, so far, been approved for storage of individual units out to seven days (apheresis platelets, Gambro Corp. and whole blood derived platelets, Pall Corp). However, they cannot be used in an clinical application until a bacterial screening test is approved.

Pre-storage pooling has historically been seen as an increased bacterial risk because if one of the platelet units used to make up the pool is contaminated, the bacteria could proliferate to a higher load over the storage period due to the larger volume than they would if they were stored as single units. Thus a bacterial detection device that is approved for release of platelet pools will be needed prior to approval of platelet pre storage pooling. In addition, the pooled product storage bags will need to be validated to demonstrate that they preserve platelet efficacy when stored in a pool out to 5 and 7 days. The validation of the bags and the bacterial detection device for platelet pools was a topic of a March 2003 BPAC topic.

The FDA has had an ongoing discussion with other agencies and blood organizations on how to move forward in this area. A public meeting on this subject was held with the DHHS Advisory Committee on Blood Safety and Availability in April 2004. Capt. McMurtry will summarize this meeting during his presentation today. Also, the AABB has created a Bacterial Detection Task force, which held its first face-to face meeting on June 2, 2004, and the outcome of this meeting and the efforts of the task force will be summarized by Dr. Kleinman.

Progress has been made in determining how data on clinical performance of bacterial detection devices can be collected. FDA has revised its proposed approach in attempts to minimize the projected cost of such studies. Some of the proposals made by the FDA include changing from a study design that would compare contamination rates of platelets on days 5 and 7 after these have been screened by the device on day 1. The current approach is to compare the residual risk of a 7-day-old product that was initially screened at day 1 to the bacterial risk of an unscreened platelet product. Such an approach would use a day 1 culture to define the risk of unscreened platelets and a day 7 culture to define the residual risk and thus decrease the number of culture tests. In addition FDA proposed that the 7 day culture could be done by pooling of the samples since bacterial levels in contaminated units stored out to 7 days should be high and dilution through pooling with other samples would not decrease sensitivity for detection at day 7. However, validation studies would be needed to insure adequate analytical sensitivity of the day 1 culture on pooled platelets.

The current FDA plan is to continue working with all other parties interested in this issue to develop a field trial protocol that will generate data on specificity, sensitivity and predictive value of a bacterial detection test. Once a protocol is finalized, the investigators could seek funding for the study from the NIH and from the test kit manufacturers.

Reference:

1 )Bacterial Contamination of Blood Components: Risks, Strategies, and Regulation:  
Joint ASH and AABB Educational Session in Transfusion Medicine. Hillyer et al.  
Hematology (Am Soc Hematol Educ Program). 2003;:575-89

**AABB Interorganizational Task  
Force on Bacterial Contamination  
of Platelets**

**Steven Kleinman MD  
Chair**

**March 2004 – AABB Standards  
require detection of bacterial  
contamination in all platelets.**

## Overall Purpose of the Task Force

- Centralize issues within AABB
- Monitor activity
- Provide forum for discussion
- Obtain input from agencies

## Task Force Membership

- **Blood organizations** – AABB; ABC; ARC; DdD
  - Transfusion services
  - Blood collection facilities
  - Users of apheresis platelets
  - Users of whole blood derived platelets
  - AABB committees – Standards; CTMC; TTD
- **Government Agencies** – HHS; FDA; CDC; NHLBI

## **Actions**

- **Convened public meeting – included test manufacturers**
- **Prepare further surveys and data collection**
- **Prepare further guidance**
  - **Follow-up to positive culture tests**
  - **Follow-up to positive surrogate tests**
  - **Clinician/patient notification**
  - **Donor notification**

## **Actions (cont'd)**

- **Monitor effects of testing requirements on platelet availability**
- **Develop clinical protocol to permit extension of dating period for apheresis platelets and pooled whole blood platelets**
- **Encourage development of new bacterial detection methods, especially for point of release testing**
- **Consider potential public health reporting**

