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ASCO SPECIAL ARTICLE

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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Editor's note: This American Society of Clinical Oncology clinical practice guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose

To provide evidence-based guidance on the use of platelet transfusion in people with cancer. This guideline updates and replaces the previous ASCO platelet transfusion guideline published initially in 2001.

Methods

ASCO convened an Expert Panel and conducted a systematic review of the medical literature published from September 1, 2014, through October 26, 2016. This review builds on two 2015 systematic reviews that were conducted by the AABB and the International Collaboration for Transfusion Medicine Guidelines. For clinical questions that were not addressed by the AABB and the International Collaboration for Transfusion Medicine Guidelines (the use of leukoreduction and platelet transfusion in solid tumors or chronic, stable severe thrombocytopenia) or that were addressed partially (invasive procedures), the ASCO search extended back to January 2000.

Results

The updated ASCO review included 24 more recent publications: three clinical practice guidelines, eight systematic reviews, and 13 observational studies.

Recommendations

The most substantial change to a previous recommendation involved platelet transfusion in the setting of hematopoietic stem-cell transplantation. Based on data from randomized controlled trials, adult patients who undergo autologous stem-cell transplantation at experienced centers may receive a platelet transfusion at the first sign of bleeding, rather than prophylactically. Prophylactic platelet transfusion at defined platelet count thresholds is still recommended for pediatric patients undergoing autologous stem-cell transplantation and for adult and pediatric patients undergoing allogeneic stem-cell transplantation. Other recommendations address platelet transfusion in patients with hematologic malignancies or solid tumors or in those who undergo invasive procedures. Guidance is also provided regarding the production of platelet products, prevention of Rh alloimmunization, and management of refractoriness to platelet transfusion (www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki).

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INTRODUCTION

The purpose of this guideline is to provide updated recommendations regarding the use of platelet transfusion in people with cancer. ASCO first published a guideline on platelet transfusion in people with cancer in 2001.[1] The guideline recognized the important role of platelet transfusion in the prevention and treatment of bleeding in patients with treatment-related thrombocytopenia but also sought to avoid the overuse of platelet transfusions by identifying patients who are most likely to benefit. The expense of platelet transfusions, coupled with potential adverse effects such as febrile and allergic reactions, transfusion-related acute lung injury, and bacterial contamination,[2] point to the importance of evidence-based transfusion practice. This guideline update reaffirms several of the earlier recommendations but includes some important changes, such as reconsideration of the need for prophylactic platelet

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Guideline Question

When and how should clinicians use platelet transfusion to prevent or manage bleeding in people with cancer?

Target Population

Adults and children (≥ 4 months of age) with hematologic malignancies, solid tumors, or hypoproliferative thrombocytopenia.

Target Audience

Clinicians administering intensive therapies to patients with cancer.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Key Recommendations

Preparation of Platelet Products

Platelets for transfusion can be prepared either by separation of units of platelet concentrates (PCs) from whole blood using either the buffy coat (BC) or the platelet-rich plasma (PRP) method, which can be pooled before administration, or by apheresis from single donors. Comparative studies have shown that the post-transfusion increments, hemostatic benefit, and adverse effects are similar with any of these platelet products. Thus, in routine circumstances, they can be used interchangeably. In most centers, pooled PCs are less costly. Single-donor platelets from selected donors are necessary when histocompatible platelet transfusions are needed (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Prevention of Rh Alloimmunization

UPDATED. Prevention of RhD alloimmunization resulting from platelet transfusions to RhD-negative recipients can be achieved either through the exclusive use of platelet products collected from RhD-negative donors or via anti-D immunoprophylaxis. These approaches may be used for female children and female adults of child-bearing potential being treated with curative intent. However, because of the low rate of RhD alloimmunization in patients with cancer, these approaches need not be applied universally (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Leukoreduction

UPDATED. The incidence of alloantibody-mediated refractoriness to platelet transfusion can be decreased in patients with acute myeloid leukemia (AML) receiving induction chemotherapy when both platelet and RBC products are leukoreduced before transfusion. It is therefore appropriate to provide leukoreduced blood products to patients with AML from the time of diagnosis to ameliorate this important clinical problem. Although randomized trials have not been conducted in other patient groups, it is likely that alloimmunization can also be decreased in patients with other types of leukemia and in other patients with cancer who are receiving chemotherapy. There are fewer data in patients who are not receiving chemotherapy in the same time periods that the transfusions are being administered (eg, aplastic anemia, myelodysplasia), although the consensus would favor its use in these patients as well. In the United States and in several other countries, the overwhelming majority of blood products are now leukoreduced at the time of blood collection and component preparation. Other advantages of prestorage leukoreduction include a substantial reduction in transfusion reactions and in transmission of cytomegalovirus (CMV) infection (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Prophylactic Versus Therapeutic Platelet Transfusion

Prophylactic platelet transfusion should be administered to patients with thrombocytopenia resulting from impaired bone marrow function to reduce the risk of hemorrhage when the platelet count falls below a predefined threshold level. This threshold level for transfusion varies according to the patient's diagnosis, clinical condition, and treatment modality (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Platelet Transfusion Threshold in Patients With Hematologic Malignancies

