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Platelet Transfusion: An Update on Indications and Guidelines

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Platelet Transfusion

An Update on Indications and Guidelines

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KEYWORDS

• Platelet transfusion • Guidelines • Prophylactic • Therapeutic • Review

KEY POINTS

- Although platelet transfusion thresholds have not changed, the demand for platelets has increased, with most of the transfusions used in managing patients with hematologic malignancies.
- Platelet products are prepared either by concentrating the platelets from whole-blood donations (known as platelet concentrates [PCs]), or by collecting platelets directly from donors via automated apheresis procedures (known as apheresis platelets [APs] or single-donor platelets). APs are more widely used in the United States and have certain advantages and drawbacks compared with PCs.
- Platelet transfusion guidelines have been published; however, they are not consistently being followed, lack recommendations on some clinical scenarios, or differ in the platelet threshold recommendations in some clinical settings.
- Platelet transfusion guidelines from different medical societies concur with strongly recommending prophylactic platelet transfusion in the setting of severe hypoproliferative thrombocytopenia ($\leq$10,000/μL) following chemotherapy or allogeneic bone marrow transplant.
- Platelet transfusion decisions, whether for prophylactic or therapeutic indications, should be weighed against the risks of transfusion side effects, refractoriness, contraindications in some clinical settings, and platelet product availability.

INTRODUCTION

Platelets are commonly transfused blood components in many clinical settings, either therapeutically to manage acute hemorrhage or prophylactically to prevent bleeding when the platelet count decreases to less than a certain threshold or before a procedure. Platelets maintain hemostasis by controlling hemorrhage after blood vessel

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endothelial disruption. This process involves platelet adhesion, activation, and aggregation to form a platelet plug at the site of injury, thus maintaining vascular integrity.[1]

According to the American Red Cross, approximately 7000 units of platelets are transfused daily in the United States.[2] The demand for platelets has increased in spite of the unchanging prophylactic platelet transfusion thresholds.[3] Some factors that could have contributed to the increase in platelet demand are a growth in the general population, an increase in the incidence of hematologic malignancies in an aging population, and changing practices in managing hematologic malignancies.[4] It is estimated that two-thirds of platelet components are used in managing patients with hematologic malignancies.[5]

Some platelet transfusion guidelines have been developed[6–8]; however, platelet transfusion practices are still heterogeneous because the available transfusion guidelines are not consistently followed and their implementation may be challenging in some practices.[9] In addition, these guidelines either lack recommendations or differ in the platelet threshold recommendations in some clinical settings, such as surgery and invasive procedures.[6–8] When deciding on platelet transfusions, physicians are encouraged to consider the possible adverse events of transfusion, and the costs and labor associated with platelet acquisition. It is worth noting that platelet triaging processes followed by blood banks to maintain an adequate inventory can sometimes affect the decision to transfuse platelets. This article presents an update on platelet transfusion, focusing on transfusion guidelines and platelet thresholds in different clinical settings.

PLATELET PRODUCTS

Platelet products are manufactured in 2 ways: concentrated and pooled from units of whole blood (WB), or collected directly from donors via an automated apheresis instrument.[10]

Platelet concentrates (PCs) are also known as random donor platelets or pooled platelets. The number of platelets in each concentrate is variable, but 4 to 6 units of PCs need to be pooled to provide a therapeutic dose of at least 3×10^{11} platelets for adult patients. Apheresis platelets (APs) are also known as single-donor platelets. A typical apheresis procedure often can collect sufficient platelets to be split into 2 or even 3 doses of platelets, with each dose providing approximately the equivalent of 6 or more units of PCs (ie, 3–6 $\times$ 10^{11} platelets).[11] APs are more widely used in the United States and have certain advantages and drawbacks compared with PCs (**Table 1**).

