Perioperative Platelet Transfusions

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Platelets are critical for clot formation. A normal platelet count is 250 × 10^3 cells/μl of blood, and there are approximately 2 × 10^{12} platelets in the whole body, with two thirds in circulation and one third sequestered in the spleen. Platelets provide both primary hemostasis through the formation of a platelet plug and secondary hemostasis by providing "rafts" of negatively charged surface phospholipids on which the amplification and propagation phases of plasma coagulation occur.[1] If lost or dysfunctional platelets need to be replaced quickly, transfusion of stored donor platelets is the only widely available therapy.

It is sometimes hard to know when to transfuse platelets. Stored platelets are a complex biologic therapy, and transfusion results depend on the donor, processing, and storage. Most perioperative practices are not supported by high-quality evidence. Traditionally, it is acceptable to perform percutaneous procedures with platelets greater than or equal to 20 × 10^3 cells/μl, do abdominal surgery with greater than or equal to 50 × 10^3 cells/μl, and do neurologic or posterior ocular surgery with greater than or equal to 100 × 10^3 cells/μl (table 1). These are apparently acceptable limits—the true physiologic thresholds are probably lower—and exceptions abound. For example, research in trauma suggests that actively bleeding patients do better when platelets are administered early, even when counts are maintained above 100 × 10^3 cells/μl.[2] On the other hand, patients taking antiplatelet agents who have nonsurgical intracranial hemorrhage may be harmed by platelet transfusion.[3] Optimal platelet therapy is also hampered by a lack of tests that can stratify bleeding risk, rapidly and accurately differentiate causes of coagulopathy, or reliably guide physicians at the bedside.

This paper will discuss guidelines, physiologic evidence, and the results of randomized clinical trials as they affect perioperative platelet therapy. By "perioperative" we mean any procedure in which a patient might be under the care of an anesthesiologist. In most cases, specific, actionable evidence is missing, so it is impossible to provide a formal systematic review.[4] All references were found by searching Medline or from the citations of references found in Medline. For the interested reader, we have provided a list of particularly influential primary clinical research (table 2).

A Brief History of Platelet Collection and Transfusion

Platelets were recognized as a constituent of blood in the 1870s, and their function identified shortly after, but for 70 yr there was no way to isolate them in a closed system.[5] In 1959 it was demonstrated that exchange transfusion in children with severe thrombocytopenia could correct their platelet counts and stop bleeding.[6] Research in the 1960s and 1970s produced improved storage methods and the discovery that storing platelets at room temperature preserved their lifespan after transfusion,[7] and that pools of platelets from multiple donors resulted in higher posttransfusion platelet counts.[8] Most platelets in the United States are now obtained by apheresis from a single donor, but the doses established in these studies are still used today.[9]

Rationale for Perioperative Platelet Transfusion

Platelets are transfused perioperatively either as prophylaxis against bleeding or as therapy to stop it. The value of platelet transfusion at extremes of thrombocytopenia, injury, and blood loss is not in question,[10] but an anesthesiologist is more likely to encounter situations where the marginal utility of platelets is uncertain. Attempts to establish practical transfusion triggers in common scenarios usually fail to produce consensus.[11–13] Appropriate triggers according to functional tests such as platelet function analyzers and viscoelastic testing are also unclear, and may not be superior to algorithms based on platelet count alone.[11,14] It is not surprising that anesthesiologists report using patient history, the surgical scenario, and the amount of blood loss to guide platelet therapy with only partial reference to laboratory values. Not surprisingly, there is a wide variation in perioperative platelet transfusion practice.[15,16]

Common Platelet Products for Transfusion

There are many different platelet products available in the United States, and they have a range of effects depending on the donor, processing, and storage.[17] Misunderstanding the composition of platelet products has been implicated in unnecessary transfusions.[18] The most important questions for the anesthesiologist are, "what is the total platelet

