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Proposed approach to clearance of bacterial detection devices for screening of platelet products prior to transfusion.
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Issue: FDA is considering the appropriate approach to evaluate the efficacy of bacterial detection devices in a clinical setting for screening of platelet products prior to transfusion. Such methods are necessary to decrease the incidence of platelet product transfusion-associated bacteremia and sepsis.

Background:

Bacterial contamination of platelet products at the time of collection is reported to occur with a frequency of 1/2000 units. The contamination of the product may occur as a result of improper skin prep, sampling of a pocket of bacteria hidden in or under scar tissue as the needle cuts through the skin or asymptomatic bacteremia in the donor at the time of donation. The level of contamination at the time of collection is low most likely on the order of 0-5 CFU/ml. However, since platelets are stored at room temperature the bacteria can proliferate to levels of 100-1000s of CFU/ml in a matter of days. Transfusion of bacterially contaminated products can lead to serious morbidity and mortality in approximately 1/100,000 transfusions.

FDA recently cleared two devices for detection of bacterial contamination of platelet products with the intended use for quality control of platelet collection process in a blood center. The clearance of the devices was based on in vitro data in which platelet products were intentionally contaminated at the time of collection with different species of bacteria. A sample of the platelet product was taken under sterile conditions at 24-48 hours and inoculated into the automatic bacterial culturing devices (1,2,). Sample collection 24 hours or longer after blood draw is necessary to allow for the natural proliferation of the bacteria to increase the chance obtaining enough bacteria in the sample to detect by the device. The species of bacteria chosen was based on the frequency of these organisms in platelet products reported in literature (1). The species used to clear these devices are listed below:

Bacillus cereus
Bacillus subtilis
Clostridium perfringens
Corynebacterium species
Echerichia coli
Enterobacter cloacae
Klebsiella oxytoca
Propionibacterium acnes
Pseudomonas aeruginosa
Serratia marcesens
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes

Streptococcus viridans

Candida albicans (fungus)

This list includes both gram-positive and negative organisms and a fungal organism. Most of the organisms readily proliferate in the automatic culture devices at 37 C and can be detected within 24 hours of culture. However, there are several organisms that grow slowly even under ideal conditions and may not be detected until 48 hours in culture. These include Staph epidermidis and Propionibacterium acnes. Staph Epi. is a skin contaminant and has been reported to account for approximately 50% of the bacteria identified in contaminated platelet products. To detect these organisms a sampling taken at 48 hours and cultured for 48 hours may be the most sensitive approach.

Proposed clinical study

The sensitivity of the devices range from 1-10 CFU/ml as defined by in vitro testing. The in vitro tests do not fully represent actual clinical use conditions and thus the FDA has decided not to accept in vitro data alone as proof that the devices will be able to identify platelet products contaminated during collection or processing. The FDA will propose that each device be tested in a clinical setting. The test design will have an initial sampling of the platelet product at a time that was determined to be optimal by in vitro studies of the particular device tested. The product will then be stored at room temperature and sampled a second time either at the point of transfusion or at outdate if the product is not used. The second sampling and culture is more likely to detect a contaminated unit since the bacteria have had a chance to proliferate in the platelet product. The second culture thus serves as a confirmation of the results obtained by the first sampling and culture. Since the contamination rate is on the order of 1/2000 units, the whole study will need to sample approximately 10,000-12,000 units. The sampled platelet products will be useable for transfusion if the sampling is done with a sterile connecting device. Ideally the confirmatory culture should be done at out date (after day 5 of storage) to make sure that any slow growing organisms would have the possibility to proliferate. However, that would preclude the use of these products for transfusion and thus, taking the second sample at the time of release will be acceptable. To assure that an adequate number of confirmatory samples are taken on day 5 old platelets these should account for at least 3000 units (25%) of the total study. Similarly, 4 day old, 3 day old and 2 day old platelets should each account for 25% of the second samples.

In the early 1980s platelet products had 7 day shelf life but the long storage time at room temperature allowed for bacterial proliferation that led to transfusion associated sepsis. To reduce this problem the shelf life of platelets was limited to 5 days in the mid 1980s. Adequate bacterial screening will make it possible to extend the shelf life of platelet products back to 7 days as long as platelet storage bags have been validated to maintain platelet quality for this period. A clinical study aimed at demonstrating that a bacteria detection device is capable of detecting contaminated platelet units stored out to 7 days, will have a design similar to that described above. The confirmatory culture will need to

be done at outdate of the product (day 7) and these samples should account for at least 25% of the total number tested. The rest of the samples should be distributed between day 6, day 5 and day 4 samples at approximately 25% each.

In addition to a clinical trial, a post-marketing survey will be needed to assure that actual clinical use of the device to screen platelets does not lead to an increase in contamination rates or transfusion associated bacteremic reactions. This study would be done after a limited roll out of the cleared device to a small number of transfusion centers. The results of all platelet units tested would be compiled and sent to the FDA at prescribed intervals.

Discussion:

A device that can be cleared as a method for screening platelets prior to transfusion and to extend the shelf life of platelets should have 1) a high detection accuracy rate (95% or better), 2) not cause additional contamination of the units with the screening process, and 3) not have a high false-positive rate that could lead to discarding platelet products unnecessarily. Initial evaluation of the device would be done with in vitro studies to define the sensitivity and optimal sampling strategy that will be used to design an appropriate clinical trial. The study should be of sufficient size so that it could detect 5-6 naturally occurring contaminated platelet units. The readout of the initial screening sample has to be compared to a recognized confirmatory detection method that could be either a thioglycolate culture manual method, a cleared automated detection system with known sensitivity or the device itself used later in the storage time when bacteria are more easily detected. If only a small volume of the platelet product is used for testing and the sample was collected using a sterile connecting device, the product may be transfused if it is less than 5 days old. Platelets that are not transfused by day 5 can be sampled at day 5 and then at day 7 to obtain data on the feasibility of the device for screening platelets for storage out to 7 days. The design of studies for 7 day storage may require collection of the first sample later in storage to allow for proliferation of the slow growing organisms.

References:

- 1) Brecher, M. E. et al. Evaluation of an automated culture system for detecting bacterial contamination of platelets: an analysis with 15 contaminating organisms. *Transfusion* 41:477-482, 2001
- 2) AuBuchon, JP et al. Experience with universal bacterial culturing to detect contamination of apheresis platelet units in a hospital transfusion service. *Transfusion* 42:855-861, 2002