The Panel recommends a threshold of $< 10 \times 10^9$/L for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, or coagulation abnormalities (eg, acute promyelocytic leukemia) and in those undergoing invasive procedures or in circumstances in which platelet transfusions may not be readily available in case of emergencies, as might be the case for outpatients who live at a distance from the treatment center (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Platelet Transfusion Threshold in the Setting of Hematopoietic Stem-Cell Transplantation

UPDATED. The Panel recommends a threshold of $< 10 \times 10^9$/L for prophylactic platelet transfusion in adult and pediatric patients undergoing allogeneic HSCT. Prophylactic platelet transfusion may be administered at higher counts based on clinician judgment. In adult recipients of **autologous** HSCT, randomized trials have demonstrated similar rates of bleeding with decreased platelet usage when patients are transfused at the first sign of bleeding rather than prophylactically, and this approach may be used in experienced centers. This recommendation is not generalizable to pediatric patients (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate).

Platelet Transfusion in Patients With Chronic, Stable, Severe Thrombocytopenia Who Are Not Receiving Active Treatment

Patients with chronic, stable, severe thrombocytopenia, such as individuals with myelodysplasia or aplastic anemia, who are not receiving active treatment may be observed without prophylactic transfusion, reserving platelet transfusions for episodes of hemorrhage or during times of active treatment (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Platelet Transfusion Threshold in Patients With Solid Tumors

UPDATED. The risk of bleeding in patients with solid tumors during chemotherapy-induced thrombocytopenia is related to the depth and duration of the platelet nadir, although other factors contribute as well. The Panel recommends a threshold of $< 10 \times 10^9$/L for prophylactic platelet transfusion, based on extrapolation from studies in hematologic malignancies. Platelet transfusion at higher levels is appropriate in patients with active localized bleeding, which can sometimes be seen in patients with necrotic tumors (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Platelet Count at Which Surgical or Invasive Procedures May Be Performed

The Panel recommends a threshold of 40×10^9/L to 50×10^9/L for performing major invasive procedures in the absence of associated coagulation abnormalities. Certain procedures, such as bone marrow aspirations and biopsies, and insertion or removal of central venous catheters, can be performed safely at counts $\geq 20 \times 10^9$/L. There are sparse data, and no randomized trials, addressing the safety of other invasive procedures at much lower count levels. If platelet transfusions are administered before a procedure, it is critical that a post-transfusion platelet count be obtained to prove that the desired platelet count level has been reached. Platelet transfusions should also be available on short notice, in case intraoperative or postoperative bleeding occurs. For alloimmunized patients, histocompatible platelets must be available in these circumstances (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).

Monitoring for Refractoriness to Platelet Transfusion

UPDATED. Although there are no empirical data to suggest that monitoring and acting on the post–platelet-transfusion count decreases the incidence of hemorrhagic events, the Panel consensus is that platelet counts performed 10 to 60 minutes after transfusion should be obtained after all transfusions, when refractoriness is suspected. Because patients may have a poor increment to a single transfusion, yet have excellent platelet increments with subsequent transfusions, a diagnosis of refractoriness to platelet transfusion should be made only when at least two transfusions of ABO-compatible units, stored for < 72 hours, result in poor increments, as defined in the supporting text of the recommendation (Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Managing Refractoriness to Platelet Transfusion

Alloimmunization is usually due to antibody against HLA antigens and only rarely to platelet-specific antigens. Patients with alloimmune-refractory thrombocytopenia, as defined previously, are best managed with platelet transfusions from histocompatible donors matched for HLA-A and HLA-B antigens. Many blood suppliers have access to computerized lists of such donors. For patients (1) whose HLA type cannot be determined, (2) who have uncommon HLA types for whom suitable donors cannot be identified, or (3) who do not respond to HLA-matched platelets, histocompatible platelet donors can often be identified using platelet cross-matching techniques. In many patients, these two techniques are complementary (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines and at www.asco.org/guidelineswiki. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

transfusion in adult patients undergoing autologous stem-cell transplantation at experienced centers.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following clinical questions: (1) How should platelets for transfusion be prepared? (2) In what circumstances should providers take steps to prevent Rh alloimmunization resulting from platelet transfusion? (3) In what circumstances should providers use leukoreduced blood products to prevent alloimmunization? (4) Should platelet transfusions be given prophylactically or therapeutically? (5) What is the appropriate threshold for prophylactic platelet transfusion in patients with hematologic malignancies? (6) What is the appropriate threshold for prophylactic platelet transfusion in the setting of hematopoietic cell transplantation (HSCT)? (7) Is there a role for prophylactic platelet transfusion in patients with chronic, stable, severe thrombocytopenia who are not receiving active treatment? (8) What is the appropriate threshold for prophylactic platelet transfusion in patients with solid tumors? (9) At what platelet count can surgical or invasive procedures be performed? (10) When and how should patients be monitored for refractoriness to platelet transfusion? (11) How should refractoriness to platelet transfusion be managed?

