White Paper

Considerations regarding the mitigation of the risk of bacterial contamination of platelets

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The purpose of this White Paper is to clarify and address the implications of the recommendations in the FDA Draft Guidance "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion" issued December 2018.[1]

- **Options included in the Draft Guidance**:
  - Pathogen Reduction (PR):
    - Randomized clinical trials of PR (INTERCEPT Blood System for Platelets, hereinafter referred to as Intercept or IBS) to date have been conducted in hematology oncology patients.[2] There have not been controlled trials in trauma, surgical, or other patients.
    - FDA required a post-marketing study to assess acute lung injury (ALI), including acute respiratory distress syndrome (ARDS), with INTERCEPT-treated platelets.[3] To date, no results have been reported.[4]
    - Radiolabeling studies of IBS-treated platelets were conducted to determine recovery and survival. Results did not meet the long-established FDA acceptance criteria for approval, although these criteria have been applied for other platelet studies (e.g. platelet additive solutions such as Intersol Solution and Isoplate Platelet Additive Solutions).[5, 6, 7]
    - In one large randomized controlled trial, although the hemostatic efficacy of Intercept-treated platelets in thrombocytopenic patients with hematologic malignancies was noninferior to platelets in additive solution, such noninferiority was not achieved when comparing PR platelets with platelets in plasma.[8]
    - A Cochrane Group review[9] noted the following:
      - The number of patients experiencing platelet refractoriness was significantly greater in those receiving Intercept-treated platelets (93/605) compared to standard platelets (33/616) Risk ratio 2.85 [95% CI 1.96-4.15].[10,11 12,13,14,15,]
      - The number of patients experiencing platelet refractoriness and platelet alloimmunization was also significantly greater in those receiving Intercept-treated platelets (36/605) compared to standard platelets 19/616) Risk ratio 1.90 [95% CI 1.11-3.26].[16 17,18,19,20,21]

- One-hour post-transfusion platelet count increments were significantly lower among recipients of Intercept-treated platelets compared to recipients of standard platelets. -10.08 x 10^9/L [95% CI -11.67 to -8.48].[22,23,24,25,26]

- Twenty-four-hour post-transfusion platelet count increments were also significantly lower among recipients of Intercept-treated platelets compared to recipients of standard platelets. -8.39 x 10^9/L [95% CI -9.82 to -6.96].[27,28,29,30,31]

- One-hour post-transfusion platelet corrected count increments (CCIs) were significantly lower among recipients of Intercept-treated platelets compared to recipients of standard platelets. -4.11 x 10^3/L [95% CI -4.87 to -3.35].[32,33,34,35,36,]

- Twenty-four-hour post-transfusion platelet CCIs were also significantly lower among recipients of Intercept-treated platelets compared to recipients of standard platelets. -3.5 x 10^3/L [95% CI -4.18 to -2.82].[37,38,39,40,41]

- Recipients of Intercept-treated platelets received 30% more platelet transfusions than recipients of standard platelets. This represented a strong statistical trend: 1.3 [95% CI 0.84-1.77].[42,43,44,45,46]

- Recipients of Intercept-treated platelets had a statistically significant shorter time interval between transfusions compared to recipients of standard platelets: -0.50 days [95% CI -0.61 to - 0.38].[47,48,49,50,51]

- In an analysis of patients who had any bleeding event (WHO grade 1 to 4 or equivalent) with follow-up more than 7 days, there was a slight but statistically significant increase in bleeding among recipients of Intercept-treated platelets (374/477) compared to standard platelets (361/498). Relative risk 1.07 [95% CI 1.01-1.13].[52,53,54,55]

- The number of patients who developed an infection while receiving transfusions was greater in recipients of Intercept-treated platelets (181/477) compared to recipients of standard platelets (141/498). Risk ratio 1.36 [95% CI 1.14-1.62].[56,57,58,59]

- Large Volume Delayed Sampling (LVDS) (if cleared as a safety measure):

  - Eight “near-misses” of bacterially contaminated units detected just prior to transfusion.[60]

  - Between 2012 and 2017, treating physicians referred for evaluation more than 600 possible septic reactions following transfusion of LVDS platelets. However, only one case has been adjudicated as caused by transfusion owing to very strict imputability criteria that require samples from the donor/component and patient be cultured; if culture positive, bacteria must match. It is not clear how many such evaluations have been possible as bacteremia may be transient resulting in negative patient cultures and components may be discarded, thus preventing reculture.[61,62,63,64,65,66]

- The UK's reduction in reported septic reactions after introduction of LVDS as their initial culture protocol was not different than the reductions in septic reactions experienced in the US after implementation of primary culture.[67]

- The UK has reported that 1/3,218 apheresis platelets cultured at issue/outdate following a negative primary culture with the LVDS protocol yielded a positive result.[68] This rate is strikingly similar to the 1/3,069 positive results observed in the US following a negative primary culture in a population of more than 27,000 components (post-market surveillance study of the Platelet PGD Test)[69] suggesting no improvement offered by LVDS compared to current early culture.

