AABB Interorganizational Task Force on Bacterial Contamination of Platelets

Steven Kleinman, MD

Chair

Purposes of task force

- Serve as focal point for all issues related to the AABB bacterial detection standard that took effect in March 2004
- Provide forum for discussion between transfusion medicine community (transfusion services and blood centers), subject matter experts, and PHS agencies (FDA, CDC, HHS, NHLBI) on specific safety/availability issues
- Interact with test manufacturers as appropriate

Purposes of task force

- Provide guidance to AABB membership
  - Issues to be addressed include standardized definitions of test results, follow-up of initially positive tests, identification of organism, what to do if a positive platelet unit has been transfused, notification and possible deferral of the donor, and possible interaction with public health departments
- Survey blood centers/hospitals to assess current practices
  - Data on impact on inventory/transfusion practice

Current platelet usage

- Three million whole blood derived platelets
  - Assumed to be transfused in pools of six, leading to 500,000 therapeutic doses
- One million apheresis platelets
  - An apheresis collection from a given donor may produce one, two, or three transfusable apheresis units
- Trend has been for increasing use of apheresis, but there is substantial regional variation
  - Ranges from ~100% apheresis to ~ 100% wb derived

Impact of bacterial detection testing on platelet availability

- Current information (April 2004 AABB survey, anecdotal reports) indicates no severe shortages but some impact on availability
- Solutions to increase availability:
  - Licensure of pre-pooled wb derived platelets for 5 day storage
  - Extension of shelf life of apheresis platelets to 7 days

Critical issue: The need for 5 day storage of wb derived pre-pooled platelets

- According to the April 2004 AABB survey, the primary methods used for bacterial detection of whole blood derived platelets are pH and glucose
  - These surrogate tests have poor sensitivity and poor specificity
  - Each institution is determining its own assay cutoff based on its own validation studies

Critical issue: The need for 5 day storage of wb derived pre-pooled platelets

- Culture based testing is not generally being performed for several reasons:
  - QC culture based tests require leukoreduced platelets
  - The volume required decreases the therapeutic dose
  - Each of the 4-6 platelet concentrates in a therapeutic dose requires an individual test; this is extremely expensive
- Sensitive point of care direct detection methods are not yet available
  - Several under development, but none have completed clinical trials

Pre-pooling of wb derived platelets with culture-based assay of the pool

- Culture based testing is done on pre-pooled buffy coat derived platelets in many European countries
- Would require FDA to license a bag for 5 day storage and approve culture based tests on the pool
  - Detection of bacteria in analytic spiking studies in platelet pools recently reported (Transf 2004; 44:1174)
- Would likely require leukoreduction of the pooled product prior to bacterial detection
- A positive test would need to be tracked to the individual platelets comprising the pool

Critical issue: 7 day storage of apheresis platelets

- Although bacterial detection testing has not resulted in severe platelet shortages, there are consequences
  - Reduction of up to one day of shelf life due to later release of apheresis platelets
  - Revised inventory management procedures to avoid shortages on specific days of the week
  - Possibility of local shortages
  - Increased expense of the product

Clinical study to validate bacterial safety of 7 day stored platelets

- FDA has stated that a large clinical trial is required to license an assay(s) for a bacterial screening claim and to use that assay(s) to allow platelets to be stored for 7 days
- The sample size (50,000 units) and the need to retain the expired product (a platelet that has not been transfused and is available for testing at 7 days) make this study logistically complex and very expensive

Clinical study to validate bacterial safety of 7 day stored platelets

- A task force committee is working with FDA to develop a protocol that fulfills FDA requirements and is logistically feasible
  - Significant scientific and logistic issues have been addressed, but some remain
  - Funding has not yet been addressed
- At the same time, subject matter experts continue to believe that such a clinical trail is not necessary based on scientific or safety concerns

Concerns with the need to perform the clinical trial

- European countries have allowed 7 day storage using the same bacterial culture system
- Multiple studies have documented that the major clinically significant bacteria are detectable with an initial culture set up at 24- 48 hours
  - 7 day storage could be studied with analytic spiking studies

Concerns with the need to perform the clinical trial

- It will take at least one year to perform the cultures required in this study, probably delaying extended storage for up to 2 years
- Does this study set a precedent for the need to perform large scale clinical trials of bacterial detection assays on expired products to further extend platelet storage beyond 7 days?

Recently resolved issues in the study protocol

- Use of whole-blood derived platelets specifically manufactured for study purposes
  - Allows for control of product, centralizing of protocol in several facilities, and avoids the need to retrieve expired products from hospitals
- Use of leukoreduced platelets
  - Meets approved use for the two culture-based QC tests
  - Introduces additional step in manufacturing process and additional cost

Current issues in the study protocol

- Need for gram stain to rule out false negative seven-day cultures due to senescence
  - Available unpublished data being compiled to show this does not occur [no senescent cultures (n =158) on days 7-14, inoculating 15 different organisms]
- Study end points unresolved with regard to anaerobic bacteria
- Use of multiple manufacturers test systems in protocol

Preliminary study budget

- 50,000 specially manufactured leukoreduced whole blood derived platelets: $2 million
- Cultures: aerobic and anaerobic BacTAlert at days 1 and 7 and Pall eBDS at day 1: $4 - $4.5 million
- With four sites and a one year testing period, equipment is needed to incubate 4,000 BacTAlert bottles at any given time: $800,000
- Other equipment: $100,000
- Project management/data analysis/etc.: $100,000

Study funding

- Tentative budget of $7-$8 million
- Potential funding sources include manufacturers and NHLBI
- Study funding has not yet been seriously pursued because protocol has not yet been finalized

This is an expensive study and sufficient funding is likely to be difficult to obtain