New York State Council on Human Blood and Transfusion Services

GUIDELINES FOR THE ADMINISTRATION OF PLATELETS

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New York State Council on Human Blood and Transfusion Services
New York State Department of Health
Wadsworth Center
Empire State Plaza – P.O. Box 509
Albany, New York 12201-0509

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Blood and Tissue Resources Program
New York State Department of Health
Wadsworth Center
Empire State Plaza
P.O. Box 509
Albany, New York 12201-0509

Phone: (518) 485-5341
Fax: (518) 485-5342
E-mail: BTRAXESS@health.state.ny.us
Website: *www.wadsworth.org/labcert/blood_tissue*

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†Chairperson, Guideline Working Group
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NEW YORK STATE COUNCIL ON HUMAN BLOOD AND TRANSFUSION SERVICES

GUIDELINES FOR THE ADMINISTRATION OF PLATELETS

I. INTRODUCTION

The following guidelines are intended to provide general information about platelet transfusion. Platelets for transfusion are available in two forms: pools of whole blood-derived platelet concentrates, and platelets collected via apheresis. Platelet concentrates are prepared from donated whole blood, separated within eight hours of collection, and contain a minimum of 5.5×10^{10} platelets. The usual quantity transfused to adults is a pool of four to six units, containing a total of 200 to 300 mL of plasma. Individual platelet concentrate units, which contain 40 to 50 mL of plasma, may be used for infants or small children. Apheresis platelets are collected from a single donor and contain a minimum of 3×10^{11} platelets suspended in 200 to 300 mL of plasma.

In adults, a pool of four to six whole blood-derived platelet concentrates, or a single apheresis unit, should achieve a clinically meaningful increase in circulating, functioning platelets, and is considered to be a therapeutic dose. Autogeneic transfused platelets have been found to survive four to five days in healthy subjects. However, because 7,000 to 10,000 platelets/μL are consumed daily in plugging endothelial gaps, platelet survival in thrombocytopenic patients is reduced. In order to assess the patient's response to the transfusion, a corrected count increment (CCI) can be calculated based on the patient's platelet count 10 to 60 minutes after transfusion and the number of platelets administered (see below). A CCI of >7,500 or a platelet count increase > 5,000/μL per platelet concentrate unit administered is considered an expected response for the transfusion. However, an adequate CCI does not necessarily indicate that a clinically adequate post-transfusion platelet count has been reached. If the increment observed is significantly lower than expected on two or more consecutive occasions, in the absence of infection, splenomegaly, active bleeding, disseminated intravascular coagulation, recent hematopoietic progenitor cell transplant, autoimmune thrombocytopenia, and other circumstances associated with platelet destruction, the patient may be alloimmunized to human leukocyte antigen (HLA) or platelet antigens.

Corrected count increment:

$$CCI = \frac{(\text{posttransfusion count} - \text{pretransfusion count}) \times \text{body surface area } (M^2)}{\text{platelets given} \times 10^{11}}$$

One unit of platelet concentrate should contain a minimum of 5.5×10^{10} platelets, and one unit of apheresis platelets a minimum of 3.0×10^{11} platelets. The exact platelet count of the transfused component should be used for calculating CCI to assess possible refractoriness.

II. BENEFITS OF PLATELET TRANSFUSION

Patients who may benefit from platelet transfusion include those with thrombocytopenia (hereditary or acquired) or platelet function disorders (hereditary or acquired). In either situation, platelet transfusions may be prophylactic or therapeutic. Prophylactic platelet transfusions are typically administered prior to an invasive procedure to patients at significant risk for platelet-related bleeding or to patients with severe thrombocytopenia who are at risk for spontaneous bleeding. Patients with autoimmune thrombocytopenia may not respond to platelet transfusions and should receive platelets only in case of life-threatening bleeding.

Platelet transfusions are administered to patients who are bleeding or have a potential for bleeding due, at least in part, to either thrombocytopenia or platelet dysfunction. The guidelines below set forth more specific criteria. However, applying the guidelines strictly to individual patients may not always be appropriate. Before a transfusion is ordered, patients should be assessed to determine the likely benefit. The assessment should include determination of the current platelet count, evaluation of any bleeding to determine the likelihood that it is platelet related, and consideration of any co-morbidities that may increase the risk of such bleeding.