Pathogen Inactivation of Platelets

Despite increased laboratory testing and more stringent donor selection criteria, transfusion-transmitted infections still occur. Current testing is not fully effective against bacterial contamination, and septic transfusion reactions remain one of the leading causes of transfusion-related mortality and serious adverse events. The currently available testing also does not test for all potential pathogens, and testing can only be implemented for new emerging pathogens after the agent has been identified. As a strategy developed to not only proactively inactivate all the pathogens that are the targets of current infectious disease testing of blood components but also inactivate all viruses, bacteria, and protozoa, pathogen inactivation (PI) technologies significantly reduce the risks of transfusion-transmitted infections. At present, three PI technologies of platelets are available, using amotosalen hydrochloride plus ultraviolet A light (INTERCEPT Blood System, Cerus Europe BV,

Table 1
Advantages and disadvantages of platelet concentrates versus apheresis platelets

	PCs	APs
Advantages	• Less costly • Coproduct of WB collection • Collection of WB and concentration of platelets easy to perform	• Single donor exposure per adult dose • Donor matching (based on HLA, ABO type, and so forth) possible • Low RBC and WBC content • Meets leukoreduction criteria[a] • Easier to perform bacterial testing • Can be treated with FDA-approved pathogen inactivation technology in the United States
Disadvantages	• Must be pooled to provide an adult dose • Increased donor exposure • Donor matching impractical • Higher RBC and WBC content • More labor intensive to perform bacterial testing	• Expensive • Collection requires dedicated procedure, apheresis operator, and instrument • Time consuming and less convenient for the donor

Abbreviations: FDA, US Food and Drug Administration; HLA, human leukocyte antigen; RBC, red blood cell; WBC, white blood cell.
[a] Integrated leukoreduction system is available on most instruments.

Amersfoort, The Netherlands), riboflavin plus ultraviolet light (Mirasol Pathogen Reduction Technology, Terumo BCT Biotechnologies, Lakewood, CO), or ultraviolet C light (Theraflex UV, MacoPharma, Mouvaux, France). All 3 achieve inactivation of a broad range of pathogens by causing extensive photochemical damage to the nucleic acids.[12]

The 3 different systems are in various stages of clinical use and regulatory approvals. At present, only the INTERCEPT technology is licensed in the United States for APs. Both INTERCEPT and Mirasol are clinically available in Europe AP and PC products, whereas the Theraflex UV system is still in development. The US Food and Drug Administration (FDA) also approved the INTERCEPT technology as a safety measure to reduce bacterial contamination of platelets, and, as such, a replacement for both primary and secondary bacterial testing, including both culture-based and rapid bacterial detection point-of-release tests (eg, Verax Platelet PGD Test System, Verax Biomedical, Marlborough, MA).

PLATELET TRANSFUSION STRATEGIES: PROPHYLACTIC VERSUS THERAPEUTIC

Prophylactic Platelet Transfusion

Most platelet transfusions are given prophylactically to patients on chemotherapy, following hematopoietic stem cell transplant, or before invasive procedures. Platelet transfusion thresholds have been established by various medical societies (**Table 2**).

Hypoproliferative thrombocytopenia

Thrombocytopenia is a common problem in hematology and oncology patients. Despite the major development of platelet growth factors and thrombopoietin molecules, platelet transfusions remain the most common treatment for patients with thrombocytopenia.[13] Most platelet components are transfused prophylactically to prevent bleeding in the setting of hypoproliferative thrombocytopenia secondary to bone marrow involvement with malignancy, or as a result of treatment mostly with

Table 2
Prophylactic platelet transfusion thresholds according to different guidelines

	Platelet Transfusion Threshold (Level of Evidence)		
Indication/Procedure	**AABB[6]**	**ASCO[8]**	**BSH[7]**
Major surgery	<50,000/μL (WR)	<40,000–50,000/μL (WR)	<50,000/μL (WR)
CNS or ophthalmic surgery	NR	NR	<100,000/μL (WR)
Central venous catheter placement	<20,000/μL (WR)	NR	<20,000/μL (SR)
Lumbar puncture	<50,000/μL (WR)	NR	<40,000/μL (WR)
Epidural or spinal anesthesia	NR	NR	<80,000/μL (WR)
Bone marrow aspirate or trephine biopsy	NR	NR	Platelet transfusion not indicated (SR)
Percutaneous liver biopsy	NR	NR	<50,000/μL (MR)
Hypoproliferative thrombocytopenia following chemotherapy or allogeneic BMT	≤10,000/μL (SR)	<10,000/μL (SR)	<10,000/μL (SR)
Hypoproliferative thrombocytopenia following autologous BMT	NR	Platelet transfusion not indicated (MR)	Platelet transfusion not indicated (MR)
Chronic bone marrow failure (including patients on low-dose oral chemotherapy or azacitidine)	NR	NR	Platelet transfusion not indicated (MR)
Chronic bone marrow failure on intensive chemotherapy	NR	NR	<10,000/μL (SR)

