Managing Platelet Refractoriness: ‘The Truth is Out There’

Karlstrom C, et.al. HLA-selected Platelets for Platelet Refractory Patients with HLA Antibodies: A Single Center Experience. Transfusion. 2019;00: 1–8.

Exposures to blood products can cause alloimmunization to platelet antigens, which may then result in a post-transfusion state called refractoriness. In such an event, there is insufficient increase in platelet count as the platelets are removed from circulation, increasing the likelihood for bleeding. There are numerous strategies devised to improve responsiveness to platelet transfusions, such as matching the specific donor platelet antigens called Human Leukocyte Antigen (HLA) or Human Platelet Antigen (HPA) to the recipient antigen phenotype and/or performing a laboratory serologic cross-matching test.

The article by Karlstrom et al. in Transfusion adds the authors experience to this ongoing debate. The nine-year study period, 2007–2016, consisted of a retrospective review of blood bank records at the Karolinska University Hospital (KUH, Stockholm Sweden) for 32 patients who received a total of 142 platelet products. The study subjects had a wide range of hematologic diseases; 11 patients had undergone allogeneic stem cell transplantation. All subjects were adults with known anti-HLA antibodies (those with antibodies against HPA were excluded), whose pre-transfusion platelet counts were \(<30 \times 10^9/L\). To be diagnosed as refractory, the patient needed at least one non-matched platelet transfusion with either a 1-hour corrected count increment (CCI) below \(5 \times 10^9/L\) or 2 consecutive 24-hour CCIs below \(2.5 \times 10^9/L\).

KUH provided specialized-platelet products by the following methods: the first through molecular genomic typing and then selecting donors that match the patient’s HLA Class I A and B antigens followed by serologic cross-matching. The second method utilizes an electronic online program called HLAMatchmaker (http://www.epitopes.net/), software that matches the donor and patient compatibility by comparing the inputted HLA alleles to the level of amino acids that carry epitopes (i.e. the specific antigen binding sites). Along with the donor and patient HLA alleles, patient HLA antibody specificities and the strength of their serologic reactivity (measured as mean fluorescent intensity, MFI) were entered into the database. The HLAMatchmaker generates an ‘eplet score’ to guide which product is selected.

By genomic matching, 22 of the 142 transfusions were identical to the recipient and 19 (86%) of these had successful 1-hour CCIs (platelet count \(>7.5 \times 10^9/L\)) For the remaining 120 transfusions, success rates trended downward as products were increasingly antigen mismatched (33% success rate when all tested HLA antigens differed). The presence of patient antibodies also had a negative impact.

In the news

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Cover photo: 1866 Mathew Brady photo of Clara Barton. Official U.S. Signal Corps Photo.

This issue of PLUS was written by Red Cross Physicians: Bachowski G, Fialkow B, Goldberg C, Mair, D, Mazzei C, Reddy, R. & West, B.
with transfusion outcomes significantly improving if antibody specificities were honored, or as the strength of the HLA antibody reactivity diminished. Using HLAMatchmaker, ‘eplet scores’ were more predictive of the transfusion responses, but the positive correlation was not as strong as that seen by avoiding antibodies against the HLA Class I A and B antigens. Nonimmune factors, such as bleeding, infection, and ABO mismatches were also considered, but the study was underpowered to draw such conclusions.

The authors’ final summation was that genomic HLA typing should be the first-line treatment for alloimmunized-refractory individuals, followed by platelets mismatched at the HLA A and B loci as long the antibody specificities of the recipient were honored. If only HLA incompatible platelets are available, then products should be chosen by ‘eplet score’, as is generated by the HLAMatchmaker, or by transfusing incompatible HLA platelets matched to antibodies with the lowest MFI.

The investigators acknowledged several limitations including the study’s retrospective design, its small number of subjects, and that changes in treatment regimens over the nine-year period could have influenced CCIs. Nevertheless, this study is informative to a field lacking clear guidance on the best way to treat refractory patients and may serve as the foundation for future investigations.