**Monitoring of Platelet Bacterial Contamination  
By Culture and Extension of Shelf Life of Platelets**

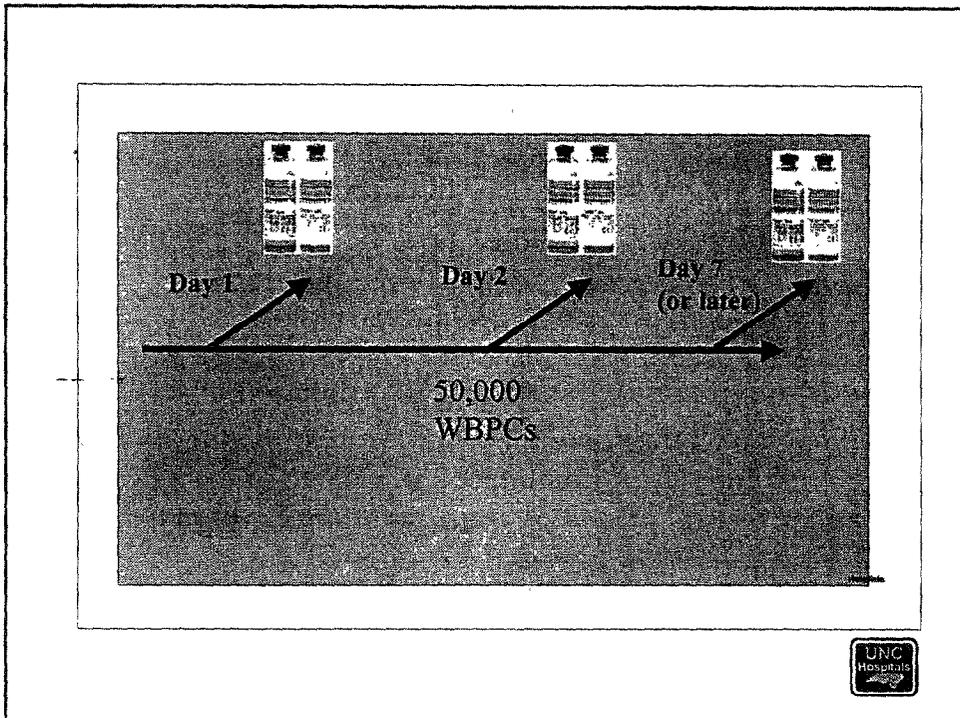
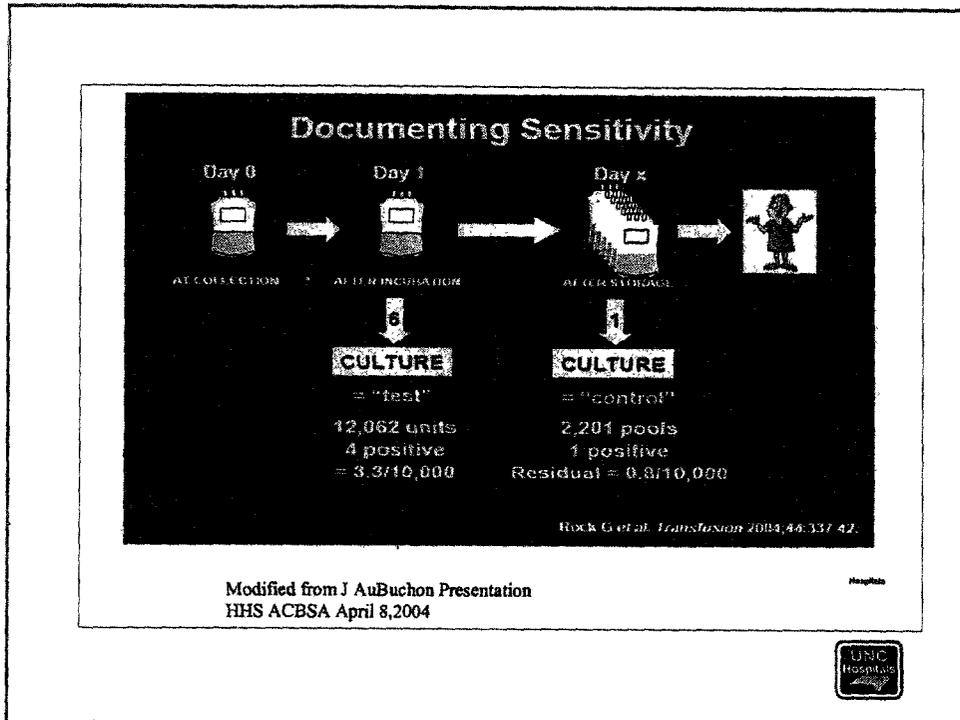


**Specific aim**

**To assess the predictive value of an early bacterial culture of platelet components (products sampled on days 1 and 2 of storage for detection of bacterial contamination).**

**The goal will be to detect 80% or more of all bacterially contaminated platelets with an early culture with a residual risk  $<1/10$ .**





### Size of study:

Per FDA analysis this study would require approximately 50,000 early cultures to provide reasonable assurance of a residual risk less than 10,000 for pre-screened units (95% UCL for 0/50,000 is 0.7 per 10,000)



### To interdict 80 %

Rate early culture	Number of positives with early culture	Allowable positive late cultures
1/1000	50	12
1/2000	25	6
1/4000	13	3