Abbreviations: AABB, American Association of Blood Banks (former name); ASCO, American Society of Clinical Oncology; BMT, bone marrow transplant; BSH, British Society for Haematology; CNS, central nervous system; NR, no recommendation is provided; MR, moderate recommendation; SR, strong recommendation; WR, weak recommendation.

chemotherapy.[4,5] The current evidence from published literature and guidelines supports prophylactic platelet transfusion in hypoproliferative thrombocytopenia.

The AABB (formerly known as the American Association of Blood Banks) strongly recommends that hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia should be transfused to reduce the risk of spontaneous bleeding.[6] The AABB recommends transfusing with a single apheresis unit or equivalent when the platelet count is less than or equal to 10,000/μL. The American Society of Clinical Oncology (ASCO) shares the same platelet transfusion recommendation in this setting.[8] This recommendation applies to patients receiving intensive chemotherapy or undergoing allogeneic stem cell transplant. The platelet count threshold is generally increased to 15,000 or 20,000/μL when patients have risk factors of bleeding.[9,14]

Fever, infection, and inflammation are among the risk factors of bleeding reported in the literature[9,15,16]; however, studies are still warranted to identify these risk factors and what platelet threshold should be the trigger for transfusion. Prophylactic platelet transfusion to patients who had autologous stem cell transplant and are not bleeding is not encouraged.[17,18] Prophylactic platelet transfusion is not recommended for patients with chronic bone marrow failure (eg, myelodysplasia and aplastic anemia) even if they are taking low-dose oral chemotherapy or azacitidine, whereas platelet transfusion is recommended for those receiving intensive chemotherapy.[7]

Before invasive procedures and surgery

Platelet threshold recommendations are variable for invasive procedures and surgeries. This recommendation relates to the lack of evidence and subsequently the unavailability or weakness of platelet transfusion guidelines.[6–8] The AABB, ASCO, and the British Society for Haematology (BSH) agree on a platelet threshold of 20,000/μL and 50,000/μL for central venous catheter placement and major non-neuraxial surgery, respectively. Although the available literature is low quality and sparse, a platelet count more than 100,000/μL is usually recommended before neurosurgery or ophthalmic surgery involving the posterior segment of the eye.[7,19,20] Evidence on platelet transfusion for lumbar puncture is weak without any randomized clinical trials (RCT) to provide evidence.[21] The AABB advocates platelet transfusion for elective diagnostic lumbar puncture when the platelet count is less than 50,000/μL.[6] Despite lack of data, a platelet count of 80,000/μL is considered safe for epidural or spinal anesthesia in the absence of bleeding risk factors other than thrombocytopenia.[22,23] Platelet transfusion is not indicated before bone marrow aspirate or trephine biopsy because the risk of significant bleeding is less than 0.1%[7]; bleeding can typically be stopped by applying pressure on the biopsy site.

Bronchoscopy with or without bronchoalveolar lavage can be safely performed in patients with severe thrombocytopenia (platelet count of $\geq$10,000/μL).[24,25] Endoscopic interventions are fairly safe in patients with platelet count greater than 50,000/μL. Nonetheless, a platelet count of greater than or equal to 20,000/μL might be an appropriate threshold for platelet transfusion if a higher threshold is difficult to attain.[26,27] The data on percutaneous liver biopsy in patients with thrombocytopenia are heterogeneous. However, knowing the low overall incidence of serious bleeding, a platelet count of at least 50,000/μL is considered safe to perform percutaneous liver biopsy.[28]

Therapeutic Platelet Transfusion

Clinically significant bleeding usually refers to bleeding that is more than skin bleeding or epistaxis, and lasts more than 30 minutes, typically classified as World Health Organization (WHO) grade 2 or higher.[29] Complicated by highly diverse and complex clinical scenarios, variable definitions, and subjective assessment of bleeding, high-quality evidence to guide platelet transfusion therapy in actively bleeding patients is limited, and some variations in the recommendations of different guidelines are unsurprising.

