Experience with universal bacterial culturing to detect contamination of apheresis platelet units in a hospital transfusion service

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BACKGROUND: Bacterial contamination of platelet units poses one of the greatest risks of morbidity and mortality to platelet transfusion recipients. A routine culture of all units (WBC-reduced apheresis platelet units) was instituted on Day 2 over a 2-year period to reduce this risk.

STUDY DESIGN AND METHODS: A sterile connecting device was used to attach a small transfer pack on the morning of Day 2 after collection, and 10 mL of the unit were transferred to the small bag. After disconnection from the unit, about half of this volume was transferred to an aerobic culture bottle of an automated bacterial detection system. Units were maintained in available inventory until and unless a report was received of growth in the sample. When available, the unit or a retained aliquot was recultured if the initial sample was positive. Units were held up to 2 days beyond their 5-day outdate and used for transfusion if no other suitable units were available to meet the clinical need or were evaluated with in vitro testing on Day 8.

RESULTS: Of 2678 units cultured, 16 (0.6%) were positive on initial culture. Thirteen could be recultured, and all of these samples were negative. Shortly after the 2-year period of the study, two units (split from the same collection) were documented as growing coagulase-negative *Staphylococci* 12 hours after sampling. Units transfused on Day 6 or 7 (n = 40) yielded expected clinical responses, and CCI available on 21 recipients 10 to 60 minutes after transfusion demonstrated acceptable results (mean, 14,400 ± 8800; median, 12,191; 90% > 7500). More than 96 percent of units tested on Day 8 had pH greater than 6.2 and continued to demonstrate swirling.

CONCLUSIONS: Routine culturing of apheresis platelet units is feasible, can be accomplished with a low rate of false positivity, and can detect contaminated units. The cost of such a protocol could be mitigated with extension of the storage period, and clinical experience with units held for 6 or 7 days was satisfactory.

Bacterial contamination poses one of the greatest risks of morbidity and mortality faced by the recipients of platelet transfusions. Approximately 1 in 22,000 to 1 in 3000 units of platelets are contaminated with bacteria originating from the donor's skin or bloodstream.[1,2] Although only a portion of these result in clinically recognized post transfusion septic events and not all of these are fatal, careful follow-up of platelet transfusion recipients in France has documented that the death rate from bacterially contaminated units is seven per million apheresis units transfused, or 1 in 140,000.[3] In the United States, longitudinal study of platelet transfusion recipients in one institution has documented the risk of sepsis after receipt of apheresis platelets as 75 per million (1/13,000) and 402 per million (1/2500) after whole blood-derived platelet units; the risks of fatality were documented as 14 per million (1/71,000) and 62 per million (1/16,000), respectively, for these two platelet sources.[4] These risks exceed those of HIV and HCV transmission by more than an order of magnitude.[5,6]

Various approaches have been suggested to reduce the chance of bacteria being collected with the unit or to detect their presence. Augmented skin cleansing preparations and diversion of the first milliliters of blood may reduce by 75 to 90 percent the risk of skin commensal bacteria entering the unit.[7-9] Consumption of glucose by contaminating bacteria may be detected directly or through changes in pH that then may also be reflected as

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loss of swirling.[10-14] The sensitivity of these techniques appears suboptimal, although averaging 75 percent, and a large, potentially fatal, inoculum (in excess of 10^6 CFU/mL) must be present before the necessary change can be detected. Similarly, microscopic examination of a smear from the unit shortly before transfusion, using either gram staining or a fluorescent stain, such as acridine orange, have sensitivities in the range of 10^5 to 10^6 CFU per mL with a substantial false-positive rate.[15,16] A variety of methods to detect bacteria in platelet units are under development by commercial manufacturers.

