

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The New Paradigm for Transfusion of Platelets



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H&O What is the rationale behind platelet transfusion?

RK We administer platelets to people with qualitative or quantitative problems with their platelets for 2 main reasons: to prevent or reduce the risk of bleeding, or to treat active bleeding. The majority of prophylactic platelet transfusions are administered to patients who have low platelet counts due to treatment with myeloablative therapies such as chemotherapy. Other patients need prophylactic platelet transfusion because they have a low platelet count prior to an invasive procedure, such as major surgery or surgery to place a central line.

H&O What are some of the challenges associated with platelet transfusion?

RK One of the biggest challenges is that platelets, unlike other blood components, do not circulate in a transfused recipient if they have been refrigerated. In the United States, red blood cells normally are stored under refrigeration for up to 6 weeks and plasma typically is stored frozen. By contrast, platelets must stay at room temperature. This can cause several problems.

The first problem is that bacteria can grow in the platelets during storage. It is possible to culture out bacteria from approximately 1 out of 3000 to 1 out of 5000 platelet units. These are typically gram-positive bacteria from skin flora, such as streptococcus or staphylococcus. Bacterial growth does not always cause a problem for the recipient, but a heavy growth of bacteria has the potential to cause severe and even fatal septic reactions.

The second problem, which is related to this problem of potential bacterial growth, is that platelets can be stored for only a few days. Right now, the US Food and Drug Administration (FDA) limits storage to 5 days after collection. The FDA has tried extending this period to 7 days a couple of times, and both times the limit was changed back to 5 days because of increased reports of septic reactions to the platelets.

As one can imagine, is very difficult to keep a blood product with a short shelf life in inventory. Complicating matters further, the working shelf life is actually closer to 3 days because it takes at least a couple of days to get results back from routine testing for pathogens such as hepatitis B and C and HIV. The supplies become like highly perishable produce at a grocery store, and managing the inventory presents an extreme challenge. The potential for wastage is very high.

H&O Is there any way to extend the shelf life of platelets?

RK A new pathogen reduction technology was recently licensed for use in the United States. This involves adding a DNA cross linker to each unit of platelets, and then shining ultraviolet light on the product. This has been shown to kill a variety of different pathogens by several logs. If implementation of this technology proves successful, it could lead to the ability to store platelets for up to 7 days. One of the US researchers who has been investigating the extended storage of platelets is Dr Sherrill Slichter. Some research has looked at storing platelets even longer—up to 14 days—but I think the most realistic extension we are

Table. AABB Guidelines on Platelet Transfusion in Adults

Recommendation	Strength of Recommendation	Quality of Evidence
1. Prophylactic platelet transfusion recommended for hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia who have a platelet count of 10×10^9 cells/L or less ^a	Strong	Moderate
2. Prophylactic platelet transfusion suggested for patients having elective central venous catheter placement with a platelet count less than 20×10^9 cells/L	Weak	Low
3. Prophylactic platelet transfusion suggested for patients having elective diagnostic lumbar puncture with a platelet count less than 50×10^9 cells/L	Weak	Very low
4. Prophylactic platelet transfusion suggested for patients having major elective nonneuraxial surgery with a platelet count less than 50×10^9 cells/L	Weak	Very low
5. Routine prophylactic platelet transfusion not recommended for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass (CPB); transfusion suggested for patients having CPB who exhibit perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction	Weak	Very low
6. Benefit of platelet transfusion unclear for patients receiving antiplatelet therapy who have intracranial hemorrhage	Uncertain	Very low

^aTransfusion dose should be no more than a single apheresis unit. For a typical adult patient, a half-unit is as effective as a full unit.

likely to see anytime soon in the United States is to 7 days. Those 2 extra days can make a huge difference. Countries that have gone from a 5-day to a 7-day limit have seen a substantial drop in wastage.

H&O What are the other potential side effects of platelet transfusion beside infection?

RK The risks of HIV and hepatitis C are extremely low, along the lines of 1 in 2 million, thanks to appropriate donor screening and highly sensitive testing of every platelet unit. Another risk is allergic reactions, which can range from minor urticarial reactions to severe and even fatal anaphylactic reactions. Febrile reactions also can occur.

Another risk of platelet transfusion is transfusion-related acute lung injury (TRALI), which is mainly caused by human leukocyte antigen (HLA) antibodies in donor platelets. If the donor has previously been exposed to a foreign HLA antigen, such as can occur during pregnancy, the anti-HLA antibody can end up in the platelet product and be passively transfused through a recipient. If the recipient has the cognate HLA antigen, this can lead to severe and sometimes even fatal pulmonary reactions. Steps are being taken to reduce that risk, such as testing platelet units for the presence of HLA and placing restrictions on platelet donation by certain multiparous women.

H&O What made the AABB decide to develop platelet transfusion guidelines for the first time?

RK The AABB (formerly the American Association of Blood Banks) had put forth guidelines on transfusion of

plasma and then red blood cells, so the next step was to complete that triad with platelets. These guidelines are important because platelets are a precious and limited resource that has both serious risks and important benefits. Our goal in writing these guidelines was to provide clinicians who order platelets with the best advice available on how they should maximize the clinical benefit while helping to limit risks and conserve the resource.

H&O Could you talk about these guidelines?

RK The guidelines (see the table), which were based on a systematic review of the literature, were written using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework—meaning that the evidence in the literature is assessed separately from the strength of each recommendation. They were first published online in November 2014.