However, most consensus guidelines recommend a platelet count of less than 50,000/μL as the threshold for platelet transfusion in patients with major or severe bleeding, including trauma,[7,20,30–34] and disseminated intravascular coagulation (DIC).[35] Platelet count should be maintained at greater than 100,000/μL in the presence of multiple trauma, central nervous system (CNS), or ocular bleeding. The role of therapeutic platelet transfusions in specific scenarios is discussed further here.

Minor bleeding

Many minor bleeding (WHO grade 1) episodes consist of mucocutaneous hemorrhages that are limited in size and/or duration (eg, epistaxis <1 hour, petechial lesions <2 mm in size, ecchymosis <10 cm in size), and often spontaneously resolve without consequence. Data on the necessity and efficacy of platelet transfusions in minor bleeding episodes are sparse. Although earlier studies showed that many severe bleeding episodes were preceded by minor bleeding,[36] recurrent event analysis of data from the randomized TOPPS trial, which was a randomized controlled trial comparing the use of prophylactic platelet transfusion with no prophylaxis in adult thrombocytopenic patients with hematological malignancies, failed to show minor bleeding as predictive for WHO grade 2 to 4 bleeding.[16]

The 2016 British Committee for Standards in Haematology (BCSH) guidelines recommend that patients with WHO grade 1 bleeding and no additional risk factors should be transfused if platelet count is less than 10,000/μL, the same as patients without any bleeding. If the bleeding is more significant but not severe or life threatening, platelet transfusion can be considered if platelet count is less than 30,000/μL.[7] The benefits of platelet transfusion in patients with minor bleeding should be weighed against the potential risks and evaluated along with alternative measures such as antifibrinolytics, local measures at bleeding site, and close monitoring.

Trauma

Low platelet count has been correlated with increased morbidity and mortality in massively transfused patients with trauma.[37,38] However, platelet count may also be less predictive of outcome in the trauma setting because of platelet dysfunction and other coagulopathies.[39] Consequently, the evidence to support particular thresholds for platelet transfusion is weak.

The empiric administration of platelets in predefined ratios with other blood products in patients with trauma who are not necessarily thrombocytopenic is controversial, as well as the optimal ratio or timing. A meta-analysis[40] and a systematic review[41] of retrospective and observational studies showed improved survival among patients with trauma receiving high platelet and plasma to red blood cell (RBC) ratios; however, such data are subject to confounding factors such as survivorship bias. In contrast, a review of 6 RCTs, 5 in patients with trauma, found no evidence of improved patient mortality or morbidity when comparing transfusing at 1:1:1 plasma and platelet to RBC ratio with a 1:1:2 ratio or standard care of primarily laboratory-guided transfusions.[42] The current BCSH guidelines only recommend early use of platelets in addition to transfusion of plasma and RBCs at a 1:1 ratio in patients with trauma with, or at risk of, massive bleeding.[32]

Disseminated intravascular coagulation (DIC)

The cornerstone of DIC treatment should be addressing the underlying cause. Platelet transfusion in patients with DIC should be reserved for patients with active bleeding or at high risk for bleeding (eg, postoperative, preinvasive procedure) to maintain the platelet count greater than 50,000/μL. Transfusions should not be withheld for fear of "fueling the fire" in such patients.

In nonbleeding patients with DIC, guidelines have recommended platelet count of 10,000 to 20,000/μL as the threshold for prophylactic platelet transfusion for patients with no additional risk factors for significant bleeding.[35,43]

Intracerebral hemorrhage

Although most guidelines recommend maintaining the platelet count at greater than 100,000/μL in patients with CNS bleeding, data on the impact of platelet transfusion

are overall limited. High-quality studies have mostly been focused on antiplatelet therapy (APT) –associated spontaneous intracerebral hemorrhage (sICH) and traumatic intracerebral hemorrhage (tICH). Earlier cohort studies showed slightly, but not statistically significant, improved mortalities following platelet transfusion.[44,45] However, in the more recent, randomized controlled PATCH trial of 190 patients with APT-associated sICH,[46] patients who received platelet transfusions were surprisingly more likely to have poor outcomes and higher mortality at 3 months, as well as increased hematoma growth at 24 hours. The mechanisms for the poorer outcomes associated with platelet transfusion are unclear. The PATCH trial was critiqued for low enrollment, stringent inclusion criteria, imbalance between the study arms, and underrepresentation of patients requiring neurosurgical intervention.[47] A separate RCT of patients with APT-associated sICH who required neurosurgical intervention showed that platelet transfusions were associated with a reduction of postoperative hemorrhage and mortality from 34% to 15% at 6 months.[48] For patients with APT-associated tICH, 2 recent systematic reviews and meta-analyses of mostly small retrospective observational studies also failed to identify clear benefits of platelet transfusion.[49,50] In summary, the available data suggest that platelet transfusions should be minimized in patients with APT-associated intracerebral hemorrhage (ICH) but may be considered for the subset of patients requiring neurosurgical intervention.