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Reference:

Chillin’ with my Platelets


Getz TM. Physiology of Cold-stored Platelets. Transfusion and Apheresis Science. 2019;58: 12–15

Standard room temperature platelets (RTP) are maintained at 20–24°C for five days, an extension for an additional two days is possible for some products if bacterial testing is performed. There is growing evidence that altering storage environments can influence the clotting activity of platelets. One such factor is temperature: keeping platelets in the cold may improve their function and extend shelf life.

Two current review articles summarize how cold temperatures can preserve platelet basal metabolism and therefore increase survivability. Platelet mitochondria play a key role in generating ATP, the cellular energy metabolite, by an oxygen-dependent process. During RTP storage oxygen is depleted, driving metabolism towards glycolysis for ATP synthesis. This results in an accumulation of lactate and reactive oxygen species promoting a stressful environment that causes premature activity, aggregation, and cell death. With refrigeration (2–6 °C), the basal respiration is decreased, and the generation of these toxic byproducts is reduced.

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Hemovigilance plays a crucial role in blood safety. It involves monitoring and reporting adverse transfusion-related events from blood donation through transfusion. Since the establishment of the first hemovigilance programs in the early 1990’s by France and Japan in response to infectious disease transmissions, thirty-four countries have participated in the International Hemovigilance Network, with many of them having developed their own, independent programs.

The United States has developed such a hemovigilance program, established by the Centers for Disease Control in 2010. The program, the National Healthcare Safety Network (NHSN) Hemovigilance Module (HM), is the sole nationwide system committed to a comprehensive surveillance of transfusion safety. A recent paper by Edens et al. in the journal Transfusion, and the related editorial by Whitaker, offers an update on the state of hemovigilance in the United States and particularly an assessment of the NHSN HM. The authors compared data submission for the voluntary enrolled facilities of the national HM with that of the compulsory reporting structure for the Massachusetts’ Department of Health transfusion surveillance program. The study period spanned the inception of NHSN HM in 2010 to 2016.

A key study finding was that although NHSN HM enrollment had improved, by 2016 only 6% (277/4690) of the national acute care facilities were enrolled. Of interest, 25% of the 277 NHSN HM reporting facilities were from Massachusetts, reinforcing that a statewide participation mandate was more successful for data accumulation. This compulsory requirement also ensured marked improvement in timeliness of data submission as the facilities became accustomed to the process. By 2016, data submission within 30 days of the adverse event occurred with 72% of Massachusetts hospitals, while that of the NHSN HM remained low at 48.2%.

During the study period, modifications were performed on the NHSN HM questionnaire with the removal of non-severe type of reactions and clarification of adverse event definitions, as well as regular monthly quality checks performed on the submitted information. Overall these changes enhanced the final quality of the data. However, as the study demonstrated, ongoing incorrect classification of complications such as febrile nonhemolytic transfusion reactions (FNHTRs) underscore the continued need to educate clinicians on standardized definitions.

The sentiment from the authors is that, despite the slow growth of the program, there is potential value and success for NHSN HM. Such a program requires continued focus on goals that include adoption of common (harmonized) definitions, robust participation with mandatory enforcement, with high quality reporting via standardized quality checks and ongoing education of the medical staff who document the adverse events. Such accumulated hemovigilance data can have sufficient strength to translate into future clinical recommendations for the enhancement of blood safety.

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Blood Type Matters: A Look at Platelet Compatibility


It has been well established that persons of O blood type are less likely to be at risk for thrombotic conditions such as heart attacks. For this reason, the question arises whether the presence of ABO antigens can impact normal platelet function during a bleeding episode.

Clotting begins with the binding of platelets to Von Willebrand Factor (VWF), a subendothelial protein that is exposed when the blood vessel wall is damaged. Platelet glycoprotein (GP) receptors interact with VWF in two phases, initially a temporary ‘tethering’ by GP1bα, followed by permanent adhesion via the platelet’s GPIIbIIIa. Of interest, platelets are known to express antigens similar to ABO, that are carried in the GP1bα receptor region.