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Table 1. Common Platelet Count Thresholds for Procedures and Platelet Transfusion

Procedure	Platelet Count	Society	Strength of Recommendation/ Level of Evidence
Neurologic or posterior ocular surgery	100×10^3/μl	British Committee for Standards in Haematology[63]	Strong/low
Epidural catheter placement or removal	$75–100 \times 10^3$/μl	Society for Obstetric Anesthesia and Perinatology[43]	Not graded or endorsed, but acknowledged as common practice
	80×10^3/μl	British Committee for Standards in Haematology[63]	Moderate/low
Bleeding after cardiopulmonary bypass	$50–100 \times 10^3$/μl	Society of Cardiovascular Anesthesiologists[49]	Not graded
Major nonneuraxial surgery	50×10^3/μl	AABB (formerly the American Association of Blood Banks)[38]	Weak/low
	$40–50 \times 10^3$/μl	American Society of Clinical Oncology[39]	Weak/low
Gastrointestinal endoscopy	20×10^3 /μl (50×10^3/μl for biopsies)	American Society for Gastrointestinal Endoscopy[64]	Not graded
Central line placement	20×10^3/μl	AABB (formerly the American Association of Blood Banks)[38]	Weak/low
Bronchoscopy		British Thoracic Society[65]	Weak/low
Prophylaxis of spontaneous bleeding	10×10^3	AABB (formerly the American Association of Blood Banks)[38]	Strong/moderate

content of the product?" and "what volume of plasma is also in the product?" (fig. 1). A single "unit" of "random donor" platelets derived from 500 ml of donor whole blood usually contains at least 55×10^9 platelets in 40 ml of plasma and is stored at 22°C. Transfusing one random-donor unit will raise the recipient platelet count by approximately 5×10^3 cells/μl, and so it is common to make "pools" of five or six random donor units in approximately 200 ml of plasma. In a stable, nonbleeding, and afebrile adult, transfusing one pool will raise the recipient platelet count by approximately 30×10^3 cells/μl, but this varies inversely with body mass and area: the platelet count may only rise 15 to 20×10^3 cells/μl in an obese, 100-kg patient, and may rise 40 to 50×10^3 cells/μl in a thin, 50-kg one.[19] Apheresis, or "single-donor" platelets, are a concentrate collected from a single donation and usually contain 3 to 4×10^{11} platelets in approximately 280 ml of plasma. This is equivalent to a platelet pool, and transfusing one apheresis unit will also raise the platelet count by approximately 30×10^3 cells/μl.[17] Random-donor and apheresis platelets are collected in donor plasma with a coagulation factor activity similar to any other unit of plasma. However, apheresis platelets in the United States are often modified by replacing two thirds of the plasma with an additive solution. This improves platelet lifespan and reduces the rate of minor transfusion reactions but may decrease the acute hemostatic utility of the unit compared to apheresis platelets in plasma.[20,21] More than half of the platelet units supplied by the American Red Cross (Washington, D.C.) are stored in additive solution, with a system-wide goal of 70% by the end of 2020 (J. Weiss, M.D., American Red Cross, Madison, Wisconsin, email communication, October 2020).

"Cold" Platelets, Whole Blood, and Other Uncommon Platelet Products

"Cold" platelets are platelets stored at 4°C instead of the conventional 22°C. Cold platelets are cleared from the circulation more rapidly than conventional platelets, but may have greater immediate hemostatic efficacy.[22–25] Trials of cold-stored platelets in cardiac surgery and other clinical scenarios are ongoing. Whole blood for transfusion contains red cells, plasma, and platelets; is stored cold at 4°C; and is increasingly common in civilian trauma resuscitation.[26] Platelet counts after whole blood transfusion in bleeding patients are comparable to those obtained with balanced multicomponent resuscitation.[27] In centers where it is available, it is common to begin resuscitation with whole blood and then switch to laboratory-guided component therapy after major bleeding is controlled.[28] Other products also exist, such as frozen or lyophilized platelets, but these are not licensed in the United States.