In bacteriology, culture is regarded as the "gold standard" for sterility testing. This approach poses challenges in transfusion medicine, however, because the initial inoculum may be so low (often projected at 0.1-10 CFU/mL) that detection by culture would require culturing so large a portion of the unit that its therapeutic effectiveness would be diminished significantly. Furthermore, blood banks and transfusion service laboratories do not culture units routinely and may lack automated equipment that facilitates large-scale culturing. The inevitable time lag between obtaining the culture and detecting growth further complicates the management of platelet units because of their short shelf life.

To reduce the substantial threat posed by bacterial contamination of platelet units, we began culturing all apheresis platelet units in May 1999. Our approach was modeled after techniques implemented successfully in several European blood centers[17-20] and was also based on observations in our laboratory and elsewhere that a small volume cultured on Day 2 after spiking bacteria into a platelet unit would consistently contain bacteria despite a low initial inoculum.[12,21] By retaining units beyond their usual 5-day outdate, we accumulated data augmenting that obtained in a formal clinical trial of extended platelet storage.[22] Furthermore, transfusion of platelet units on Day 6 or 7 of storage, when in-dated units were unavailable to meet pressing clinical needs, demonstrated the clinical utility of platelets stored up to 7 days. This manuscript reports the first 2 years of our experience of routine culture of platelet units.

MATERIALS AND METHODS

Procedure for sampling and culturing

All units of platelets entering the transfusible inventory but not issued before the morning of Day 2 were cultured. All of these were WBC-reduced apheresis platelet units. Approximately 90 percent were collected on-site; approximately 75 percent of these were collected using a cell separator (Spectra LRS Turbo, Gambro BCT, Lakewood, CO), and the remainder were collected using another cell separator (MCS+, Haemonetics, Braintree, MA). The standard procedure for donor arm preparation before on-site collection included an iodophor and polyvinyl pyrolidone scrub (0.75% iodine) for 30 seconds followed by application and drying of a povidone iodine solution (1% iodine). Units were held at 22 to 24°C on a flat-bed rotator in a monitored environment throughout storage. Initially, units were discarded after reaching the end of their usual 5-day dating period. Beginning approximately 6 months into the protocol, units were held in quarantine after reaching midnight of Day 5 until they were transfused or until the morning of Day 8 (when subjected to in vitro analyses). All units were subjected to visual examination before transfusion to ensure the maintenance of swirling.

On the morning of Day 2 after collection, or, for units collected by an external supplier, on receipt of the unit, the unit was cultured in the transfusion service laboratory. The unit was mixed well by hand, and all of it was transferred to a single bag (if the contents were being stored between two bags). A 150-mL transfer pack (Fenwal, Baxter, Round Lake, IL) was attached by use of a sterile connecting device (SCD312, Terumo, Elkton, MD), and 5 to 10 grams (10 mL) of the unit were transferred to the transfer pack. Following separation of the transfer pack by heat sealing, a sampling site coupler was inserted into the sample bag, the septum of the needle access was swabbed with an alcohol swab, and a 5- to 9-mL sample was withdrawn from the transfer pack into a syringe using a 16- or 20-gauge needle. The cap of an aerobic blood culture bottle (FA, bioMerieux, Durham, NC) was removed and swabbed with a fresh alcohol swab. The contents of the syringe were then transferred to the bottle using the same needle used for sample aspiration. (This bottle is intended to receive this volume [5-9 mL] of blood for patient blood cultures.) The bottle was promptly delivered to the Microbiology Laboratory (Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, NH) and incubated in an automated bacterial detection system (BacT/Alert, bioMerieux) at 35 to 37°C for up to 5 days or until growth was detected by the system. If a report of growth was received while the unit remained in inventory, the unit was immediately quarantined and the unit recultured. If no report of growth had been received by the time the unit was released for transfusion, approximately 5 mL were retained in one of the two platelet storage bags of the unit to allow reculture in case of a later report of growth from the Day 2 sampling. (This retention aliquot was added to the protocol approximately 6 months into the trial. We believed this would help assess the specificity of the protocol.) The organisms detected in positive cultures of platelet units were identified using standard microbiologic techniques.