METHODS

Guideline Update Development Process

This systematic review-based guideline product was developed by an Expert Panel with multidisciplinary and patient representation and by ASCO guidelines staff with health research methodology experience (Appendix Table A1, online only). The Expert Panel met via teleconference and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

Two 2015 systematic review-based guidelines by the AABB (formerly known as the American Association of Blood Banks)[3] and the International Collaboration for Transfusion Medicine Guidelines (ICTMG)[4] formed the starting point for the ASCO review. The AABB search included publications from 1946 to the first week of September 2014, and the ICTMG search included publications from 1946 to December 2013. For clinical questions that were addressed by either the AABB or the ICTMG, the ASCO search included publications from January 1, 2014, through October 26, 2016, using both PubMed and the Cochrane Library. For clinical questions not addressed by the AABB and the ICTMG (leukoreduction; patients with chronic, stable, severe thrombocytopenia; and patients with solid tumors) or that were partially addressed (invasive procedures), the ASCO search included publications from January 1, 2000, through October 26, 2016. The updated search was guided by the signals[5] approach, which is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The Methodology Supplement (available at www.asco.org/supportive-care-guidelines) provides additional information about the signals approach.

Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: adults and children (≥ 4 months of age) with hematologic malignancies, solid tumors, or hypoproliferative thrombocytopenia
- Intervention: prophylactic or therapeutic platelet transfusion
- Outcomes: bleeding, alloimmunization, platelet refractoriness
- Publication types: clinical practice guidelines, systematic reviews and meta-analyses, randomized controlled trials (RCTs), and observational studies

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; or (3) published in a non-English language.

The guideline recommendations were crafted, in part, using the Guidelines into Decision Support methodology.[6] In addition, a guideline implementation review was conducted. Ratings for the type and strength of

recommendation and the quality of the evidence are provided with each recommendation. These ratings are described in the Methodology Supplement.

Detailed information about the methods used to develop this guideline update is available in the Methodology Supplement at www.asco.org/supportive-care-guidelines, including an overview (eg, Panel composition, development process, and revision dates); literature search and data extraction; and the recommendation development process.

The ASCO Expert Panel and guidelines staff will work with the co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision-making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 24 more recent publications met the eligibility criteria and form the evidence base for the updated guideline recommendations: three clinical practice guidelines,[3,4,7] eight systematic reviews,[8-15] and 13 observational studies.[16-28] Cochrane reviews (2015) were available for two clinical questions addressed by this guideline update: prophylactic versus therapeutic platelet transfusion[8] and platelet count thresholds for prophylactic platelet transfusion in patients with hematologic disorders after myelosuppressive chemotherapy or stem-cell transplantation.[11] Cochrane reviews have also addressed platelet transfusion thresholds before insertion of central lines[9] and use of platelet transfusions before lumbar puncture or epidural anesthesia,[10] but no completed RCTs were identified. Evidence tables are provided in the Data Supplement.

RECOMMENDATIONS

Clinical Question 1

How should platelets for transfusion be prepared?

Recommendation 1. Platelets for transfusion can be prepared either by separation of units of platelet concentrates (PCs) from whole blood using either the buffy coat (BC) or the platelet-rich plasma (PRP) method, which can be pooled before administration, or by apheresis from single donors. Comparative studies have shown that the post-transfusion increments, hemostatic benefit, and adverse effects are similar with any of these platelet products. Thus, in routine circumstances, they can be used interchangeably. In most centers, pooled PCs are less costly. Single-donor platelets from selected donors are necessary when histocompatible platelet transfusions are needed (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. The effectiveness and safety of whole-blood–derived versus apheresis platelets was addressed in a 2015 systematic review[4] and in a post hoc analysis of the Platelet Dose (PLADO) trial.[28] The systematic review included evidence from RCTs[29] and from more recent, nonrandomized studies. After considering both the risk of bleeding and the risk of transfusion reactions, the ICTMG recommended that when leukoreduced platelet products are available, whole-blood–derived platelets should be used as equivalent products to apheresis platelets.[4] This was a strong recommendation based on a moderate level of evidence. In the PLADO trial, all platelet products were leukoreduced, and the risk of a transfusion-related adverse event did not vary significantly by platelet source (whole-blood derived or apheresis).[28]

Clinical interpretation. **Platelet use.** During the 1980s and most of the 1990s, the use of platelets increased more than did the use of other blood components,[30] and platelet use continues to increase. From 2011 to 2013, there was a 15% increase in platelet units transfused by AABB member hospitals in the United States (1.3 million units transfused in 2013).[31]