Perioperative Thrombocytopenia

Thrombocytopenia is defined as a platelet count less than 150×10^3 cells/μl. Five to ten percent of patients will be thrombocytopenic preoperatively, and an unknown number will develop thrombocytopenia in the perioperative period.[29] Perioperative thrombocytopenia is usually caused by hemodilution and consumption, but can also be the result of antiplatelet therapy, heparin, other medications, decreased production, increased sequestration, immune destruction, and laboratory artifact.[30] Any degree of preoperative thrombocytopenia is associated with higher odds of transfusion, complications, long-term care, readmission, reoperation, and death in a dose-dependent fashion,[31] and patients who require platelet transfusion also have a higher odds of red cell transfusion, reoperation, and death.[29]

One in three of cases of platelet refractoriness is associated with alloimmunization against donor platelet antigens.[32] The most common alloantibodies are against human leukocyte antigens A or B, and are usually seen in multiparous or multiply transfused patients.[33] Platelet crossmatching, selecting donors with the same antigen phenotype as the patient, or selecting donors who lack the cognate antigens to the patient's antibodies can produce improved platelet increments.[33] All these techniques require additional

Table 2. Suggested Important and Influential Studies on Perioperative Platelet Transfusion

Authors	Title	Description	Notes
Slichter *et al.*[9]	Dose of prophylactic platelet transfusions and prevention of hemorrhage. (PLADO Trial)	Trial of 1,272 stable medical cancer patients receiving one of three different doses of prophylactic platelets to prevent grade 2 or higher bleeding.	Note figure 1. Risk of grade 2 or higher bleeding in stable patients low and constant at platelet counts between 10 and 80 × 10^3 cells/μl.
Avidan *et al.*[14]	Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery.	Trial of 102 patients receiving postbypass transfusion during coronary artery bypass graft guided by algorithms based on point-of-care *vs.* laboratory coagulation tests to reduce blood loss and transfusion. Results were compared to a historical control group where transfusion was guided by physician judgment alone.	One of the stronger studies providing evidence for the superiority of laboratory testing–guided transfusion algorithms over physician judgment in postbypass bleeding.
Holcomb *et al.*[52]	Transfusion of plasma, platelets, and red blood cells in a 1:1:1 *vs* a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR randomized clinical trial.	Trial of 680 severely injured trauma patients predicted to require massive transfusion who received platelets, plasma, and red blood cells in an initially fixed 1:1:1 or 1:1:2 ratio.	Although not the primary outcome, hemorrhagic death was significantly less common in the 1:1:1 arm.
Cardenas *et al.*[2]	Platelet transfusions improve hemostasis and survival in a substudy of the prospective, randomized PROPPR trial.	Subgroup analysis of PROPPR trial participants who received only the first cooler of products.	Although conclusions are limited by the *post hoc* nature of the analysis, the study strongly suggests that early, empiric platelet administration in massive traumatic bleeding is associated with survival.
Li *et al.*[59]	Effect of acetylsalicylic acid usage and platelet transfusion on postoperative hemorrhage and activities of daily living in patients with acute intracerebral hemorrhage.	Trial of 780 patients undergoing emergency craniotomy for hypertensive basal ganglia hemorrhage. Patients on aspirin with an aspirin effect detectable by aggregometry were randomized to receive 0, 1, or 2 units of frozen apheresis platelets.	Frozen apheresis platelets are not currently used in the United States; however, this suggests that there is benefit for laboratory-guided platelet transfusion to reverse bleeding associated with aspirin.
Baharoglu *et al.*[3]	Platelet transfusion *versus* standard care after acute stroke due to spontaneous cerebral hemorrhage associated with antiplatelet therapy (PATCH): A randomised, open-label, phase 3 trial.	Trial of 190 patients on antiplatelet therapy with supratentorial intracerebral hemorrhage who received platelet transfusion or standard of care.	Patients in the platelet arm had higher death-or-dependence, although this may have been partly due to baseline imbalances.

time and expertise, and advance consultation with transfusion medicine specialists is usually necessary.