Whether these ABO antigens can interfere with platelet activity was the focus of study for a recent publication by Eimear Dunne’s group. Blood samples from 87 healthy persons, 33 of type O and 54 of non-O type were injected into VWF-coated chambers to simulate flow conditions seen in an artery. Platelets from type O individuals were observed to be less likely to bind to VWF, especially if the VWF originated from a type O donor. The authors proposed that not only did the presence of non-O type antigen promote the platelet’s GP1bα conformational change (thereby enhancing binding to VWF), but that the associated glycosylation pattern imparted by ABO type between the platelet and VWF antigen might be a contributing factor.

The impact of ABO blood type compatibility on platelet function was further assessed in a large international pediatric observational study published by Marianne Nellis. The investigation evaluated platelet transfusions in 503 critically ill pediatric patients, 3 days to 16 years old; with the majority (68%, 342/503) of patients receiving ABO compatible units. The findings indicated that there was no observed clinically significant difference in platelet count increments regardless of product ABO compatibility status and bleeding status of the patient. Among the limitations of this study were lack of reporting on clinical impact including bleeding control and organ impact.

Overall, these studies show that while there are detectable differences between platelet function from type O and non-O individuals, the clinical implications including hemorrhagic control and impact on organ function remains unclear. Consequently, further studies are needed to determine how this will ultimately affect the overall practice of prophylactic and therapeutic platelet transfusions in the medical community.

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Pathogen Reduced Platelets for Pediatric Patients: Is There Need for Concern?


To date there has been few publications in the literature that address the safety and utility of pathogen-reduced platelets (PR PLT) for pediatric patients. This despite the fact that children (<16-years-old) are significant users of blood products, receiving about 14% of platelet transfusions. In addition, these young recipients are as at risk as adults for bacterial contamination of platelets, a leading cause of transfusion-related mortality.

Yale University recently conducted a non-randomized trial to investigate the impact of PR PLT transfusions on 240 patients who received a combined 1,932 platelet transfusions. The 21 month study monitored effects of platelet transfusions in patients ranging in age from newborns to 18 years old. The need for additional platelet transfusions and evaluation of hemostatic control was assessed during the first 48 hours after receiving either a PR PLT or conventional plasma-based unit.

The primary finding was that there was a minor but statistically significant increase in platelet transfusion for patients 1-18 years old who had received an initial PR PLT, rather than a standard platelet unit. However, this did not translate to a lack in bleeding control, as the number of RBC units were similar in the two arms of the study. In contrast to the older children, there was no demonstrable difference in platelet usage for neonates and infants (1-year-old or younger); for the neonates it was true regardless of whether they were in the NICU or not.

The authors of this paper also reported that there was no significant difference in the incidence of transfusion associated reactions, which were observed to be of minor types, allergic and febrile non-hemolytic. A sub-study, evaluating patients undergoing phototherapy who are particularly sensitive to the presence of psoralen, as found in PR PLT, showed no observed new rash in the test subjects.

This study did have some limitations: the sample size was small and patients were not randomized to be transfused exclusively with either PR PLT or conventional SDP. For these reasons, results had to be extrapolated through indirect observations of hemostatic control. Taking this into account, the study findings support FDA approval of PR PLT for all clinical indications and patient populations that require platelet transfusion.

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References:


Whole Blood

**IT’S ALL IN THE BAG**

Your one-stop solution for massively bleeding patients when every second counts.

