

TITLE: Platelet Refractoriness

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Slide 1:

Hello, my name is Matthew Karafin. I am an Associate Medical Director for the Blood Center of Wisconsin and an Assistant Professor at the Medical College of Wisconsin. Welcome to this Pearl of Laboratory Medicine on “Platelet Refractoriness.”

Platelet transfusions are a common therapeutic intervention in patients who are bleeding, or who are at risk for bleeding and are thrombocytopenic. While each transfused unit of an apheresis platelet product should increase a patient’s platelet count by about 30-60 thousand, cases arise where there is no apparent improvement in platelet count.

Slide 2: Definition

Every now and again, a platelet transfusion will not provide a desired therapeutic benefit or increase in platelet count. This is not uncommon, and can be due to many reasons, many of which do not need specific medical intervention. However, when a patient repeatedly does not respond adequately to their platelet transfusions, they are defined as being refractory to platelets, and, in these cases, an etiology should be sought.

Slide 3: Causes

When platelet transfusions do not provide an anticipated response, the reason often can be identified by simply evaluating the patient’s medical history. In general, inappropriate responses to platelet transfusions are often due to either the rapid loss of platelets or sequestration of the infused platelets. Both non-immune and immune conditions can lead to this loss.

Slide 4: Non-immune causes

There is a well-known relationship between changes in platelet count and platelet survival, where those factors that effectively act to reduce platelet survival, also reduce platelet increment after transfusion. Some common causes of reduced platelet survival include fever, sepsis, rapid or severe bleeding, DIC, GVHD, VOD, and a number of medications. Unlike other non-immune causes, splenomegaly is unique in that transfused platelets can become sequestered in a large spleen without necessarily influencing their survival, but can cause problems regarding improving platelet count from transfusion.

Slide 5: Immune Causes

Unexpected and rapid removal of transfused platelets can also be due to the patient's own immune system.

Autoantibodies against platelet antigens, such as in the disease immune thrombocytopenic purpura (ITP), can not only lead to thrombocytopenia from the rapid removal of the patient's own platelets, but can also effectively remove any transfused donor platelets. Of note, platelet transfusion in ITP is relatively contraindicated because of its known lack of effectiveness in improving one's platelet count.

On the other hand, patients who have been previously exposed to foreign leucocyte or platelet antigens from pregnancy or previous transfusion can develop an immune response against these antigens. The anti-leukocyte or platelet alloantibodies, once formed, can effectively remove any future platelets that contain these foreign proteins.

Lastly, platelets can have A and/or B carbohydrates on their surfaces depending on the ABO type of the patient. Patients who receive ABO-incompatible platelets can have reduced post-transfusion platelet recoveries due to naturally occurring A and B antibodies from transfused donor plasma. Moreover, studies have shown that those who receive ABO incompatible platelet transfusions are also at greater risk for forming antibodies against foreign leukocyte and platelet antigens noted previously.

Slide 6: Immune Causes

The 2 most common causes of alloimmune refractoriness to platelets are antibodies to foreign human leukocyte antigens (HLA), and human platelet antigens (HPA). Antibodies against HLA proteins are the most common source of platelet refractoriness, representing 30-40% of immune platelet refractory cases. HLA antigens are critical in immune system function, and are highly pleomorphic, and so differences between donors and recipients are very common. Platelets contain only class one HLA antigens, and so antibodies can form to either the A or B HLA class 1 subtypes.

Human platelet antigens are a class of important proteins that assist with platelet adhesion and aggregation, and are much less common causes of platelet refractoriness. There are about 32 human platelet antigens, and of these, anti-1b and 5b represent the most common cause of refractoriness in this group.

Antibodies to both foreign HLA or HPA antigens arise from exposure, most commonly from previous transfusions or pregnancy.

Slide 7: Diagnosis

The first step to determining if a patient is refractory to platelet transfusions is as simple as measuring a platelet count. To look for potential platelet refractoriness from alloantibodies, first determine what your patient's platelet count is prior to the platelet transfusion by ordering a standard CBC. Then, after the platelet transfusion is complete, measure the patient's platelet count again 10 minutes to no more than 1 hour after the transfusion. The reason for this specific timeframe is that alloantibodies cause active and rapid removal of transfused platelets, and catching this active process as it is happening is critical for a good diagnosis. As noted earlier, this process needs to be repeated after at least 2 platelet transfusions to ensure that the patient is responding similarly to platelets despite the use of different platelet donors.

Slide 8: Diagnosis

Once you have determined the pre- and post-transfusion platelet count, one can use a number of techniques to determine if the patient is refractory. First, if the change in absolute platelet count after transfusion is less than 10,000 on more than one occasion, platelet refractoriness should be highly suspected. Second, one could use more sophisticated equations that take into account additional key factors, including patient blood volume and platelet dose. Examples of this are the percent platelet recovery calculation or the corrected count increment calculation.

The percent platelet recovery calculates the percent of platelets that are circulating in the patient after transfusion, correcting for patient blood volume and the dose of platelets transfused. In this calculation, a recovery of less than 30% is considered refractory.

The corrected count increment, on the other hand, calculates the number of platelets that are circulating after a platelet transfusion, correcting for patient body surface area and the dose of platelets transfused. In this calculation, an increment less than 7,500 is considered refractory.

Again, refractoriness is suspected in each case if the calculation yields a lower than expected value after 2 or more transfusion events.

The specific calculations and their use will follow on the next slides.