Prophylactic Platelet Transfusions before Percutaneous Procedures

A normal platelet count is much higher than what is required for successful thrombin generation and maintenance of endothelial integrity at rest.[34] Based on large trials in hematological malignancies, the risk of clinically significant bleeding is modest and constant down to a platelet count of 10 × 10^3 cells/μl, and prophylactic platelet transfusions to prevent spontaneous bleeding are usually not necessary above a platelet count of 5 to 10 × 10^3 cells/μl.[9,35]

Data for prophylactic platelet transfusions before percutaneous procedures are sparse. One small trial and a few larger observational studies suggest that central lines placement by experienced providers is low-risk at platelet counts greater than or equal to 10 to 20 × 10^3 cells/μl.[12,36] For high-risk procedures such as liver biopsy, the Society of Interventional Radiology (Fairfax, Virginia) recommends a transfusion threshold of less than 50 × 10^3 cells/μl because observational studies found a slightly increased risk of bleeding below this level.[37] The AABB (formerly the American Association of Blood Banks; Bethesda, Maryland) recommends platelet transfusion before lumbar puncture for patients with a platelet count less than 50 × 10^3 cells/μl, and the American Society of Clinical Oncology (Alexandria, Virginia) recommends a threshold of 50 × 10^3 cells/μl for lumbar puncture in newly diagnosed pediatric patients with leukemia and 20 × 10^3 cells/μl for stable pediatric patients.[38,39]

All society guidelines regarding platelet counts before percutaneous procedures are weak recommendations based on low-quality evidence. They are also conservative: a review of 5,223 consecutive lumbar punctures in 958 children at a pediatric cancer center, including 199 children with counts less than 20 × 10^3 cells/μl, found an increase in the proportion of traumatic punctures, but not one serious complication.[40] A Danish cohort of 64,730 patients undergoing 83,711 lumbar punctures found that the hematoma rate was relatively constant around 0.2%, regardless of platelet count, although these results may be biased by patient selection.[41] There is no good evidence that preprocedural platelet transfusion reduces the risks of severe complications, and providers frequently fail to verify the results before starting the procedure.[42]

Thrombocytopenia and Prophylactic Platelet Transfusions before Neuraxial Anesthesia

The American Society of Anesthesiologists (Schaumburg, Illinois) and the Society for Obstetric Anesthesia and

