SEPTIC TRANSFUSION REACTIONS CAUSED BY BACTERIAL TRANSMISSION FROM INTERCEPT-TREATED PLATELET CONCENTRATES

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On December 02, 2021 the FDA released a document to the public titled "**Important Information for Blood Establishments and Transfusion Services Regarding Bacterial Contamination of Platelets for Transfusion"**[1]

FDA stated it was updating a communication from April 16, 2019 in which the Agency had described four platelet components collected by apheresis in which contamination by *Acinetobacter spp.* had been identified.[2] These cases were subsequently reported in detail in an article published by the CDC in MMWR.[3] This report described four patients transfused in three states with apheresis platelets: Utah (storage day 4), California (storage day 5), and Massachusetts (two components transfused to separate patients in Connecticut on storage day 4). The patients were transfused during May–October 2018 and experienced septic reactions following transfusion. The platelets in California and Connecticut were bacterially contaminated with Acinetobacter calcoaceticus-baumannii complex (ACBC) and *Staphylococcus saprophyticus* (*Ss*). The unit in Utah was contaminated with ACBC. One patient (Utah) died. Whole genome sequencing analyses indicated a potential common source of bacterial contamination which to date has not been identified. One implicated platelet unit had been treated with the INTERCEPT pathogen-reduction (PR) technology (California). This case was the subject of a peer-reviewed publication[4] No bacterial growth was detected in primary cultures of the three units transfused in Utah and Connecticut. The unit in California did not undergo a primary culture. The two units transfused in Connecticut were split products from the same donation and showed negative results with the original PGD Rapid Test. The PGD Test has since been updated to include detectability of ACBC (see below).

In the December 02, 2021 communication, the Agency called attention to three additional cases of septic transfusion reactions from INTERCEPT-treated apheresis platelets contaminated with *Acinetobacter* spp., *Ss*, *Leclercia adecaboxylata*, or combinations thereof. These reactions occurred in North Carolina, Virginia, and Ohio. The North Carolina case has been reported in a peer-reviewed publication.[5] The Agency noted that prior to these reports, Acinetobacter spp. had been only rarely identified as platelet contaminants. Genetic testing of the implicated bacteria from the recent reports has indicated a relatedness of the organisms, but no common source has been identified.

Each of the implicated components in the three cases noted in the December 02 2021 communication were prepared in platelet additive solution and then processed with the INTERCEPT PR device. Two of the septic cases resulted in fatalities. In total, since 2018, 7 cases of platelet septic transfusion reactions have been reported to FDA associated with *Acinetobacter* spp., *Ss*, and/or *Leclercia adecaboxylata*. **Four of these, including the two fatalities, have resulted from the transfusion of an INTERCEPT-treated platelet. (Table 1)**

FDA noted additional reports of potential septic transfusion reactions and positive bacterial cultures with *Acinetobacter* spp. along with certain other bacterial species are under investigation. **The Agency emphasized these cases demonstrate the need to recognize the residual risk of bacterial contamination of platelets, including PR platelet components.**

Suspected transfusion reactions should be reported by the treating health care provider to the transfusion service who, in turn, should notify the blood supplier. The Agency reminded the institutions receiving the FDA communication that the Agency must be notified as soon as possible when a complication of transfusion is "confirmed to be fatal" (21 CFR 606.170).

In order to facilitate investigations, FDA advised blood establishments and transfusion services to contact FDA when a suspected contamination of platelets with *Acinetobacter* spp., *Ss*, or *Leclercia adecarboxylata* is identified, or when a septic transfusion reaction involving PR platelet components occurs, by reporting such cases via the MedWatch Program.

FDA transfusion fatality reports for FY 2015 – FY 2019 report 13 deaths from bacterial contamination of apheresis platelets and one from a pooled platelet concentrate.[6] Given that approximately 2 million platelet doses are transfused annually in the US, this equates to an overall reported septic fatality rate of ~1:800,000 including the death from an INTERCEPT-treated platelet (14 cases in 12 million doses). It is striking that in limited use there have already been reports of 2 fatal septic events caused by PR-treated platelets. The FDA has not yet released the transfusion fatality report for FY 2020. It is not possible at present to estimate the death rate following transfusion of INTERCEPT-treated platelets, platelets that have had only a primary culture, and platelets that have had some other mitigation strategy applied. Given that there were two deaths associated with PR platelets during a time when the majority of platelets did not undergo INTERCEPT treatment, it is plausible that the death rate following transfusion of INTERCEPT-treated platelets will prove to be as high or higher than that caused by transfusion of other platelets.