Most hematologists and transfusion medicine specialists now agree that stable patients generally do not develop significant spontaneous bleeding until the platelet count falls below 10,000/μL. Other factors, such as coexisting coagulopathy, infection, other co-morbidities, and certain medications, may increase the likelihood of bleeding; such high-risk patients should be maintained at higher platelet counts with prophylactic transfusions. The threshold platelet count for thrombocytopenic patients who are to undergo an invasive procedure is less clear. A common practice is to raise the platelet count to at least 50,000/μL, except for procedures involving the central nervous system or eye, for which the count is often increased to at least 100,000/μL. The validity of these numbers is unclear, since few data on this subject are available. Nonetheless, they are generally considered to be adequate platelet counts for most procedures.

More problematic is the effect of antiplatelet drugs on the risk of bleeding. For instance, aspirin increases the bleeding time in most patients, although usually not beyond the upper limit of normal. In theory, this should increase the incidence of bleeding, but in practice, that does not appear to be the case, at least in stable patients with no other bleeding risk factors. Desmopressin acetate (DDAVP) improves platelet function in such cases, and platelets are almost never indicated. Drugs such as clopidogrel, abciximab, and other platelet receptor blockers increase the risk of bleeding. Understanding the mechanism of action and pharmacokinetics of specific antiplatelet drugs may guide treatment options. Approximately 10% of circulating platelets are replaced every day, so even if all platelets were completely inactivated by a drug, numbers of functional platelets sufficient for hemostasis should be attained in a few days after the last drug dose. Patients who are bleeding, and have recently taken one or more of these drugs, may need platelet transfusions.

Generally, nonbleeding patients may be treated more conservatively. Alternatives to platelet transfusion should be considered whenever possible. Antifibrinolytic drugs, such as epsilon aminocaproic acid (EACA) and tranexamic acid (TA), appear to lessen bleeding in some thrombocytopenic patients, as does desmopressin acetate. Recombinant factor VIIa (rFVIIa) has been used for platelet function defects with some success, but additional studies are needed to determine its usefulness definitively.

There are no specific indications for using apheresis platelets rather than pooled platelet concentrates. The extremely low prevalence of infectious diseases in the donor population makes it unlikely that pooled platelet concentrates would pose a significantly greater risk than do apheresis platelets. Previously, pooled platelet concentrates may have carried a higher risk of bacterial contamination than apheresis platelets, but the current AABB (formerly known as American Association of Blood Banks) and College of American Pathologists' requirement that all platelets be tested for bacterial contamination is thought to have eliminated this difference. Routine leukoreduction has diminished the likelihood of immunization to HLA or platelet-specific antigens, and apheresis platelets are considered equivalent to pooled platelet concentrates in risk for such alloimmunization.

III. REFRACTORINESS TO PLATELET TRANSFUSION

Development of platelet refractoriness due to alloimmunization to HLA or platelet-specific antigens is an inherent risk for patients on chronic platelet transfusion therapy. If refractoriness does develop, it usually appears within weeks of the first transfusion. The response to platelet transfusions should be monitored by obtaining a platelet count 10 to 60 minutes after each transfusion. Poor posttransfusion platelet count increments following at least two consecutive transfusions of ABO-compatible platelets suggest platelet refractoriness. *In vitro* demonstration of platelet antibodies (HLA antibodies or platelet-specific antibodies, or both) confirms the diagnosis of immune mediated platelet refractoriness. Once a patient is alloimmunized, subsequent unselected platelet transfusions are unlikely to be beneficial. If alloimmunization is not demonstrated, other factors should be considered; these may be temporary or reversible. In a neutropenic patient with a malignancy being treated for an infection, drug-dependent platelet-reactive antibodies may temporarily cause refractoriness.

Patients who are refractory to platelet transfusions because of alloimmunization may benefit from HLA-matched or crossmatch-compatible platelets because these platelets are presumed to lack antigen(s) against which the patient has formed antibodies. Any HLA or platelet-specific antibodies should be identified to facilitate provision of HLA-matched and/or crossmatch-compatible platelets for transfusion. Platelets carry ABO antigens on their surface, and ABO-matched platelets have been found to survive better than those that are ABO-incompatible with the recipient's plasma. Unfortunately, neither HLA compatibility nor platelet-crossmatch compatibility is a guarantee of a good posttransfusion increment or of platelet hemostatic effectiveness in any given alloimmunized patient.

When no other option is available for the severely thrombocytopenic, actively bleeding patient who is refractory to the usual doses of platelets, a constant or intermittent platelet infusion may be attempted. A maximum of one platelet concentrate unit per hour may be administered to adults, with up to four units being released at one time.