PLATELET TRANSFUSION IN SPECIFIC SETTINGS

Immune Thrombocytopenia

Primary immune thrombocytopenia (ITP) is characterized by the presence of platelet-specific autoantibodies. Prophylactic platelet transfusion in ITP is not recommended.[6] However, platelet transfusion can be considered before an invasive procedure or surgery when other treatments have failed. Administration of intravenous immunoglobulin (IVIg) with platelets was shown to be associated with rapid restoration of adequate platelet counts.[51] However, platelet transfusion can have a role in serious bleeding.[52]

Posttransfusion purpura (PTP), which is considered a delayed transfusion reaction, is a rare condition caused by antibodies against platelet-specific antigens. Sometimes PTP results in significant bleeding, which can be fatal.[53] Prophylactic platelet transfusion is not recommended in the setting of PTP, and management is based on IVIg. Nevertheless, platelet transfusion is reserved for life-threatening bleeding.

Inherited and Acquired Platelet Disorders

Inherited platelet disorders are characterized by platelet dysfunction with or without thrombocytopenia. The 2 described conditions are Bernard Soulier syndrome (BSS) and Glanzmann thrombasthenia (GT). Antifibrinolytics and hormonal therapies are usually the first-line treatment in managing bleeding diathesis in BSS and GT.[54] However, platelet transfusion remains a common approach in managing major bleeding and for prophylaxis. The risks of alloimmunization and platelet refractoriness should be seriously entertained before platelet transfusion.[54]

Acquired platelet disorders are also characterized by platelet dysfunction caused by platelet-extrinsic factors. Common clinical scenarios include drug-induced platelet dysfunction, uremia, and trauma. There is weak evidence to support the use of platelet transfusion to reverse APT. Platelet transfusion is contraindicated in APT-associated ICH (discussed earlier in relation to ICH).[46]

Platelet dysfunction in uremia is multifactorial and includes abnormal platelet–vessel wall interaction and platelet intrinsic defects.[55] Platelet dysfunction should be

corrected in patients with active bleeding or those who are planned for surgical procedures. Treatment options include correction of the underlying cause of uremia, dialysis, desmopressin, cryoprecipitate, or estrogen therapy.[56]

Platelet dysfunction can occur in trauma-induced coagulopathy even with a normal platelet count.[57] There is evidence that platelet transfusion in patients with trauma improves outcome.[58] Massive transfusion protocols are a clear example of this practice.

PLATELET TRANSFUSION IN PEDIATRIC PATIENTS

The normal platelet count of a healthy newborn is the same as that of older children and adults. In preterm neonates, the incidence of thrombocytopenia is inversely correlated to the gestational age at birth; however, a clear relationship between thrombocytopenia and clinically significant hemorrhage has not been established.[59] Evidence-based guidelines for optimal platelet transfusion are lacking in pediatric patients, and recommended transfusion thresholds for term infants and older children are primarily based on those for adults, with additional safety margins built-in for preterm infants, higher-risk patients, or clinical scenarios based on local norms and expert opinions.[60,61] Not surprisingly, large variations and ambiguities exist in transfusion practices.[62,63]

For example, most institutions use a platelet count of 50,000 to 100,000/μL as the transfusion threshold for neonates on extracorporeal membrane oxygenation because of the higher bleeding risks,[64,65] but there are no data from RCTs examining the efficacy and safety of the different thresholds. Another recommendation based on guidelines for adults is the threshold of platelet count less than 50,000/μL before lumbar puncture.[6,60,61] However, some investigators have suggested using 100,000/μL in the presence of circulating blasts or a traumatic lumbar puncture.[66,67]