Our hypothesis was that growth of any bacteria would be detected in the automated bacterial detection system before they reached a clinically critical inoculum in the unit. This was based on knowledge of growth curves in platelet packs (80th percentile of detection, $\leq$48

hr)[21,23] and that the platelet units were being held at a temperature lower than the culture bottles. Therefore, units were made available for transfusion at any time they were needed clinically following labeling (usually on Day 1).

Transfusion experience

In-date platelet units meeting all standard criteria for release were issued to patients as needed. Culture results were not sought before release of units. On occasion, the inventory of suitable platelet units became depleted and could not be replenished from either internal or external sources (3 hr distant) before a definable clinical need for transfusion. In such circumstances, the pathologist covering the transfusion service was contacted and, if clinically appropriate, specifically authorized the issuance of a Day-6 or Day-7 unit that continued to have no detectable bacterial growth in the automated bacterial detection system and if swirling was evident.

The platelet transfusion routine in this institution includes determination of a CCI 1 hour (10-60 min) after transfusion to assess posttransfusion recovery whenever possible.[24,25] The CCI was calculated according to a standard formula using the following approximation of body surface area: body surface area (in cm^2) = (body mass in $kg)^{0.425} \times$ (height in $cm)^{0.725} \times 71.84$.[26] In addition, the patient's response to each transfusion using platelets stored for 6 or 7 days was assessed.

In vitro analyses

Platelet units that remained available on the morning of Day 8 (approx., 10-12 hr after passing midnight on Day 7 after collection) were examined by a trained, experienced laboratory staff member to assess qualitatively the presence or absence of swirling. A sample was taken for determination of pH measured at 37°C (Model 855, Bayer, Norwood, MA).

RESULTS

During the first 24 months of this protocol, 2678 units of WBC-reduced apheresis platelets were cultured. Of these, 16 (0.6%) grew bacteria (Table 1). Aliquots or the units themselves were available to reculture in 13 cases. All of these repeat cultures were negative despite the repeat cultures occurring a day or more after the initial culture (i.e., after additional time for any contaminating bacteria to proliferate). Five of the units had been transfused before detection of bacterial growth in the initial samples. The patients' physicians were notified, and blood cultures were collected from the patients, all of which were negative. The patients had no unusual symptomatology associated with these transfusions as determined by chart review and interviews. Aliquots had been reserved and remained available for reculture in three of these cases; all of these follow-up cultures were negative.

Incidents of bacterial growth appeared to cluster around the introduction of new laboratory personnel to the culturing protocol. Despite careful training of staff before beginning to perform the steps of the protocol, documentation of competency in its techniques, and adherence to a written standard operating procedure, contaminated samples in the first week or two of new staff taking responsibility for this aspect of laboratory operations were not uncommon. Additional training resulted in a reduction of aliquots contaminated in the process of sample collection.

TABLE 1. Results of bacterial cultures

Case number	Time to detection (hr)	Bacterium identified	Unit disposition	Results of aliquot reculture
During the 2-year study				
1	10.0	Coagulase-negative *Staphylococci*	Quarantine	Negative
2	12.0	*Bacillus* sp.	Quarantine	Negative
3	21.5	*Bacillus* sp.	Quarantine	NT
4	51.0	Coagulase-negative *Staphylococci*	Transfused	NT
5	25.5	Coagulase-negative *Staphylococci*	Transfused	NT
6	24.0	Coagulase-negative *Staphylococci*	Quarantine	Negative
7	58.0	*Bacillus* sp.	Quarantine	Negative
8	39.0	Coagulase-negative *Staphylococci*	Quarantine	Negative
9	30.0	*Bacillus* sp.	Quarantine	Negative
10	69.0	*Bacillus* sp.	Transfused	Negative
11	32.7	*Bacillus* sp.	Quarantine	Negative
12	12.2	*Bacillus* sp.	Quarantine	Negative
13	11.0	*Bacillus* sp.	Quarantine	Negative
14	27.0	Coagulase-negative *Staphylococci*	Transfused	Negative
15	30.8	Coagulase-negative *Staphylococci*	Quarantine	Negative
16	25.7	Coagulase-negative *Staphylococci*	Transfused	Negative
After the 2-year study				
17A	12.0	Coagulase-negative *Staphylococci*	Quarantine	Positive*
17B	12.0	Coagulase-negative *Staphylococci*	Quarantine	NT

* Bacterium identified as coagulase-negative *Staphylococci*.