The difficult task of caring for patients who have become refractory to platelets has prompted the development of preventive strategies. Leukoreduced blood components have been the option most frequently employed in the U.S. and are now used routinely. Such components reduce exposure to the leukocyte-associated HLA antigens thought to be responsible for inducing HLA alloimmunization. Apheresis platelets and pooled whole blood-derived platelet concentrates are considered equivalent in risk.

IV. ADVERSE REACTIONS TO PLATELET TRANSFUSION

Reactions to platelet transfusions are similar to those associated with other blood components. The risk of allergic reactions and of transmission of transfusion-associated viral diseases, such as hepatitis B and C, and HIV, are likely the same as for other cellular and plasma containing components. Storage of platelets at room temperature (20 to 24°C) can lead to the accumulation of various biologic response modifiers, such as cytokines, in plasma and can result in febrile reactions. Febrile, nonhemolytic transfusion reactions have been mitigated with the near universal use of prestorage leukoreduction. Platelets also pose a greater risk of bacterial contamination than do other blood components because of their room temperature storage. For this reason, AABB and CAP require testing of all platelet components for bacterial contamination using an FDA-approved method prior to transfusion. The availability of new rapid assays designed for point-of-issuance testing shortly before release offers another means of testing for bacteria.

Whole blood-derived platelet concentrates contain an average of 0.5 mL of RBCs. Although the risk of alloimmunization is low (<4% of patients), Rh-negative patients who must receive whole blood-derived platelets from an Rh-positive donor should be considered candidates for RhIG, especially if the recipient is a female with childbearing potential. A 300 μg dose, with a half-life of 21 days, may cover up to 15 mL of Rh-positive RBCs. After that time, additional RhIG may be indicated. In apheresis platelets, the RBC contamination is very low (0.0004 mL).

Development of a positive direct antiglobulin test and/or hemolysis has been reported in cases in which group O platelets with high titer IgG ABO antibodies (usually anti-A) have been transfused to patients of other ABO groups (usually group A). For infants and children, the plasma of platelet components should be ABO-compatible with the recipient's red cells whenever possible. If it is necessary to transfuse platelets whose plasma is ABO incompatible with the recipient's red cells, particularly group O platelets to a group A patient, it may be appropriate to assess the anti-A or anti-B antibodies present in the plasma of platelet components. When possible, components with an antibody titer exceeding a predetermined threshold should be reserved for group-compatible transfusion.

A standard dose of platelets contains 200-300 mL of plasma. The administration of platelet components carries a risk for the development of Transfusion Related Acute Lung Injury (TRALI), especially when the component is derived from female donors with a history of pregnancy. The elimination of female donors, or the screening of female apheresis platelet donors for a history of pregnancy or the presence of anti-HLA antibodies are risk reduction strategies that have been implemented by many blood centers in the United States. These strategies have been demonstrated to significantly decrease the risk of TRALI caused by the transfusion of plasma-containing blood components.

The storage of platelets in platelet additive solutions decreases the amount of plasma in the components and thus provides an alternate TRALI mitigation strategy and may decrease the risk of allergic reactions as well as hemolytic reactions due to ABO incompatibility. The posttransfusion survival of platelets stored in a platelet additive solution is slightly less than those stored in plasma, but no differences in bleeding outcomes have been noted. The selective use of platelets stored in additive solutions for patients with history of multiple allergic reactions versus universal use of such platelets needs additional study.

V. INDICATIONS FOR PLATELET TRANSFUSION

A. Prophylaxis in patients with platelet counts <10,000/μL

The typical prophylactic platelet transfusion threshold in nonbleeding thrombocytopenic patients is 10,000/μL. For counts 10,000/μL to 20,000/μL, clinical judgment must be exercised, with consideration of clinical circumstances that increase the risk of bleeding by compromising platelet function or survival. Aplastic patients are not usually transfused in the absence of serious bleeding.

- Prophylactic transfusion to maintain a platelet count >10,000/μL generally involves the administration of an apheresis platelet component (containing 3×10^{11} platelets), or four to six platelet concentrates. Recently published data have demonstrated that lower doses of platelets can successfully prevent significant bleeding in hospitalized cancer patients. However, if lower platelet doses are used, more frequent platelet transfusions and the careful monitoring of platelet counts may be required. Notably the patient's

body surface area must be known in order to determine the amount of platelets to administer if not using a standard adult therapeutic dose.