PCs from whole blood. Often referred to as random-donor platelets, PCs are prepared by centrifugation of standard units of whole blood. There are two methods for doing this: (1) the PRP method and (2) the BC method.[32] The PRP method is used in the United States, whereas the BC method is in common use in Europe, Australia, South Africa, and Canada. In the PRP method, an initial low G force (soft) spin produces PRP, which is separated from the

red cells. The PRP is then centrifuged at a higher G force (hard) spin, and most of the platelet-poor plasma is removed. In the BC method, PCs are obtained from 40- to 50-mL BCs collected at the red cell/plasma interface after high-speed centrifugation of 450 mL of whole-blood donations.[33-35] Four to six BCs are then pooled, diluted in plasma or a crystalloid platelet additive solution, and centrifuged at low speed to suspend the platelets in the supernatant, which is then transferred into a large-volume storage bag. Storage can be extended to 5 days if the procedure is performed in closed systems. A number of studies indicate that BC-PCs produce comparable in vivo platelet survival and contain similar numbers of less-activated platelets compared with PCs prepared with the PRP method.[36-38]

Single-donor platelets produced by apheresis. Although the Food and Drug Administration term for this component is platelets, apheresis, the component is often called single-donor platelets. If histocompatible platelets are required for patients who are refractory to random-donor transfusions, apheresis platelets from donors selected by HLA typing or cross-matching should be used if available. Donors usually undergo two venipunctures, and blood pumped from one vein passes through a blood-cell separator centrifugation system (apheresis instrument) that separates the platelets and returns the plasma and RBCs to the donor's other arm. Plateletpheresis usually requires approximately 1.5 to 2 hours and involves processing 4,000 to 5,000 mL of the donor's blood,[39-45] which results in a product that contains the number of platelets equivalent to six to nine units of PC prepared from whole blood. However, many centers split their apheresis collections into two or three products so that the dose actually may be more equivalent to four to five units of PC. Clinicians are therefore advised to check on the policies of their local blood supplier so as to best determine the appropriate number of units to transfuse in particular clinical situations. Evidence from a large clinical trial using a prophylactic platelet transfusion approach showed that at doses per transfusion between 1.1×10^{11} and 4.4×10^{11} platelets per square meter, the number of platelets in the transfused product had no effect on the incidence of bleeding.[46]

Current standards in the United States and the European Union require that a bag of apheresis platelets contain at least 3 and 2×10^{11} platelets, respectively.[47,48] Platelets obtained by plateletpheresis are processed, tested, and labeled in a manner similar to that of whole-blood products described previously. The number of platelets contained in each bag is determined, although this information may not be recorded on the label. Each apheresis product has a volume of approximately 200 mL, but larger products may be produced if the donor center was attempting to collect a larger dose. The WBC content varies, depending on the instrument and technique used for collection, but most plateletpheresis products now contain $< 5 \times 10^6$ leukocytes and are considered to be leukocyte reduced.

PC and apheresis single-donor platelet products are labeled with ABO and Rh typing and are tested for all required transfusion-transmitted diseases. They contain few red cells; therefore, red cell cross-matching is not necessary. Incompatible plasma (eg, O donor to A or B blood type recipient) from platelet transfusions can put patients, particularly children, at risk of hemolysis.[49] ABO-compatible products should be provided whenever possible, although inventory issues occasionally preclude this. Fortunately, the occurrence of clinically significant hemolysis is unusual in adult recipients. All platelet products are stored at 20°C to 24°C using continuous gentle horizontal agitation in storage bags designed specifically to permit oxygen and carbon dioxide exchange to optimize platelet quality.[50-55] Plasma can be replaced partially with a crystalloid platelet additive solution, thus reducing the amount of plasma that might be infused to plasma-incompatible recipients.[35,56] The combination of storage container, agitation, temperature, and the use of the appropriate volume of plasma or plasma/additive solution permits satisfactory preservation of platelets for up to 7 days.[57,58] However, several instances of bacterial contamination of PCs stored for this period of time have been reported,[59,60] and the storage time from collection to transfusion is limited to 5 days.[61] In some countries and jurisdictions, the latter can be extended to 7 days if approved tests for bacterial detection or pathogen reduction technologies are used to further decrease the risk of transfusion-transmitted infections.[62,63] Transfusion-associated bacteremia should be suspected if patients experience severe febrile reactions either during or shortly after platelet transfusions. The transfusion should be discontinued, cultures obtained from the platelet bag and blood, and strong consideration given to treatment with antibiotics, particularly in neutropenic recipients.

To address this fortunately uncommon but potentially serious and occasionally fatal complication, commercial methods of pathogen reduction using UV irradiation after incubation with a photosensitizer have been developed and recently approved in the United States and the European Union. Platelets and plasma treated in this fashion are now provided by some blood centers, while a second method, using broad-spectrum UV irradiation and riboflavin, is available in many European countries.[64,65]

Volume reduction. If the volume of plasma in the final pooled component is too large, as might be the case for some pediatric recipients, some of the plasma can be removed before transfusion. From 15% to 55% of platelets are lost during this additional centrifugation step.[66,67] Volume reduction should therefore be limited to the uncommon situations in which patients require severe volume restriction, where platelets containing ABO-incompatible plasma are the only available PC for a child or for the occasional patient with severe plasma-mediated allergic transfusion reactions. Platelet washing with resuspension in platelet additive solutions can be used in the latter circumstance.