In the published report from the California case[4], Fridey et al. described a male patient with relapsed acute lymphoblastic leukemia who had been successfully treated for central catheter–associated *Staphylococcus aureus* bacteremia in 2018. Chills, rigors, and flushing developed immediately after an INTERCEPT-treated platelet component collected from a female donor was infused on storage day 5 through a central catheter. Septic shock ensued requiring intensive care. Bacterial cultures of the catheter line and peripheral blood, transfused bag saline flushes, environmental samples, and the untransfused PR co-component were performed. Peripheral blood and catheter cultures grew ACBC. Mass spectrometry on the bag flush identified ACBC and *Ss*. Environmental cultures, some done after decontamination, were ACBC/*Ss* negative. ACBC sequences obtained from posttransfusion patient plasma and bag flush were genetically identical. No Y-chromosome was detected in the bag flush providing evidence against retrograde contamination. Spiking PR studies demonstrated >5.9-log inactivation for both isolates. Donor skin cultures for *Acinetobacter* were negative. The authors concluded that

the pathogen reduction process had been successful and that environmental sources and undetected bag defects "may have contributed" to post-manufacturing PR platelet component bacterial contamination.

In the North Carolina case, Fadeyi et al. reported a fatal septic transfusion reaction in a 63-year-old patient with kidney and liver disease who received an INTERCEPT-treated platelet transfusion (storage day 5) prior to surgery in 2020.[5] The residual platelet component was cultured, with the detected microorganisms undergoing genotype sequencing. Pressure testing and microscopic examination were performed on the storage bag. Environmental culture screening was performed by the transfusing hospital.

The platelet component and the patient's blood grew ACBC, *Leclercia adecarboxylata* and *Ss*. These strains were effectively inactivated with >7.2, 7.7, and >7.1 log10 kill, respectively by the IINTERCEPT treatment process. A leak was demonstrated (only with pressure testing) in the platelet storage container. Environmental cultures showed no growth. The contamination source was not determined. The authors concluded that their findings were "compatible with post-processing environmental contamination of a pathogen reduced platelet concentrate via a non-visible, acquired storage container leak."[5]

Confirmed cases of sepsis from PR platelet transfusions reported in the United States are summarized in Table 1.

The false-negative PGD Test results in the Massachusetts/Connecticut cases and described in the MMWR [3] prompted Verax Biomedical to adapt its rapid test to include detection of *Acinetobacter* spp. Unlike culture and pathogen reduction, the test can be readily modified to improve performance and to add detection of new or emerging species and strains. As rapid testing is performed on the day of transfusion, it is more likely to interdict highly contaminated units even if the contamination is speculated to have occurred post-processing or post-manufacture. This updated rapid test is the Platelet PGD*prime*® Test, which is currently available from Verax Biomedical. Results of its use have been reported in a peer-reviewed publication.[7] This report describes the detection of several *Acinetobacter* strains by the updated PGD*prime* Test at clinically relevant CFU/ml levels (i.e. levels associated with septic transfusion reactions). PGD*prime* successfully detected *Acinetobacter* growing in various non-PR platelet components after an initially low inoculum. In PR platelets, the Test yielded a positive result with the 3 implicated bacteria in the North Carolina case (ACBC, *Ss*, and *Leclercia adecarboxylata*) in 48 h or less after inoculation and 48–72 h earlier than the reported time of transfusion of contaminated PR platelets. As noted previously, ACBC and *Ss* were detected in cultures of the residual in the platelet bag in California and Connecticut and ACBC without *Ss* in the bag residual in Utah.[3]

Additionally, it is noteworthy that reports have been submitted to the FDA for other possible, probable, or highly probable transmissions of bacteria by platelet components

that have undergone treatment with the INTERCEPT process. The reader is referred to these reports in the FDA MAUDE database for details.[8]

The worrisome multiple reports of transmission of bacteria by INTERCEPT-treated PR platelet components confirm a residual risk of bacterial contamination and suggest a role for the use of the PGD*prime* Test prior to the transfusion of these PR-platelets, perhaps on day 3 or later of storage. Policy makers should consider such a recommendation to enhance patient safety. Given that no additional safeguards have been put in place to prevent transfusion of contaminated PR platelets, the risk of future morbidity and mortality events will remain high. Major policy decisions regarding infectious agents have been made with respect to the transfusion of blood components with less demonstrated morbidity and mortality from certain other infectious agents.

The FDA Final Guidance on mitigation of the risk of transfusing bacterially contaminated platelets is now in force.[9] The recent Agency communication suggests the FDA has continuing concerns about its effectiveness. This should prompt modifications to the document as appropriate to further protect public health.

TABLE 1: SEPSIS FROM THE TRANSFUSION OF PATHOGEN-REDUCED PLATELETS IN THE US

Year	Location	Component	Storage Age	Reaction	Patient Culture	Product Culture	Reference
2018	CALIFORNIA	Apheresis in PAS	Day 5	SEPSIS	ACBC	ACBC, SS	Fridey et al.[4]
2020	NORTH CAROLINA	Apheresis in PAS	Day 5	FATAL SEPSIS	ACBC, *La, Ss*	ACBC, *La, Ss*	Fadeyi et al.[5]
2021	OHIO	Apheresis in PAS	*	FATAL SEPSIS	*	*	FDA COMMUNICATION[1]
2021	VIRGINIA	Apheresis in PAS	*	SEPSIS	*	*	FDA COMMUNICATION[1]

*unpublished to date

ACBC: *Acinetobacter calcoaceticus/baumannii complex*

Ss: *Staphylococcus saprophyticus*

La: *Leclercia adecarboxylata*

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