The culturing protocol was continued after the 2-year study period. In the subsequent 6 months, two units (split from the same apheresis collection by an external supplier) grew coagulase-negative *Staphylococci* within 12 hours of culture on Day 2. Repeat culture of one of the units confirmed this finding.

During the 2-year study period, six febrile transfusion reactions following platelet transfusions (0.2% of transfused units) were reported. In one case, a temperature rise of 2°C or more was noted, but neither blood culture of the patient nor repeat culture of a retained aliquot of the unit was positive. None of these cases had other clinical evidence suggestive of bacterial contamination as the cause of the fever following transfusion.

Ninety-one units collected with the Spectra LRS were available for further testing on the morning of Day 8. Swirling was detected in 87 units (96%). The pH of these units was 6.86 (± 0.245) (measured at 37°C) and was above 6.20 (6.30 at 22°C) in 88 (97%). (One unit that had no detectable swirling had a pH > 6.20.) The highest pH recorded was 7.26 (7.47 at 22°C). Fewer units collected on the MCS+ were available for study, but the results of analyzing them on Day 8 were similar (data not shown).

Because of periodic inventory shortages and the distance to external suppliers, 40 transfusions using Spectra LRS units stored for 6 or 7 days were given to patients who required platelets without delay. All of these appeared to yield expected clinical results. In 21 of these transfusions, the patient's clinical condition allowed evaluation of CCIs measured 10 to 60 minutes after transfusion. These Day-6- and Day-7-units yielded a CCI of 14,400 ± 8800 (median, 12,191); 90 percent of the CCIs were above 7500, and all but one was above 5000 (Fig. 1).

DISCUSSION

Our experience with routine culturing of platelet units demonstrates that this protocol is practical in an American tertiary care medical center and can contribute to the improvement of transfusion recipient safety. Although no units could be confirmed to contain bacteria during the initial 2-year study period, the discovery of a bacterially contaminated collection shortly thereafter places the contamination rate we encountered at approximately 1 per 3000 units, a rate commonly quoted in the literature.[27]

We interpret the first 16 occurences of initial culture positivity during the 2-year study period as most likely representing false-positive results, that is, introduction of bacteria that were not present in the unit during the sampling process. The 13 cases in which a reserved aliquot was culture-negative on subsequent culture reinforces this contention. The finding of the same bacterium in the two parts of a split "double" plateletpheresis collection shortly after the study period ended would appear to be a documented case of contamination occuring around the time of collection.

Five units had been transfused by the time that bacterial growth had been detected. None of the patients appeared to acquire an infection as a result of the transfusion, and reculture of the aliquots reserved from three of these units revealed no growth. These three units would appear not to have been contaminated. The true status of the two other units (without reserved aliquots available for reculturing) that were positive on initial culture but already transfused without incident cannot be determined.

The clinical risks associated with bacterially contaminated platelet units presumably increase with the length of storage of the platelet unit and the additional time allowed for bacterial proliferation. After developments in bag technology allowed the FDA to extend the storage period for platelets from 3 to 5 and ultimately 7 days, the agency noted an increase in the number of reports of bacterially contaminated platelet units.[28] The FDA subsequently reduced the dating period from 7 to 5 days to limit the time during which bacterial proliferation could occur before transfusion. The importance of the time over which the unit was being held at room temperature was highlighted by Morrow et al.[29] who noted that although less than 10 percent of their institution's platelet transfusions occured on Day 5 of storage, these transfusions accounted for 57 percent of septic reactions. In the preliminary report of the Bacterial Contamination (BaCon) study coordinated through the CDC, all platelet units implicated in clinically apparent septic reactions had been stored for 4 or 5 days.[30]