Irradiation of blood products. Transfusion-associated graft-versus-host disease is a rare, but usually fatal, complication of transfusion of blood components. It is a consequence of transfusion of viable lymphocytes capable of immune attack against the recipient, which can be prevented by pretransfusion gamma irradiation of blood products. Leukocyte depletion by itself does not eliminate the possible occurrence of this problem. Patients at greatest risk include recipients of autologous and allogeneic stem-cell transplants, those receiving blood products from partially matched family members whose WBCs presumably are not rejected by the host immune system, patients whose cancers are associated with severe immunosuppression (eg, Hodgkin's lymphoma) and/or those who have received markedly immunosuppressive therapy with drugs such as fludarabine and other purine nucleoside analogs, antithymocyte globulin and alemtuzumab (anti CD 52).[68]

Pretransfusion irradiation with a minimal dose of 25 Gy is recommended for these conditions by the British Commission for Standards in Hematology,[69] while the AABB recommends irradiation of transfusions from relatives. Routine irradiation is not suggested for patients with acute leukemia receiving standard therapies or for patients with AIDS or solid tumors. However, the results of a survey conducted by the College of American Pathologists in 2014 suggested that the policies and practices among the approximately 2,100 laboratories that responded were strikingly heterogeneous, with a minimum of > 30% of centers not irradiating routinely for indications about which there is a consensus that irradiation is indicated.[70] Clinicians should therefore be aware of the irradiation policies of their local blood suppliers and be in communication with them about patients for whom irradiated products are appropriate. Some cancer centers with large numbers of different providers who order transfusions have chosen to irradiate blood products routinely for all patients to guarantee that more vulnerable recipients receive the proper products. Most smaller centers do not have blood irradiators and have to send the product to larger regional centers for irradiation, which can cause a delay in the availability of transfusions. There is evidence that the UV irradiation pathogen inactivation techniques described previously can also damage DNA in the contaminating lymphocytes, preventing cell division and hence, transfusion-associated graft-versus-host disease, and potentially eliminating the need for irradiation of platelet products in the future.

Other adverse effects of platelet transfusion are listed in Table 1.[71]

Clinical Question 2

In what circumstances should providers take steps to prevent Rh alloimmunization resulting from platelet transfusion?

Recommendation 2. Prevention of RhD alloimmunization resulting from platelet transfusions to RhD-negative recipients can be achieved either through the exclusive use of platelet products collected from RhD-negative donors or via anti-D immunoprophylaxis. These approaches may be used for female children and female adults of child-bearing potential being treated with curative intent. However, because of the low rate of RhD alloimmunization in patients with cancer, these approaches need not be applied universally (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. Updates to the previous recommendation include consideration of curative intent and an explicit statement that prevention of RhD alloimmunization need not be applied universally.

Table 1. Potential Adverse Effects of Platelet Transfusion[71]

Febrile transfusion reactions
Transfusion-related acute lung injury
Hypersensitivity reactions to plasma components
Fluid overload
Transfusion-transmitted infection
Hemolysis
Graft-versus-host disease

Reports from studies performed before 1990 indicated that anti-D could be detected in 7.8% to 19% of heterogeneous groups of RhD-negative patients with cancer exposed to RhD antigens via transfusions.[72-75] More recently, published studies indicate that this now occurs much less frequently.[22,26] The frequency of alloimmunization to RhD antigens was addressed in the 2015 ICTMG systematic review[4] and in two subsequent observational studies.[22,26] The ICTMG review identified eight nonrandomized studies published since 1971.[4] In the largest of these, 11 centers retrospectively collected data on 485 RhD-negative patients (with approximately equal numbers of immunosuppressed and non-immunosuppressed patients) who received at least one PC from an RhD-positive donor between 2010 and 2012; only seven of 485 RhD-negative recipients (1.44%) had evidence of primary anti-D alloimmunization.[76] The two additional observational studies reported no cases of alloimmunization in RhD-negative patients who received RhD-positive platelets without Rh immunoglobulin (RhIG). One of the studies analyzed 79 patients, 57% of whom had a final red cell antibody screen at least four weeks after the first D-incompatible transfusion.[26] The other study analyzed 130 patients, all of whom had a red cell antibody screen at least four weeks after the first D-incompatible transfusion.[22]

Clinical interpretation. Platelet transfusion recipients who are RhD-antigen negative may receive platelet products prepared from donors who are RhD-antigen positive, according to current transfusion medicine standards, thereby also helping to improve platelet inventory management. Platelets do not express RhD antigens on their surface, but PCs do contain a small number of RBCs.[77] Current regulations and standards do not specify a maximum acceptable RBC content for platelet components, but in recent years, the RBC content of platelet units has decreased, with reported mean levels now being approximately 0.036 mL in whole-blood–derived platelet products and 0.00043 mL in apheresis products.[76,78,79] However, there is evidence that the minimum RBC volume to elicit a primary anti-D immune response in RhD-negative recipients is only 0.03 mL, which is within the RBC content range of at least some platelet products.[80]