Premature neonates are at higher risks of intraventricular hemorrhage, therefore a platelet count of 50,000/μL has commonly been used as the prophylactic transfusion threshold.[61] However, a recent multicenter, randomized trial supports a more restrictive transfusion trigger, because higher rates of death and major bleeding within 28 days were found among infants transfused at the higher (50,000/μL) than at the lower (25,000/μL) threshold.[68]

In addition, recent subanalyses of data from the PLADO study highlighted some critical differences between pediatric and adult patients, and the limitations of extrapolating transfusion guidelines from the adult population. The study included 200 children who were randomized along with adults to prophylactically receive a low ($1.1 \times 10^{11}/m^2$ of body surface area), medium ($2.2 \times 10^{11}/m^2$), or high ($4.4 \times 10^{11}/m^2$) platelet dose when the platelet count was less than 10,000/μL. There was no association between the platelet dose and bleeding for any age group, but pediatric patients overall had significantly higher incidence of WHO grade 2 or higher bleeding, which also occurred over a wider range of platelet counts compared with adults,[69] suggesting that factors other than thrombocytopenia likely affect the bleeding risks more in children.

PLATELET TRANSFUSION REFRACTORINESS

Platelet transfusion refractoriness (PTR) has been studied well in the literature and continues to be a challenge; it is associated with increased morbidity and mortality.[70] Nonimmune causes comprise around 80% of the causes of PTR, and these include fever, infection, DIC, bleeding, splenic sequestration, bone marrow failure, and certain medications.[71] Development of antibodies to class I human leukocyte antigens (HLAs) or, less frequently, antibodies to human platelet–specific antigens (HPAs) represent around one-third of refractory cases.[72] When platelet increments are not satisfactory,

ABO-identical platelets should be used because the A and B antigens can be adsorbed to platelets, thus ABO incompatibility can contribute to increased platelet clearance from the circulation. Immune-mediated PTR can be shown by failure of an adequate corrected count increment (<5000/μL) 10 to 60 minutes following ABO-compatible platelet transfusion on 2 consecutive occasions.[73,74] It is worth mentioning that patients with class I HLA antibodies do not necessarily develop PTR. Patients who are refractory to platelet transfusions and have class I HLA antibodies should receive HLA-matched/HLA-compatible platelet transfusion. If patients continue to be refractory to HLA-matched/HLA-compatible platelet transfusion and have HPA antibodies, they should receive HPA-matched platelet transfusion.[7] In clinical practice, finding compatible platelet units can be challenging for highly alloimmunized patients.

CONTRAINDICATIONS TO PLATELET TRANSFUSIONS

Platelet transfusion practices and their association with thrombosis and mortality were evaluated in ITP, thrombotic thrombocytopenic purpura (TTP), and heparin-induced thrombocytopenia (HIT) by Goel and colleagues.[75] The study included hospitalizations of 79,980 patients with ITP, 10,624 patients with TTP, and 6332 patients with HIT. There were no significant associations between platelet transfusion and thrombosis/mortality in ITP. Platelet transfusions were associated with arterial thrombosis and mortality among patients with TTP and HIT. Platelet transfusions are contraindicated in TTP and HIT unless there is life-threatening bleeding.[7,76]

SUMMARY

Platelets are commonly transfused either therapeutically to manage bleeding or prophylactically to prevent bleeding. Platelet transfusion practices are heterogeneous, although platelet transfusion guidelines have been published from different societies. In some clinical settings, these guidelines do not agree on the same platelet transfusion threshold. Moreover, the recommendations are either weak or lacking in many clinical situations. Platelet transfusion decisions should be weighed against the risks of transfusion side effects, refractoriness, and contraindications, as in TTP and HIT.

CLINICS CARE POINTS

- Platelet products are prepared either by concentrating the platelets from whole blood donations, or more commonly by collecting platelets directly from donors via automated apheresis procedures.
- Published platelet transfusion guidelines partly lack recommendations or differ in the platelet threshold recommendations in some clinical situations.
- Platelet transfusion guidelines concur with strongly recommending prophylactic platelet transfusion for severe hypoproliferative thrombocytopenia (≤ 10,000/μL) following chemotherapy or allogeneic bone marrow transplantation.
- Platelet transfusion decisions should be weighed against the risks of transfusions and the availability of platelet products.

DISCLOSURE

The authors have nothing to disclose.

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