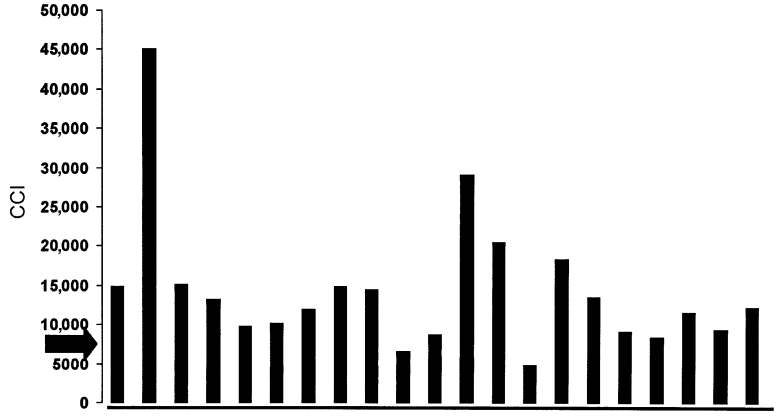

Fig. 1. CCIs of 21 patients calculated 10 to 60 minutes after transfusion of WBC-reduced apheresis platelet units on Day 6 or 7 of storage. Arrow indicates a CCI of 7500, a response indicative of a "successful" response to platelet transfusion.

Our experience corroborates the European practice in using an automated culturing system to detect bacteria and to extend the storage period of platelet units.[18,31] However, the culture protocol used in our laboratory has not been validated as capable of detecting all instances of bacterial contamination. Kinetic studies in plateletpheresis units inoculated with commonly encountered organisms to 1 CFU per mL and then subjected to repetitive 5-mL automated cultures illustrated that cultures were 100 percent sensitive beginning on Day 2 of storage.[12] A similar study using a variety of organisms reported growth in all but one sample (sensitivity >99%) when cultures were taken at this point.[21] An earlier study of the growth curves of a variety of organisms inoculated into platelet units validates that culture of a small aliquot on Day 2 is sufficient to detect bacteria if present.[23] However, it is recognized that some slower-growing organisms, such as some *Staphylococcus epidermidis,* may not be detected rapidly in an automated culture system.[21] Validation of the sensitivity of this protocol, however, might necessitate culturing units twice (once early in storage and again at a later time) to ensure detection of low inoculum in the unit. (This second culture point perhaps might be at unit expiration, Day 5 or Day 7, or at least 24 hr after the initial sampling, a time at which the growth of any initial inoculum to a detectable level could be reasonably assured.) Even assuming a contamination rate of 1 per 3000, over 11,000 units would have to be cultured to ensure (with 80% power and 95% CI) that the protocol was detecting a sufficient proportion of truly contaminated units so that extension of the storage period would not decrease the bacteriologic safety of recipients. Recruitment of centers to participate in such a protocol (or sponsors of it) would be daunting. Nevertheless, the value of routine culturing may be inferred from this report and the publications detailing the European experience.

The report of culture positivity after transfusion for one-quarter of the platelet units showing initial positivity might be regarded as diminishing the clinical utility of this protocol. However, results from repeat cultures or the clinical situation suggest that all of these were not true-positive cultures. Even in cases of true contamination, the bacteria are likely to grow more rapidly in the (warmer) culture environment than in the unit itself, and detection in the culture bottle would appear likely before the inoculum in the bag reached a critical level. The units with documented bacterial contamination were detected by automated culture in only 12 hours.