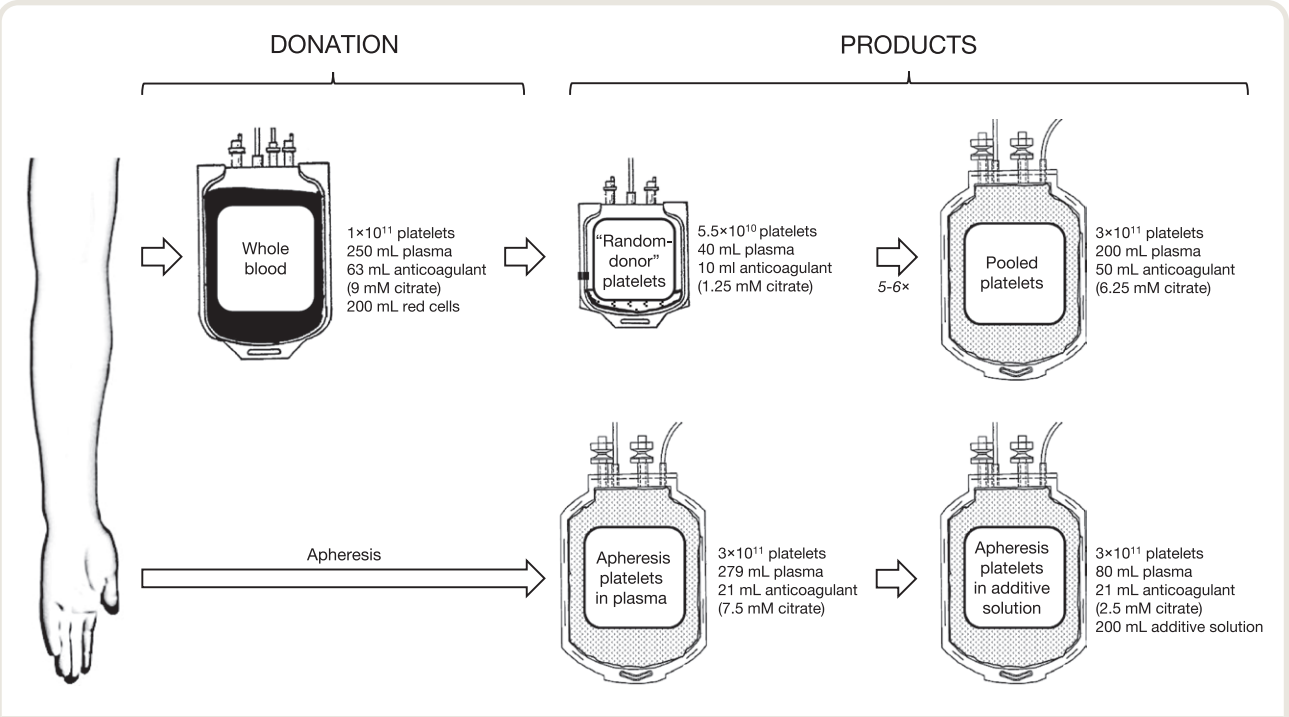

Fig. 1. An illustration of some of the varieties of platelet products available in the United States, how they are collected, and possible modifications to these products. Anticoagulant solutions are typically buffered salt solutions containing citrate and dextrose. Apheresis platelets in platelet additive solution are commonly referred to as "PAS platelets."

Perinatology (Lexington, Kentucky) do not suggest a platelet count above which it is safe to perform neuraxial anesthesia, although they acknowledge that most providers consider the threshold to be between 75 and 100 × 10^3 cells/μl.[43] Small observational studies of platelet transfusion to correct thrombocytopenia before neuraxial anesthesia have not detected any benefit, and many patients did not achieve their goal platelet count after transfusion.[13,39] Given the very low baseline rate of severe bleeding complications, it is unlikely that there will ever be definitive trial-level evidence. As with other percutaneous procedures, the anesthesiologist must weigh scant evidence against the clinical needs of the patient.

Thrombocytopenia and Prophylactic Platelet Transfusions before Airway Procedures

Limited data suggest that thrombocytopenia does not significantly increase the risks of airway procedures. A retrospective study of every bronchoscopy performed at two academic medical centers over a 5-yr period identified 72 patients with platelet counts less than 50 × 10^3 cells/μl (including 35 with counts less than 20 × 10^3 cells/μl), and none had periprocedural bleeding by British Thoracic Society (London, United Kingdom) criteria.[44] In the absence of high-quality evidence, some authors and professional societies state that oropharyngeal and airway procedures such as bronchoscopy and endoscopy can be performed at a platelet count greater than 20 × 10^3 cells/μl without excessive risk.[45]

Thrombocytopenia and Prophylactic Platelet Transfusions before Low-risk Surgery

It is traditional that major surgery can proceed at or above a platelet count of 50 × 10^3 cells/μl.[39] Perioperative thrombocytopenia is associated with worse outcomes, but platelet transfusion in retrospective studies is not associated with reduced perioperative bleeding, transfusion, or mortality.[29,31] The American Society of Anesthesiologists states that low bleeding-risk surgeries and vaginal deliveries may be performed at a platelet count less than 50 × 10^3 cells/μl, and that platelet therapy may be indicated for patients with platelet counts between 50 and 100 × 10^3 cells/μl.[46] The American Society of Clinical Oncology recommends a slightly more relaxed threshold of 40 to 50 × 10^3 cells/μl for all major invasive procedures.[39]