Slide 9: Diagnosis (Equation)

For this pearl, we will cover the corrected count increment (CCI) in more depth, as it is a very common method to determine platelet refractoriness. To do this calculation, you will need the patient's body surface area (BSA) in meters squared, the change in platelet count obtained 10 minutes to 1 hour after the transfusion is completed, and the number of platelets transfused (which is usually 3×10^{11} platelets for a single apheresis unit). Based on this equation, a poor response is when the CCI calculation is less than 7,500 after 2 or more platelet transfusion events.

Slide 10: Diagnosis (Example)

Let's try an example together: If you have a non-bleeding patient with a 1.8m^2 BSA, and this patient had a $10,000/\mu\text{L}$ platelet count increase 30 minutes after a single platelet transfusion, you would calculate the CCI by multiplying 1.8 by 10,000, and dividing that total by 3×10^{11} . As you can see, the resultant number is 6,000, which represents a poor response.

There are two points that I would like to make regarding this example: First, this method is clearly more sensitive for determining platelet refractoriness because it accounts for patient size. In this case, if the patient's BSA was larger, that $10,000/\mu\text{L}$ rise in platelet count might have been an adequate response for that person, despite the small absolute increase in platelet count. Second, one low CCI is not enough. You would need to do this calculation for the same patient on at least one other platelet transfusion occasion to determine if the patient may be refractory to platelets, and require an additional workup.

Slide 11: Diagnosis (Equation 2)

The equation for the percent platelet recovery calculation is very similar to the CCI equation and functions similarly in its ability to determine a potentially refractory patient. While I will not be going into depth about this equation, I have included the equation on this slide for completeness. Again, a patient who has a percent platelet recovery < 30% on more than one occasion should be considered as potentially refractory to their platelet transfusions.

Slide 12: Diagnosis Algorithm

Once you have identified a patient who might be refractory to platelet transfusions, the next step would be to define the cause. If the patient has clearly established non-immune factors, treating these issues might lead to improved responses to future platelet transfusions. On the other hand, if an immune cause is suspected, additional lab work to detect HLA or HPA antibodies should be undertaken. In practice, these antibody detection methods could be ordered at the same time as attempting to treat the patient's other medical issues. Moreover, as antibodies to HLA are more common than HPA, testing for HLA antibodies first would be the most efficient and cost-effective for the patient.

Slide 13: Antibody Testing

As shown on this slide, multiple techniques are used in reference labs to determine whether a patient has alloantibodies against platelets. While the details behind these specific techniques are beyond the scope of this discussion, the goal of these test methods is to accurately and specifically define the presence of, the number, and/or the identity of alloantibodies present in your patient's plasma. In the context of antibodies specifically against HLA antigens, the "panel reactive antibody" (PRA) is a useful number to have. The PRA actually represents both a specific test and a test result. As a test result, the PRA or calculated PRA provides a number that represents the percentage of the general population against which your patient is incompatible. For example, a PRA of 95% implies that the patient is incompatible with 95% of the platelet donor population. Clearly, lower PRA values are better than higher PRA values in the context of finding platelets that will be compatible with your patient.

Slide 14: Diagnosis Algorithm

If platelet alloantibodies are identified in a patient, decisions will need to be made regarding how to reduce or eliminate the patient's platelet refractoriness. If HLA antibodies are identified, the calculated panel reactive antibody can be of great clinical benefit. When the panel reactive antibody is found to be less than 20, most platelet units available should be effective in providing a reasonable increase in platelet count. In these cases, some suggest attempting ABO-matched platelets to see if this would improve platelet response. In contrast, in those who have higher panel reactive antibody values or in those who have HPA antibodies, the chances that random platelets, even if ABO-matched, would provide an adequate platelet response decreases. In these patients, working with a blood center to identify specific platelet donors that either avoid the detected antibodies or are matched specifically to your patient would be of significant benefit in improving that patient's response to future platelet transfusions. Platelet cross-matching may also be used by the blood center to ensure compatibility between the donor product and the recipient. Lastly, once a patient is placed on one of these specific transfusion protocols, continued routine clinical monitoring for transfusion effectiveness by correct count increments or panel reactive antibody evaluations would help ensure the continued efficacy of the transfusion therapy.

Slide 15: Treatment and Prevention

Finding large numbers of platelet units on an urgent basis for a patient who is known to have significant platelet antibodies can sometimes be a difficult challenge. When a patient is not bleeding, many patients can wait safely while awaiting the best platelet product. On the other hand, when an alloimmunized patient is bleeding, and matched platelets are not readily available or in high enough supply to meet the patient need, continuous platelet drips or large bolus platelet transfusions using random platelets may be of benefit to achieve hemostasis.

Unfortunately, uncontrolled bleeding can be life-threatening, and as a result, more drastic measures, such as the use of intravenous immunoglobulin (IVIG), Factor VIIa, or Rituximab has also been attempted in some situations. Please note, however, that the success of these other agents remains limited to anecdotal case reports.

Knowing that transfusing highly alloimmunized patients is difficult, prevention of alloimmunization may seem like a desirable option. However, only limited studies have suggested that using ABO compatible and leuko-reduced blood products may reduce, but not eliminate, the risk for alloimmunization in these patients.

Slide 16: Conclusion

In conclusion, platelet transfusion refractoriness requires 2 or more inappropriate responses to platelets as defined by below normal PPR or CCI. Platelet transfusion refractoriness is categorized according to whether it is immune- or non-immune-mediated, and treatments differ by etiology. Specially selected platelet products may be helpful in managing immune-mediated platelet transfusion refractoriness.

Slide 17: References**Slide 18: Disclosures****Slide 19: Thank You from www.TraineeCouncil.org**

Thank you for joining me on this Pearl of Laboratory Medicine on "Platelet Refractoriness."