Because the storage time for platelets is shorter than for any other component, more platelets outdate than any other type of component; implementation of a system to reduce the chance of transfusing a bacterially contaminated unit could reduce platelet unit outdating through increased storage time. In 1994, for example, 18 percent of platelets were reporting as outdated.[32] This contrasts with much lower outdate rates (<5%) seen during the period when platelets could be stored for 7 days.[33,34] Because almost two-thirds of platelet transfusions are now given as plateletpheresis components at a cost of approximately $500 per preparation, this outdating incurs a substantial cost in the healthcare system and reduces the availability of platelets significantly.[35] The ability to extend the outdate, such as to 7 days, would make an important contribution to healthcare efficiency and platelet availability. Several European centers have begun using this approach to ensure sterility of platelet units and reap the benefit of extended shelf life.[17,18,31] We previously reported that our (variable) costs for this culture protocol (excluding only those costs related to the capital expense of the automated culture cabinet) was $16.50 per unit.[36] The projected outdate rate today with 7-day storage of platelets is difficult to estimate because production, component type distribution, and logistics have all changed since the change of platelet storage from 7 to 5 days 18 years ago. However, even a modest reduction in outdating would be expected to provide an economic advantage to the blood supply system while improving patient safety with respect to bacterial risks. Additional savings might be achieved if such a bacterial detection technique were viewed as supporting prestorage pooling of platelet units (as is commonly performed in European centers). This would simplify handling of platelets for hospital transfusion services and permit use of a single filter to be applied for prestorage WBC reduction of platelets derived from whole blood.

Applying this culture approach more broadly across the US blood banking system remains a challenge. In situations where hospitals hold platelet units only for short periods before their transfusion, the culture would need to be performed at the blood center. This would necessitate several changes in current systems. First, a reliable system to notify hospitals of a positive culture result would need to be established to interdict the transfusion of a distributed, bacterially contaminated unit. Several European centers have created computerized alert systems to accomplish this task, and many US blood centers created just such a system when NAT was implemented without a requirement that these test results be available before distribution of the units. More significant, perhaps, would be the alteration of the mindset of blood suppliers to accept that bacterial test results were still pending when releasing platelet units to hospitals.

Although 7-day storage of platelets has previously been shown to provide viable, functional platelets, extension of the storage period to 7 days will require validation that the current systems for collecting, processing, and storing platelet units provide adequate clinical efficacy.[37-41] The results of our experience, that took advan-

tage of our unique location and platelet supply logistics, support such an extension. The pH results after extended storage indicated that almost all of the units held through 7 days of storage were likely to contain platelets that were viable and functional. The transfusion of units beyond 5 days of storage resulted in CCIs that were clearly adequate to support patient hemotherapy needs, and almost all (90%) were above the usual definition of a "successful" transfusion increment.[42] These transfusion results in patients bolster the contention based on clinical trials in this laboratory and elsewhere that platelets can be stored for 7 days and retain clinical efficacy that is indistinguishable from that of those stored for 5 days despite the documented diminution of functionality, recovery, and survival.[22,43] This assertion is also a logical extrapolation of previous experience that although there is undoubtedly the accumulation of a functional lesion associated with increasing storage time of platelets, this is not clinically distinguishable when transfusing platelets of various storage ages.[44] Concern has also been expressed that, with the advent of WBC reduction of platelet units, removal of WBCs would greatly reduce oxygen consumption and allow the pH to rise dramatically during storage, injuring the platelets as readily as a fall in pH would.[45,46] Changes in anticoagulant ratios with apheresis collections have undoubtedly changed initial levels of acidity in platelet units as well. We found no instances of pH elevation to or beyond physiologic levels in the 91 units of WBC-reduced platelets tested on Day 8, and elevation of pH to levels that would truly be injurious to platelets (>7.6 using some types of agitators) seems unlikely.[22,47]

Our experience is shared in the hope of encouraging others to develop and implement similar protocols to improve safety for platelet transfusion recipients. In combination with clinical trials demonstrating adequate functionality, recovery, and survival of platelets stored for 7 days, we hope that experiences such as ours will embolden regulatory authorities to extend the storage time for platelets in conjunction with use of a bacterial detection system and thus allow improvement of patient safety with minimization—or complete avoidance—of additional expense.

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