<table>
<thead>
<tr>
<th>Red Cells</th>
<th>Platelets</th>
<th>Plasma</th>
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<tbody>
<tr>
<td>Group O+/O-</td>
<td>Platelet-sparing filter</td>
<td>TRALI mitigated from aspirin-free donor</td>
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<tr>
<td>Low-titered (1:200)</td>
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Improving the Odds: A New Drug for Treating TTP


Thrombotic Thrombocytopenia Purpura (TTP) is an uncommon life-threatening disease that presents with an unexplained and substantial decrease in circulating platelet counts and microangiopathic hemolytic anemia. TTP is generally characterized as a condition acquired through the binding of autoantibodies to ADAMTS-13, an enzyme which cleaves the large multimeric von Willibrand Factor (VWF) into smaller units. An ADAMTS-13 activity of less than 10% is diagnostic for TTP and results in the intact VWF acting as a procoagulant that promotes platelet aggregation. The circulating platelet microthrombi then have the potential to cause ischemic damage of critical organ systems such as the heart, GI tract, and central nervous system.

The Hematology publication written by Kathryn Dane and Shruti Chaturvedi introduces the reader to a detailed outline of the current treatment modalities for TTP, as well as examples of novel therapies that are undergoing clinical trials.

With the advent of therapeutic plasmapheresis, the mortality rate has decreased significantly from 90% to <20%, becoming the first line therapy for TTP. Plasma exchange serves to remove the autoantibodies to ADAMTS-13 as well as the ultra large multimeric VWF, while introducing active ADAMTS-13 from donor plasma. The combined use of immunomodulating agents, such as corticosteroids and/or Rituximab, serve as adjunct support for faster recovery and reduced relapse TTP rates. After the plasmapheresis treatment has been completed, monitoring phase may consist of regular monthly to annual measurements of ADAMTS-13 activity.

One novel drug discussed is Caplacizumab (trade name Cablivi) which in February 2019 received FDA approved status for the specific treatment of adult patients with acquired type TTP. Cablivi works in concert with plasmapheresis and immunosuppressive agents, acting as a protective measure in the early aspect of the disease, when ischemic damage from the microthrombi can occur. The drug consists of fragments of antibody (a nanobody) that adhere to VWF; forming a complex that prevents VWF from binding platelets. Side effects are mild to moderate in nature with mucocutaneous bleeding (i.e. epistaxis, gastrointestinal) that can be corrected with administration of VWF concentrate. In addition, there is a 3% probability of developing a drug-induced antibody with no observed clinical effect.

The New England Journal of Medicine recently published findings by Marie Scully and colleagues, that evaluated the effect of Cablivi versus placebo in patients diagnosed with TTP. This randomized, double blind clinical trial of 145 enrolled subjects showed that patients taking Cablivi were 1.55 more successful in achieving normalized platelet counts. In addition, users of the drug were less likely to have a TTP-related death or relapse within 30 days after ending plasma exchange. However, in those cases where reoccurrence did occur, the ADAMTS-13 activity level remained below 10%. This last finding underscores the fact that the use of Cablivi is not curative.

Although plasmapheresis in combination with immunosuppressive agents (i.e. Rituximab, Cyclosporin, Vincristine) is highly successful in improving TTP patient outcome, there remains a ~20% mortality risk. With the addition of novel drugs such as Cablivi, these odds are likely to bring a new treatment paradigm with an improved and long lasting outlook.

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Donating Blood in the Golden Years

Goldman M et al. Safety of blood donation by individuals over age of 70 and their contribution to blood in five developed countries a BEST Collaborative group study. Transfusion 2019;00;1-6. doi:10.1111/trf.15132

According to the Population Reference Bureau, the number of Americans over the age of 65 years old is approximately 15%. This number is expected to rise to 24% by the year 2060. This older demographic is a significant contributor to the nation’s blood supply, however, worry remains regarding their safety in association with the collection process. This concern is shared by the international blood center community; indeed several countries have placed an age cap on blood donation.