RhD alloimmunization can be prevented by the exclusive use of platelet products collected from RhD-negative donors or by the administration of RhIG when platelet products collected from RhD-positive donors are given. For patients receiving multiple platelet transfusions, it may be extremely difficult to provide all units from RhD-negative donors; in these cases, RhD alloimmunization may be prevented by administering RhD immunoprophylaxis. Some RhIG products are licensed for both intramuscular and intravenous (IV) injection, while others may only be administered intramuscularly, with the potential risk of a hematoma if administered before the platelet transfusion. Extrapolating from guidelines used to prevent maternal sensitization after fetal-maternal hemorrhage, a dose of 20 μg (100 IU) of RhIG will protect against 1 mL of RBCs.[81] Rh immunoprophylaxis should be given before or soon after the platelet transfusion, although, as in the obstetric setting, it may still be efficacious if given within 72 hours of exposure to the RhD-positive RBCs. Depending on the timing of the transfusions and on the level of RBC contamination, one dose may protect against several platelet transfusions. However, because of the overall low likelihood of alloimmunization to RhD, the Panel

did not consider it necessary to routinely take steps to prevent this unless there is the possibility that the patient might become pregnant in the future.

Clinical Question 3

In what circumstances should providers use leukoreduced blood products to prevent alloimmunization?

Recommendation 3. The incidence of alloantibody-mediated refractoriness to platelet transfusion can be decreased in patients with acute myeloid leukemia (AML) receiving induction chemotherapy when both platelet and RBC products are leukoreduced before transfusion. It is therefore appropriate to provide leukoreduced blood products to patients with AML from the time of diagnosis to ameliorate this important clinical problem. Although randomized trials have not been conducted in other patient groups, it is likely that alloimmunization can also be decreased in patients with other types of leukemia and in other patients with cancer who are receiving chemotherapy. There are fewer data in patients who are not receiving chemotherapy in the same time periods that the transfusions are being administered (eg, aplastic anemia, myelodysplasia), although the consensus would favor its use in these patients as well. In the United States and in several other countries, the overwhelming majority of blood products are now leukoreduced at the time of blood collection and component preparation. Other advantages of prestorage leukoreduction include a substantial reduction in transfusion reactions and in transmission of cytomegalovirus (CMV) infection (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. Updates to the previous recommendation are the statements that leukoreduction is now performed widely in the United States and that the benefits of leukoreduction include reduction of transfusion reactions and CMV transmission.

Neither the ICTMG guideline[4] nor the AABB guideline[3] generated a specific recommendation regarding leukoreduction. The ICTMG noted that they made the assumption that "leukoreduced platelets are the standard products used in most countries with access to the type of platelet transfusion therapy discussed in this guideline (eg, apheresis collections, HLA matching, etc)."[4(p5)] The updated ASCO literature review identified two observational studies that addressed different aspects of leukoreduction.[20,24] A study conducted in Canada compared periods before and after universal prestorage leukoreduction was introduced in mid-1999.[24] Patients were receiving chemotherapy for acute leukemia or stem-cell transplantation for any diagnosis. Patients who received platelet transfusions after universal prestorage leukoreduction had lower rates of alloimmune refractoriness to platelet transfusion than did patients who received non-leukoreduced blood products in the earlier period (4% *v*14%). A study conducted in Japan compared the frequency of alloimmunization and platelet refractoriness after full implementation of universal prestorage leukoreduction with the period before, when bedside leukoreduction was performed, in patients with a broad range of hematologic diseases.[20] The frequency of immune-mediated platelet transfusion refractoriness was lower with bedside leukoreduction than with universal prestorage leukoreduction (3.2% *v* 7.3%), although the difference between groups in the frequency of alloimmunization was not statistically significant in multivariable analysis. The authors suggested that bedside filtration could be used in countries where universal leukodepletion has not, or cannot, be implemented.

A reduced risk of CMV among recipients of leukoreduced blood components (relative to recipients of blood components that were neither leukoreduced nor screened for CMV) was reported by a 2005 systematic review and meta-analysis.[14]

Clinical interpretation. Alloimmunization against histocompatibility antigens is the most important long-term complication of platelet transfusion. Older studies indicated that > 25% of newly diagnosed patients with AML will produce anti-HLA antibodies and become refractory to non-histocompatible platelet transfusions.[82-84] Despite greater understanding of the factors that influence the results of transfusion from HLA-selected donors, as many as 40% to 60% of apparently histocompatible platelet transfusions administered to alloimmunized patients are unsuccessful.[85] In addition to the costs of such transfusions, recipients of transfusions that do not produce satisfactory increments remain at risk of hemorrhagic morbidity and mortality.