Our first recommendation, which is a strong recommendation based on moderate-quality evidence, states that platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia, meaning a platelet count of 10×10^9 cells/L or less. This often applies to cancer patients who have a low platelet count after chemotherapy or stem cell transplantation. Two of the randomized controlled trials that supported this recommendation were TOPPS (Trial of Prophylactic Platelets) by Stanworth and colleagues and another study by Wandt and colleagues.

We recommend transfusing up to 1 apheresis unit or the equivalent, which is based on the results of several

studies, including the PLADO (Prophylactic Platelet Dose on Transfusion Outcomes) study that was published in the *New England Journal of Medicine* by Slichter and colleagues. This study found that higher doses are not more effective than a single unit, and doses equal to half a standard apheresis unit are equally effective. As an aside, the PLADO study based the dose on body surface area, but in our guideline we wanted to use units that would be easily understood by ordering clinicians. Blood banks that prepare low-dose platelets do need to consider the size of the recipient.

The other recommendations we made were relatively weak. Numbers 2 through 5 are weak recommendations based on low-quality evidence, and number 6 is an uncertain recommendation based on very low-quality evidence.

Recommendation number 2, which suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count of less than 20×10^9 cells/L, was based mostly on data from 2 observational studies. We had data on tunneled catheters from a single-center retrospective study by Haas and colleagues that was published in the *Journal of Vascular and Interventional Radiology* in 2010.

Our data on nontunneled central line placements came from a study by Zeidler and colleagues that was published in *Transfusion* in 2011.

The most controversial recommendation was number 3, which suggests prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than 50×10^9 cells/L. Bleeding after a lumbar puncture is rare, but potentially devastating—a spinal hematoma can lead to paralysis. We identified 21 case reports of spinal hematoma following lumbar puncture, and 17 of those cases occurred with platelet counts below 50×10^9 cells/L. In addition, we looked at a large series on platelet transfusion before lumbar puncture in children, which was published by Howard and colleagues in the *Journal of the American Medical Association* in 2000. The researchers found no bleeds in 958 children with leukemia who had a diagnostic lumbar puncture; 199 of these were done in patients whose platelet counts were at or below 20×10^9 cells/L. It is not entirely clear that those data are generalizable to adults, whose anatomy is different than that of children—adults tend to have more obesity and more fibrosis. The largest case series to look at adults included just 195 lumbar punctures in 66 patients. The researchers saw no bleeding in the 75 lumbar punctures that were done with platelet counts at or below 50×10^9 cells/L.

Recommendation number 4 suggests prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than 50×10^9 cells/L, based on a study by Bishop and colleagues. Recommendation number 5 recommends against routine prophylactic platelet transfusion for patients who are

nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass, based on a meta-analysis by Spiess and colleagues.

The final recommendation, number 6, states that the AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage. Due to a lack of evidence, we essentially decided to remain silent on this issue.

H&O How do these recommendations differ from what physicians had been doing?

RK Recommendation number 2 was the only real change. Other groups had published guidelines suggesting that the platelet count be less than 50×10^9 cells/L before platelet transfusion for central line placement, but we are suggesting a more restrictive platelet transfusion strategy in this setting. Apart from that, the recommendations generally reflect common practice.

H&O Do you have any caveats for physicians?

RK As we state in the guidelines, it is important to consider more than just platelet count in making these decisions. For example, platelet count does not tell the clinician anything about platelet hemostatic function. There is no substitute for clinical judgment when making the decision to transfuse platelets. The guideline is designed to aid in decision-making, but it is not meant to be an absolute standard for what to do in every situation.

Suggested Readings

- Bishop JF, Schiffer CA, Aisner J, Matthews JB, Wiernik PH. Surgery in acute leukemia: a review of 167 operations in thrombocytopenic patients. *Am J Hematol.* 1987;26(2):147-155.
- Haas B, Chittams JL, Terrotola SO. Large-bore tunneled central venous catheter insertion in patients with coagulopathy. *J Vasc Interv Radiol.* 2010;21(2):212-217.
- Howard SC, Gajjar A, Ribeiro RC, et al. Safety of lumbar puncture for children with acute lymphoblastic leukemia and thrombocytopenia. *JAMA.* 2000;284(17):2222-2224.
- Kaufman RM, Djulbegovic B, Gernsheimer T, et al; AABB. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med.* 2015;162(3):205-213.
- Slichter SJ, Bolgiano D, Corson J, Jones MK, Christoffel T. Extended storage of platelet-rich plasma-prepared platelet concentrates in plasma or Plasmalyte. *Transfusion.* 2010;50(10):2199-2209.
- Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med.* 2010;362(7):600-613.
- Stanworth SJ, Estcourt LJ, Llewelyn CA, Murphy MF, Wood EM; TOPPS Study Investigators. Impact of prophylactic platelet transfusions on bleeding events in patients with hematologic malignancies: a subgroup analysis of a randomized trial. *Transfusion.* 2014;54(10):2385-2393.
- Wandt H, Schaefer-Eckart K, Wendelin K, et al; Study Alliance Leukemia. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet.* 2012;380(9850):1309-1316.
- Zeidler K, Arn K, Senn O, Schanz U, Stussi G. Optimal preprocedural platelet transfusion threshold for central venous catheter insertions in patients with thrombocytopenia. *Transfusion.* 2011;51(11):2269-2276.