The international research collective, Biomedical Excellence for Safer Transfusion Collaborative (BEST) recently conducted a study to find an answer as to whether donating blood can influence the health of our older society members. In the study, 12 blood centers from five countries participated with known maximum age limits between 70 to 80’s for Australia, England/North Wales, and New Zealand. There was no such age limit for blood centers in Canada and the United States. The study analyzed data from 2016 whole blood and double red apheresis collections comparing donors of 24–70 years old to those over the age of 70 years. Metrics of the study included deferral rates and adverse reactions, specifically one of the most common complication types—vasovagal.

Ineligibility determination was significantly higher for the older subject group; gender played a role. A look at hemoglobin deferral rates indicated that females overall were more likely than males to be deferred on this criteria; however, age did not appear to be an influencing factor. In contrast older males were observed to have approximately double the deferral rate, by as much as 18.4%, for low hemoglobin counts in all five participating countries. When evaluating vasovagal type of complications, older donors, regardless of gender, showed the same or lesser incidence than their younger counterparts.

Although limitations in the study included lack of reporting all adverse donor reactions as well as details on eligibility criteria for all participant blood centers, the findings in this large multinational study indicate older donors, > 70 years of age, can safely tolerate blood donations. This is more likely due to the integration of rigorous donor eligibility assessments that excludes individuals at risk from donating in the first place. In addition, concerns that the elderly were more likely be predisposed to being anemic or developing common type of adverse reactions such as vasovagal reaction were not realized.

In summary, studies such as that discussed indicate older society members can continue to serve as contributing donors to the nation’s blood supply and that the need to set arbitrary age limits and exclusion, solely based on age, does not appear to be warranted. Considering that there is a shift in many countries’ demographics towards an aging population, reconsideration of inclusion of these individuals as blood donors, while ensuring safety measures are retained, is needed.

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Supporting Documents:


CURRENT RECOMMENDATIONS FOR RED BLOOD CELL TRANSFUSION, PERIOPERATIVE ANEMIA AND PATIENT BLOOD MANAGEMENT IN ADULTS


Patient Blood Management has as its goal the safe and effective use of blood to maximize positive patient outcomes while minimizing unnecessary transfusions. Evidence-based transfusion guidelines provide clinicians and health-care teams with information about when, how much, and who is most likely to benefit from transfusion. There is no doubt that blood saves many lives every day, however the benefits, risks, and even costs must all be considered.

In 2018 the Patient Blood Management International Consensus Conference (PBM-ICC) convened in Frankfurt, Germany to update evidence-based recommendations for red cell transfusion and to identify topics needing further study. This multidisciplinary, scientific committee identified several questions to evaluate the effectiveness of blood management practices in adult patients. To address these questions, over 17,000 citations were extracted from four large biomedical databases of the medical literature, ultimately data from 145 studies were evaluated and recommendations were made based on the strength of the evidence. The group discussed their final ten clinical and 12 research recommendations for establishing criteria for red blood cell (RBC) transfusion thresholds, preoperative anemia, and implementation of PBM programs.

In regards to perioperative anemia, clinicians were directed to manage anemia early enough to ensure an adequate response, with conditional recommendations of iron supplementation. Routine use of short-acting erythropoietin (ESA) was not encouraged, with the exception of preparation of major elective orthopedic procedures when the patients’ hemoglobin levels was <13g/dL. However, even in this scenario the PMB-ICC committee enforced balancing potential complications of anemia with thromboembolism due to ESA use.

A restrictive red cell transfusion threshold with a hemoglobin (HGB) concentration ranging from 7 to 8 g/dL was suggested based on published evidence of reduction in RBC exposure and no increased survival benefit. Recommendations included HGB triggers for implementation of RBC transfusion in the following proposed scenarios:

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<tr>
<th>RBC Transfusion Threshold HGB (g/dL)</th>
<th>Clinical Event</th>
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<tbody>
<tr>
<td>7</td>
<td>critically ill patient who is otherwise clinically stable</td>
</tr>
<tr>
<td>7.5</td>
<td>undergoing cardiac surgery</td>
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<tr>
<td>7-8</td>
<td>acute gastrointestinal bleed who is otherwise clinically stable</td>
</tr>
<tr>
<td>8</td>
<td>undergoing orthopedic surgical procedure for hip fracture and with known underlying co-morbidity such as cardiovascular disease</td>
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Implementation of PBM recommendations include incorporating a three prong approach: (1) ‘RBC transfusion’ by enforcing a restrictive RBC transfusion strategy; (2) ‘minimize blood loss’ by using hemostatic agents such as...
Tranexamic Acid; and (3) ‘optimize erythropoiesis’ with iron supplementation and ESA use. In addition use of electronic (computer) systems to improve red cell utilization was suggested. These recommendations are considered conditional as the scientific outcome on adverse events, cost, compliance and adherence remains to be determined.

Transfusion in complex clinical settings requires consideration of a myriad of factors besides laboratory results. This publication is important in that it is the first international collaboration on Patient Blood Management yielding useful medical recommendations and identifying several areas requiring additional research.

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Continued from previous page

Cold-stored platelets (CSP), are primed for use. It has been theorized that cold may trigger a shape change, resulting in a loss of the normal discoid shape. This is due to changes that include accumulation of intracellular calcium and restructuring of the cytoskeleton network. The result is expansion of the membrane surface and exposure of phosphotidylserine proteins and platelet receptors that are critical in platelet adhesion and aggregation.

Because CSP are primed for activity, these platelets are rapidly used and removed from the bloodstream (1-2 days vs. 7-9 days for RTP). Although of potential concern for hem-oncology patients, this is less of a worry in trauma situations where the need for hemostasis is more urgent.

There is also discussion about the role of cold-stored whole blood as an alternative to component therapy in critical trauma situations. The use of a platelet-sparing filter can largely conserve platelet function thereby providing an ‘all in one’ transfusion option offering the benefits of CSP as well as simplifying the logistics of patient treatment in urgent situations. The US Army has been using whole blood for some years, rapidly transitioning for use in the civilian population.

Finally, it should also be noted that chilling of PLT can significantly reduce the risks associated with bacterial contamination by binding antimicrobial agents into the clot as well as slowing the bacterial growth rate.

In summary, CSP have been shown to have significant benefits for trauma patients, with priming of platelets for ready use while allowing for longer storage survivability. Further studies are needed to determine what other uses CSP may have in other fields besides hemostasis, including regenerative medicine.

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Chillin’ with my Platelets | Continued from page 3
Meet Clara Barton, Founder of the American Red Cross

Clara Barton is one of the most honored and recognized women in American history. Born on December 25, 1821, in Oxford Massachusetts, she began her illustrious career as a teacher, and founded the first free school in New Jersey. She eventually resigned her position when the town officials, after all her efforts, hired a male principal at twice her salary.

In 1854 she was hired at the US Patent Office as the first female clerk. However, she left this position in 1861, during the Civil War, to assist in providing much needed supplies to Union soldiers. At the front lines of many major battles, she nursed, comforted and cooked for the wounded, earning the nickname the “Angel of the Battlefield.” After the war, in 1865, Clara Barton was appointed by President Abraham Lincoln to develop and oversee the Bureau of Records, locating 22,000 missing soldier remains.

In 1869, during a visit to Geneva, Switzerland to regain her health, Clara Barton met with officials of the International Red Cross, an organization that was derived from the Geneva Convention to provide aid to those injured during battle. However, before returning to the United States she organized relief efforts in Strasbourg France during the Franco-Prussian War. There she assisted in establishing military hospitals as well as developing a system where women in need of paid work made garments. Due to these efforts she was granted the Iron Cross of Merit by the German emperor, William I.

Upon her return to New York, she set to form the American Branch of the International Red Cross. By 1881, at the age 59, she began to serve as the president of the American Red Cross, for the next twenty-three years. By the force of her personal example, she opened paths to the new fields of service that we currently see within the Red Cross.

Publications Corner

Recent publications by American Red Cross scientists and physicians:


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