Substantial in vitro and preclinical evidence from murine and canine models suggest that the leukocytes contaminating platelet preparations are the primary stimulus for alloimmunization.[86-89] Platelets do not express class 2 histocompatibility antigens, and presentation of class 1 and class 2 antigens by intact leukocytes is required for initial processing by the immune system; therefore, there was considerable interest in the use of different methods of removal of leukocytes by filtration or modification of the antigen-presenting capacity of the leukocyte to reduce the incidence of alloimmunization. With regard to the latter approach, it has been shown that UVB irradiation can abolish reactivity in mixed lymphocyte reactions and that doses of UVB irradiation can be identified that do not affect platelet function in vitro.[90-92]

A number of small clinical trials evaluating leukoreduction were conducted, but definitive results were provided by the Trial to Reduce Alloimmunization to Platelets (TRAP), which was a multiinstitutional randomized trial that evaluated leukoreduction of pooled PC or single-donor platelets by filtration in the blood bank, as well as UVB irradiation in 603 patients with newly diagnosed AML who were receiving initial induction therapy. There was a statistically significant reduction in the formation of lymphocytotoxic (anti-HLA) antibody in all three groups receiving modified platelets (17%–21%), compared with the control group (45%), which received standard PCs.[82] There was no additional advantage from the use of filtered single-donor platelets compared with filtered, pooled PCs. This reduction was noted in all patients, including women with prior pregnancies. Filtration and UVB irradiation also produced a significant reduction in the incidence of immune-mediated platelet refractoriness during induction (3% to 5% *v* 13% in controls). The overall incidence of refractoriness was relatively low, probably because antibody formation tended to occur in the third to fourth week of induction, often when patients were no longer requiring platelet transfusions. It should be noted that the older clinical studies focused on the development of HLA antibodies assessed by lymphocytotoxicity, while currently many laboratories have replaced lymphocytotoxicity testing with solid

phase assays. Although the concordance with traditional lymphocytotoxicity is not known, it is likely that the newer techniques provide similar information with regard to the diagnosis of alloimmunization.

On the basis of these results, the accumulated conclusions of earlier trials, and a metanalysis,[93] it is appropriate to provide leukoreduced RBC and platelet products to newly diagnosed patients with AML and, although unproved, to adult patients with other types of cancer and acute leukemia. Pediatric patients receiving aggressive treatment regimens often require long-term platelet transfusion support, and three descriptive comparative reports of current leukodepletion approaches versus older transfusion practices support these conclusions in children as well.[94-96]

As an alternative to filtration of platelets or RBCs after storage, removal of leukocytes by filtration just after blood collection (so-called prestorage leukocyte depletion) has additional advantages; evidence suggests that most transfusion reactions are a consequence of cytokines elaborated by leukocytes and released into the plasma during storage.[97]Other than alloimmunization, it is these febrile reactions that are most disturbing and dangerous to the patient. Given its multiple clinical advantages, which also include a reduction in the incidence of transfusion-associated CMV infections,[14,98] prestorage leukodepletion of RBC shortly after collection has been adopted widely in the United States and the European Union. Last, newer modifications of apheresis techniques permit reliable collections of platelets with leukocyte contamination well below the 5×10^6 cutoff, presumably obviating the need for additional leukocyte filtration of these products.[42,99] Leukoreduction of RBCs would still be required, however.

Clinical Question 4

Should platelet transfusions be given prophylactically or therapeutically?

Recommendation 4. Prophylactic platelet transfusion should be administered to patients with thrombocytopenia resulting from impaired bone marrow function to reduce the risk of hemorrhage when the platelet count falls below a predefined threshold level. This threshold level for transfusion varies according to the patient's diagnosis, clinical condition, and treatment modality (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. A 2015 Cochrane review compared prophylactic with therapeutic (ie, if signs of bleeding were present) platelet transfusion in patients with hematologic disorders who had received myelosuppressive chemotherapy or stem-cell transplantation.[8] The review identified six completed RCTs. A therapeutic-only strategy was associated with an increased risk of bleeding (low- to moderate-grade evidence), but reduced the number of platelet transfusions per patient. The two largest and most recent trials suggested that adult patients who undergo autologous stem-cell transplantation may receive less benefit from a prophylactic transfusion strategy.[100,101] In the trial by Wandt et al,[100] grade 3 hemorrhage was rare in patients receiving autologous stem-cell transplantation, regardless of platelet transfusion strategy, and there were no grade 4 bleeds, although the prophylactic platelet transfusion approach did reduce the risk of grade 2 or higher bleeding. In the trial by Stanworth et al,[101] rates of grade 2 or worse bleeding did not vary significantly by study arm in the subgroup of patients receiving autologous stem-cell transplantation.

Clinical interpretation. The prophylactic approach has become standard practice for patients at risk of clinically significant hemorrhage and with severe thrombocytopenia.[102-104] Fatal hemorrhage is now an unusual event, even in patients with bone marrow failure or in those receiving intensive antineoplastic therapy. However, it should be emphasized that not all thrombocytopenic patients require or benefit from platelet transfusion and that the decision to administer transfusion is not based solely on the platelet count; rather, it should be individualized, with transfusions given at higher counts in specific clinical settings believed to be associated with increased risks of bleeding. Platelet transfusion is rarely needed in hemodynamically stable patients with increased platelet destruction such as autoimmune or drug-associated immune thrombocytopenia and is relatively contraindicated in patients with thrombotic thrombocytopenic purpura because of concerns about the risk of precipitating thromboses.[102,104]

It is important that clinicians are aware of the average number of platelets provided in pooled PC and apheresis products in their community so as to be able to order an appropriate number of units in specific clinical situations. A typical interval between prophylactic transfusions in patients with acute leukemia is every 2 to 4 days, depending on other clinical factors. This can usually be accomplished with doses of 4 to 6 units of PC per transfusion or one apheresis unit in adults of average size. Larger doses may be needed to achieve higher counts in patients who are bleeding or who require invasive procedures.