Therapeutic Platelet Transfusion for Bleeding after Cardiopulmonary Bypass

Cardiopulmonary bypass causes a transient platelet dysfunction associated with the selective release of platelet alpha-granule contents, which include factor V, von Willebrand factor, and fibrinogen.[1,47] It was once common practice to prophylactically transfuse platelets before

separation from bypass, but many societies explicitly recommend against this practice, and suggest that platelets should not be transfused to patients with a platelet count above 50×10^3 cells/μl who do not exhibit perioperative bleeding.[38] In those who do bleed, however, platelet transfusion seems beneficial: in a subgroup analysis of 324 patients enrolled in the Red Cell Storage Duration Study who had massive transfusion during cardiac surgery, patients given higher ratios of platelets to red cells had greater improvement in their Multiple Organ Dysfunction Score compared with patients who received lower ratios.[48] The Society of Cardiovascular Anesthesiologists (East Dundee, Illinois) suggests that platelets are indicated for bleeding patients with a count less than 50×10^3 cells/μl, and that they may be indicated for patients with a count between 50 and 100×10^3 cells/μl, but that transfusion should be guided by predefined, laboratory-guided algorithms.[49] The empiric use of 1-deamino-8-D-arginine-vasopressin to reverse cardiopulmonary bypass–associated platelet dysfunction does not significantly reduce transfusion requirements.[50] As noted, there is significant variability in transfusion rates among surgeons and anesthesiologists in cardiac surgery, even when controlling extensively for patient and procedural factors.[15,16]

Therapeutic Platelet Transfusion for Bleeding after Traumatic Injury

Traumatic injury is associated with diffuse endothelial damage and coagulopathy, and most deaths in the first 6 h after trauma are due to bleeding.[51] Thrombocytopenia after trauma is strongly associated with mortality, so early and aggressive platelet transfusion has been hypothesized to be beneficial.[28] In the Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial, severely injured patients who were predicted to need massive transfusion were randomized to receive initial resuscitation with plasma, platelets, and red blood cells in a 1:1:1 or 1:1:2 ratio.[52] Blood products were delivered by cooler, and only patients in the 1:1:1 arm received platelets in the first cooler. In the subgroup of patients who received only one cooler (and were effectively randomized to get either one or zero units of apheresis platelets), those who received platelets had significantly decreased 24-h and 30-day mortality, had a greater likelihood of hemostasis, and were less likely to die by exsanguination.[2] The American College of Surgeons (Chicago, Illinois) Trauma Quality Improvement Program now recommends transfusing red cells and platelets in a 1:1 ratio, *e.g.*, 1 unit of apheresis platelets for every 6 units of red cells.[53]

Prophylactic and Therapeutic Platelet Transfusion in the Setting of Antiplatelet Therapy

Platelet inhibitors are commonly used to prevent arterial thrombosis and coronary ischemia. Antiplatelet drugs are typically held before major surgery and resumed once the risk of perioperative bleeding has passed, although they may be continued. Aspirin is usually continued for isolated coronary artery bypass grafting, and patients requiring urgent or emergent cardiac surgery are frequently on dual therapy with aspirin plus a $P2Y_{12}$ inhibitor such as clopidogrel, prasugrel, or ticagrelor at the time of presentation. These patients are challenging to manage, and residual antiplatelet effects are associated with perioperative bleeding and transfusion,[54] so cautious delay is recommended, along with possible platelet function testing to guide operative timing.[38,55–57] The role of platelet function testing in patients on antiplatelet therapy has been recently reviewed in this journal.[58] When surgery must proceed before the antiplatelet effect has passed, limited data suggest that platelet transfusion may help in a dose-dependent fashion. A single-center trial of platelet transfusion during emergency craniotomy for basal ganglia hemorrhage found that, among patients with an aspirin effect detectable by aggregometry, 1 to 2 units of previously frozen apheresis platelets were associated with lower postoperative hemorrhage and mortality.[59] For clopidogrel and prasugrel, *in vitro* and *ex vivo* experiments suggest that 2 to 10 units of apheresis platelets may be necessary to reverse the antiplatelet effect, depending on the degree of inhibition.[60] Ticagrelor appears to be practically irreversible within 24 h of administration—a laboratory finding supported by clinical case reports—but at 24 to 48 h after administration, adequate reversal might be achieved with at least 3 to 4 units of apheresis platelets.[60] In the absence of clinical data, these doses and assumptions of efficacy must be received with caution.