- Secondary Rapid Testing:

  - Rapid testing does not affect platelet function or the number of platelets in each component.

  - Testing for bacteria in platelet components shortly before issue for transfusion provides the best opportunity for detecting contaminated components. More than 1,000,000 rapid tests of record have been performed in the U.S. without a single fatal septic transfusion reaction during or after transfusion of a test-negative product.[70,71]

- **Potential for platelet shortages caused by Draft Guidance options:**

  - PR:

    - Randomized trials with Intercept technology have demonstrated a mean 35% increase in the number of platelet transfusions given to patients and significantly reduced in vivo platelet count recoveries [72] One prospective, randomized trial demonstrated a 54% increase in platelet transfusions and a 23% increase in red cell transfusions.[73]

    - The process guard bands approved by FDA for Intercept[74] will reduce the number of components that can be processed due to platelet concentration and volume constraints.

  - LVDS (if cleared as a safety measure):

    - Large sample volume of at least 16 mL/component will reduce amount of platelet available for transfusion.[75]

    - Increased false positives due to anaerobe testing will also impact platelet inventories.[76]

- Secondary Rapid Testing:
    - Requires only a 500µL sample. Does not deplete platelet component volume or the number of platelets in a component as reculturing does.
    - Enhances platelet availability by permitting seven-day dating, thus reducing outdating without impacting split rates or reducing platelet volume available for transfusion.
    - Affords immediate platelet availability, as rapid testing can be performed any time within 24 hours of transfusion of an apheresis platelet.

- **Implementation Process for the options:**
    - PR:
        - PR increases costs associated with Intercept platelets – from initial purchase price, the need for more transfusions because of reduced effectiveness and limited storage days.[77]
        - Outpatient reimbursement is identical to that of an untreated leukoreduced apheresis platelet.[78]
    - LVDS:
        - Not currently an FDA cleared method, i.e., not a safety measure.
        - Will incur platelet delays in getting components to the hospital due to requirement for at least 48-hours between collection and initiation of culture plus at least a 12 hour hold period before release.[79]
        - Will reduce platelet component volume and platelet number due to large sample sizes (at least 16mL per component).[80]
        - There is no CMS reimbursement at the hospital level for a test performed at the blood center.
    - Secondary Rapid Testing:
        - Hospital Transfusion Services do not need to register as a Blood Establishment in order to perform secondary rapid testing unless they are extending the outdate of platelets beyond five days.
        - Hospitals do not need to relabel platelets unless they are extending the outdate beyond five days.

- A survey of hospital users of the PGD rapid test found they did not have to hire additional staff to perform the test, that implementation was easy and adapting IT to deal with it did not incur additional cost. (Survey results available on request)

- More than 200 hospitals that transfuse 20.3% of the US platelet inventory are performing rapid testing.[81]

- It is not necessary to perform rapid testing every day. It is sufficient to test an apheresis component only one time – within 24 hours prior to transfusion. For example, a platelet may be tested and transfused on storage day seven without prior PGD testing.

- Rapid test users report performing, on average, fewer than 2 tests per component. One hospital published data from two years of universal PGD testing and reported an average of 1.16 tests per component.[82]

- Outpatient reimbursement for test performed at the hospital is $25.50, in addition to the reimbursement for the component itself.[83]

- **7-Day outdate options (culturing or secondary rapid testing using a safety measure test):**

  - Culturing:

    - Reculturing individual platelet units with a safety measure culture test during storage, e.g. at day 4, with 8 – 10mL into each of two bottles[84,85,86] will add to costs. Such large sample volumes could reduce the number of platelets in many components below the FDA guidance minimum (3.0×10^{11}).[87] The number of components that qualify for this option will likely be limited.

    - If LVDS is FDA-cleared as a Safety Measure, it will incur added costs due to the need for two-bottle (one aerobic and one anaerobic) culture for each component of a split collection with at least 16mL sample volume per component.[88] This large sample volume will likely reduce split rates because of the potential for decreasing the number of transfusable platelets below 3.0×10^{11}.[89]

    - LVDS for 7-day dating will require FDA clearance as a Safety Measure.[90]

  - Secondary Rapid Testing:

    - Relabeling and registration is only necessary if dating is extended beyond five days. Registration is free and must be completed online.

    - Relabeling can be done using existing ICCBBA codes or manually, if preferable.

    - Rapid testing more than pays for itself if outdating is extended to seven days. ($25 test can conserve a $525 dose).[91]

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