- Platelet transfusion is not indicated in cases of immune thrombocytopenia purpura (ITP), post-transfusion purpura (PTP), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or heparin-induced thrombocytopenia (HIT), in the absence of life-threatening bleeding.

B. Prophylaxis in patients with platelet counts <50,000/µL prior to an invasive procedure

If surgery cannot be postponed, patients with platelet counts < 50,000/µL may require platelet transfusion. A platelet count >100,000/µL is recommended for neurosurgical and some ophthalmologic procedures.

For elective surgery, it is preferable to wait for the platelet count to rise either spontaneously or with appropriate treatment. In drug-induced and alcohol-induced thrombocytopenia, the platelet count usually returns to normal within one to two weeks after the responsible agent has been withdrawn.

C. Active microvascular bleeding attributed to platelet dysfunction or thrombocytopenia

This group includes thrombocytopenic cardiac surgery patients with ongoing abnormal microvascular bleeding in whom no surgical cause can be identified. Such patients usually have qualitative platelet abnormalities believed to contribute to a bleeding tendency even if the platelet count is normal. Bleeding in patients with platelet counts <50,000/µL, including cardiopulmonary bypass patients, is platelet-related microvascular bleeding. Occasional patients, including cardiopulmonary bypass surgery patients, may develop platelet-related microvascular bleeding even when their platelet counts are >100,000/µL. However, prophylactic platelet transfusion is not indicated, given the absence of evidence of efficacy in preventing bleeding in cardiac surgery patients. Prophylactic platelet administration after transfusion of a fixed number of red cell units is not indicated outside the setting of massive transfusion.

D. Intrinsic or acquired platelet dysfunction prior to an invasive procedure

Patients with platelet function disorders, whether hereditary or acquired, may respond to pharmacologic intervention with antifibrinolytics, desmopressin acetate, or rFVIIa. Unfortunately, none of the common assays, including platelet aggregation tests, PFA-100, and other platelet function tests, has been shown to correlate with clinical bleeding. Abnormal results on such tests alone do not constitute sufficient justification for platelet transfusion.

Acquired reversible platelet dysfunction occurs commonly in patients with renal insufficiency. In such patients, dialysis (in the case of frank uremia), desmopressin acetate, administration of erythropoietin or transfusion to reach a hematocrit of 30%, or estrogen may be employed as therapeutic strategies for bleeding. Cryoprecipitate may be effective in some patients if desmopressin acetate is unavailable, ineffective, or contraindicated. Platelet transfusion is not considered useful because transfused platelets are also affected by the uremia and thus will become dysfunctional.

In patients with drug-induced platelet dysfunction, the responsible drug should be discontinued prior to elective surgery. Approximately 10% of circulating platelets are

replaced each day; thus, enough platelets for normal hemostasis should be present within a few days after the last dose.

In patients with irreversible platelet dysfunction, as seen in myeloproliferative disorders, effective treatment of the underlying disease usually helps to correct the bleeding diathesis. However, desmopressin acetate and/or platelet transfusion may be necessary in acute surgical situations or if the patient is bleeding despite other therapies.

Patients with congenital platelet dysfunction, such as Glanzmann's thrombasthenia, Bernard-Soulier syndrome, and storage pool disease, often have bleeding beginning at an early age and usually require platelet transfusion to treat severe bleeding. Platelet transfusion is never indicated as treatment for von Willebrand disease, but desmopressin acetate may be of use (see New York State Council on Human Blood and Transfusion Services *Guidelines for the Administration of Cryoprecipitate,* 4th edition, 2012).

E. Administration of platelets at predetermined ratio in massive transfusion

Coagulopathy following hemorrhage and the massive administration of crystalloids and RBC units has been well documented, and is thought to result from a variety of factors, including the depletion and dilution of coagulation factors, acidosis, and hypothermia. In order to overcome the depletion of coagulation factors associated with massive transfusion, many institutions have developed massive transfusion protocols for specific groups of patients with trauma or obstetrical hemorrhage. These protocols specify the administration of blood components in a predetermined ratio that approximates the composition of whole blood, *e.g.,* a ratio of 1 unit of RBC: 1 unit of plasma: 1 unit of whole blood-derived platelet concentrate, or 6:6:1 if using apheresis platelets. The optimal ratio at which products should be administered has not been determined. Although the administration of platelets should be supported by laboratory data whenever possible, institutions are encouraged to develop protocols that ensure the adequate replacement of coagulation factors in hemorrhaging patients.

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