In certain circumstances, platelet therapy may be contraindicated: one trial of 190 patients with intracranial hemorrhage on aspirin or other antiplatelet therapy randomized to receive platelet transfusions or standard care found a significantly increased composite rate of death or functional dependence in the platelet arm.[3] These patients were managed without invasive interventions, and there was some baseline imbalance that may have affected the outcome, so the results should not be applied to patients undergoing open surgery.

Perioperative Platelet Transfusion for Obstetrics, Liver Disease, and Others

There are many challenging situations in which the anesthesiologist will have to make decisions about platelet therapy with little data. These include obstetric hemorrhage, advanced liver disease, and disseminated intravascular coagulopathy. For obstetric hemorrhage, the American College of Obstetricians and Gynecologists (Washington, D.C.) advocates using 1:1:1: ratios of red cells, plasma, and platelets until resuscitation can be guided by a laboratory-driven algorithm.[61] In advanced liver disease, thrombocytopenia may be a misleading indicator of the patient's true bleeding tendency, and evidence from small trials suggests that transfusion algorithms incorporating viscoelastic testing

reduce blood use but not mortality.[62] For patients with disseminated intravascular coagulopathy who require surgery, there are no specific recommendations or guidelines; the anesthesiologist should be aware that patients may require larger-than-expected doses of platelets because of ongoing consumption.

Conclusions

Platelet transfusion is the primary therapy for patients with thrombocytopenia or platelet dysfunction who require procedures or surgery. Specific platelet triggers and goals vary with the clinical circumstances, and there is no high-quality evidence to guide perioperative practice. Stored donor platelets as they are currently available may not be an optimal therapy, and yet there are not proven alternatives in most situations. Platelet therapy is best guided by predefined protocols incorporating laboratory testing. It is acceptable under most society guidelines for patients to undergo low-risk procedures such as central lines and airway management with platelet counts greater than or equal to 20×10^3 cells/μl, high-risk percutaneous procedures and major surgery with counts greater than or equal to 50×10^3 cells/μl, neuraxial anesthesia with counts greater than or equal to 75 to 100×10^3 cells/μl, and neurologic or ophthalmological surgery with counts greater than or equal to 100×10^3 cells/μl. Most patients, however, will tolerate these procedures at lower platelet counts without severe complications. High-quality clinical trials investigating platelet storage technologies, platelet function testing, perioperative transfusion strategies, and alternatives to platelets are urgently needed. The anesthesiologist must weigh limited evidence alongside patient, operator, and institutional factors as they decide when to transfuse.

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Competing Interests

Dr. J. R. Hess is a shareholder in Medcura (Riverdale Park, Maryland), has received author royalties from UpToDate.com (Waltham, Maryland) for writing a chapter on "Massive Transfusion," is a consultant for Hemerus, LLC (St. Paul, Minnesota), is the inventor of the AS-7 RBC storage solution, serves as an advisor to the licensee of the U.S. Government patents for AS-7, and receives book royalties from AABB Press (Bethesda, Maryland) for the book *Massive Transfusion*, which he coauthored. The other authors declare no competing interests.

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