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INFLECTION POINTS

TRANSFUSION

The pursuit of platelet safety

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It is humbling to be invited to join Harvey Klein, Michael Murphy, Richard Aster, and Jeffrey McCullough as a senior citizen in the transfusion medicine community to contribute to the Inflection Points series that is now a prominent feature of *Transfusion*. In considering the story to tell, I will provide a follow up to the excellent summary of the development of platelet transfusions provided by Richard Aster[1] describing platelet storage at room temperature (RT), filling in my experiences during my evolving career which have shown the risks and benefits of the RT approach.

1 | DEFINING THE PROBLEM WITH STORAGE IMPROVEMENTS

My first exposure to platelet transfusions came as a medical resident in 1974 serving at the Johns Hopkins leukemia and bone marrow transplant service. For a 20-patient ward, we were able to get only 10 bags of whole blood-derived platelets (WBDP) on weekdays, vastly underserving these patients. An initial one-bed apheresis program to provide single-donor platelets (SDP) was initiated, but inadequate platelet support was a major problem, and bleeding was a critical cause of morbidity and mortality. Not only were platelets scarce, they had only 3 days of storage capability and the increments and survival of the transfused platelets were poor from the storage bags available at that time. When I moved to San Francisco, platelets were becoming more available, and blood centers such as the Irwin Memorial Blood Bank were developing platelet apheresis programs and starting to HLA type volunteer platelet donors to deal with refractory patients. I inherited a growing apheresis program when I returned to Johns Hopkins in 1979, but reliable platelet support continued to be a major concern until the new generation of platelet bags became available in the mid-1980s providing 5-day storage, greatly reducing the availability issues with holidays and weekends that plagued 3-day platelet storage limitations.[2] We even started to move the storage period forward to 7 days based on the new bags and data suggesting that platelet recovery and survival was adequately maintained.[3]

This success story was interrupted by reports from our oncology service that patients receiving platelets stored for up to 5 days at RT were developing febrile reactions. Our evaluations showed that the problem was bacterial growth during storage. The bags allowing better platelet survival were also enhancing bacterial growth, a problem that was predictable from early case reports but largely ignored by the transfusion community. We evaluated a developing case series of septic platelet transfusion reactions (SPTRs) and noted that the reactions were more common in pools of WBDP than SDP, and the problem was exacerbated by longer periods of storage.[4] We detected these reactions in 1: 4200 transfusions to our oncology patients. Our early investigations also showed that the bacterial source was donor skin in most of the cases, but almost one-third of the septic events came from donors with a transient bacteremia.

The consequences of these SPTRs were brought home to me by a call from an oncology colleague whose patient had died from one of the events. The patient was a middle-aged female with acute leukemia who had

entered remission but was still being supported by platelets to prevent hemorrhage until her bone marrow recovered. While awaiting hospital discharge, she developed fever and shock after a transfusion and died within several hours of the implicated transfusion. I was asked to meet with the patient's family to explain what had happened, one of the most devastating meetings I have ever experienced. It was incredibly difficult to explain that the patient whose leukemia had probably been cured had died from a staphylococcal infection from platelets that we had been unable to prevent. The family found it incomprehensible that the blood collection processes could not prevent contamination with a common bacterium after the reassurances they had received about the safety of blood in the AIDS era. The human toll of SPTRs became a motivating factor for me to eliminate these events, with further studies we conducted showing SPTRs to be fatal in 20% of occurrences.[5]

2 | WORKING TOWARD A SOLUTION

Our understanding that SPTRs were more common with WBDPs led to a program to move from a mixed inventory with 50% WBDPs to 100% SDPs over a 12-year period.[5] We also reduced the dating period of platelets locally from 7 days back to a 5-day limitation before the FDA took similar action. Another attempt to reduce SPTRs was to limit the storage period at Johns Hopkins to 4 days, a futile solution since evolving studies showed that bacterial growth could become toxic after 3 days of storage. Our program to move to 100% SDP reduced the rate of reactions from 1:5000 platelet transfusions to 1:15,000, a significant but incomplete improvement.

In 2002, I attended an FDA meeting where the issues of pathogen inactivation (PI) were being discussed, mostly with emphasis upon the potential utility for eradicating transfusion-transmitted viral infections.[6] A number of my colleagues were surprised that the growing awareness and literature on SPTR was not being addressed, and the utility of PI to prevent SPTRs was being undervalued. Since it appeared that PI would not be available in the near future, we urged AABB in a letter to promote steps to limit SPTRs, leading to the requirements for blood centers and transfusion services to perform bacterial culture or take other steps to mitigate SPTRs. By 2004, culture for SDPs became routine but was not conducive for WBDPs, leading the transfusion community to greatly increase SDP utilization.[7,8]

Although bacterial culture succeeded in reducing the problem of SPTRs, data evolved showing that it eliminated only 60%–70% of cases, and the risk of SPTR persisted.[9] Our experience at Johns Hopkins was confirmed by reports of continuing SPTR events from blood centers.[7] We continued to experience cases of SPTR with a spike in 2016, which may have occurred when our American Red Cross platelet supply was switched to exclusive Amicus collections, noted to have a higher risk of bacterial contamination.[10] In 2016, we established a secondary culture system, testing all platelets originally cultured after 24 hours by the blood center with a secondary culture at the hospital on day three of storage.[11] This program eliminated SPTRs for several years of surveillance, detecting 18 cases of persistent contamination in 80,000 bags released after primary testing. We also demonstrated that the cost of our secondary culture system was much less than other preventive SPTR strategies such as the use of PI platelets.

3 | CURRENT STATUS OF SPTR REDUCTION EFFORTS

In 2019, the FDA issued guidance in recognition that primary culture of platelets was inadequate to eradicate SPTRs[12]; the documentation they provided suggested that active surveillance demonstrated infections in 1/10,000 transfusions.[13] The guidance permitted blood centers and hospitals to adopt now-licensed pathogen inactivated (PI) platelets that could be stored for 5 days or utilize large-volume delayed sampling procedures[14] that would permit storage of 5 or 7 days depending on the timing of the culture. Secondary testing by culture or a point of care test developed by Verax could also be used.[15] The guidance took effect in 2021 and hopefully has limited SPTRs to very rare occurrences.

Despite the options that are currently in use, opportunities to make additional progress are continuing to be pursued. Some concerns remain with the PI system, with platelet damage causing reduced recovery and survival, the use of a toxic ingredient that could cause harm, and high costs to transfusion services.[16] Perhaps, new PI systems can be developed to reduce the inherent platelet damage or enable PI of whole blood to facilitate WBDP platelets that could relieve platelet shortages and reduce costs. An encouraging option under intense study is the return to platelet storage in the cold.[17] There is evolving evidence that cold platelets may have better hemostatic efficacy, with potential storage up to 14 days that could make platelets more available at remote sites, maintaining protection against SPTRs. Another approach under development is platelet substitutes that would be bacterially inactivated.[18]

On the other hand, there is accumulating concern in our community about the decreased availability of platelets, with growing difficulties in maintaining or

increasing the pool of donors willing to undergo apheresis collections and the resistance of blood centers to move back to recovering platelets from whole blood. We are hearing increasing discussion about reducing the platelet content in an SDP collection, a movement that would make PI easier and allow more liberal splitting of higher count donations. If we couple this step with routine PI, I am concerned that we are reducing the efficacy of these platelets; we should require solid clinical data particularly in patients with active thrombocytopenic bleeding to support these directions. If we take the additional step of increasing the storage time of platelets with or without PI processing from 5 to 7 days, in combination with lower platelet content and PI processing, our supplies may increase but patients may be harmed by these three initiatives to increase the platelet supply.

4 | THOUGHTS ABOUT MOVING FORWARD

Getting the bugs out of our platelets has taken a long and winding road, with the current status showing major improvements, but the potential for continuing solutions remains in sight. The interactions with patients, their families, and their physicians have been a painful but constructive reinforcement that transfusion reactions should not be collected only as quality data but need our attention to prevent them. The opportunity to participate in these developments has been one of the highlights of my career, and I hope that the progress I have described, and the collaborative efforts of many colleagues will lead others to follow in this path or take new directions that we failed to recognize.

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