Clinical Question 5

What is the appropriate threshold for prophylactic platelet transfusion in patients with hematologic malignancies?

Recommendation 5. The Panel recommends a threshold of $< 10 \times 10^9$/L for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, or coagulation abnormalities (eg, acute promyelocytic leukemia) and in those undergoing invasive procedures or in circumstances in which platelet transfusions may not be readily available in case of emergencies, as might be the case for outpatients who live at a distance from the treatment center (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. More recent literature is supportive of the original ASCO guideline recommendations, which were based on a series of randomized and observational studies conducted in the 1980s and 1990s.[105-109] A 2015 Cochrane review evaluated platelet count thresholds for prophylactic platelet transfusion in people with hematologic disorders after myelosuppressive chemotherapy or stem-cell transplantation.[11] The review included three RCTs, with a total of 499 participants. The trials compared a standard transfusion threshold (10×10^9/L) with a higher threshold (20×10^9/L or 30×10^9/L). Using the lower threshold of 10×10^9/L did not increase the risk of bleeding and resulted in fewer transfusions. Of note is that some trials specified a threshold of $< 10 \times 10^9$/L, while others used a cutoff

of $\leq 10 \times 10^9$/L for prophylactic transfusion. Because the overall results were similar, the committee was comfortable with the recommendation of $< 10 \times 10^9$/L.

Clinical interpretation. The studies that form the basis of this recommendation have included adolescents but not younger children or infants. Nevertheless, the Panel considered it reasonable to use similar guidelines for children and older infants until more studies are completed in this population.

Although modern automated cell counters are accurate at low platelet counts, there can be modest variations in count because of the limitations of the counting technology. The decision to transfuse at a precise trigger level should therefore consider the clinical context and the pattern of recent platelet counts.

Clinical Question 6

What is the appropriate threshold for prophylactic platelet transfusion in the setting of HSCT?

Recommendation 6. The Panel recommends a threshold of $< 10 \times 10^9$/L for prophylactic platelet transfusion in adult and pediatric patients undergoing allogeneic HSCT. Prophylactic platelet transfusion may be administered at higher counts based on clinician judgment. In adult recipients of autologous HSCT, randomized trials have demonstrated similar rates of bleeding with decreased platelet usage when patients are transfused at the first sign of bleeding rather than prophylactically, and this approach may be used in experienced centers. This recommendation is not generalizable to pediatric patients (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate).

Literature review update and analysis. Updates to the previous recommendation are the clearer specification of a platelet count threshold for prophylactic platelet transfusion and the option of therapeutic platelet transfusion for adult patients undergoing autologous platelet transfusion in experienced settings.

Cochrane reviews of prophylactic versus therapeutic platelet transfusion[8] and platelet count thresholds[11] in patients with hematologic disorders undergoing myelosuppressive chemotherapy or stem-cell transplantation, and trials by Wandt et al[100] and Stanworth et al,[101] were discussed previously. An observational study among 125 Jehovah's Witnesses treated with high-dose chemotherapy and autologous stem-cell transplantation without transfusions provides additional information about bleeding risk among autologous transplant recipients.[17] Two major and 15 minor bleeding complications occurred. No bleeding complications occurred at platelet counts $> 5 \times 10^9$/L. Indeed, in other older studies, most bleeding events occurred at platelet counts $> 20 \times 10^9$/L and hence, would not have been prevented by prophylactic platelet transfusion.

Clinical interpretation. The threshold for prophylactic platelet transfusion has traditionally been $\leq 10 \times 10^9$/L for clinically stable patients undergoing autologous or allogeneic HSCT, with transfusions at higher counts in some cases based on clinician judgment. Randomized trials evaluating adult patients undergoing autologous HSCT have shown similar rates of clinically significant hemorrhage in patients transfused only in the event of bleeding compared with those receiving prophylactic transfusions, with a significant reduction in the numbers of transfusions administered. In fact, many patients in the therapeutic transfusion group never received a platelet transfusion. Either tactic is therefore acceptable for adults undergoing autologous HSCT, although close observation is needed when using the therapeutic transfusion approach. Although the period of thrombocytopenia is also brief using peripheral-blood stem cells for allogeneic HSCT, there are fewer comparative data, and the $< 10 \times 10^9$/L threshold remains appropriate in this setting. In addition, periods of thrombocytopenia are longer when using marrow as the stem-cell source, and there are no comparative data addressing this specific group of patients.

The studies by Wandt et al[100] and Stanworth et al,[101] which suggest that patients undergoing autologous HSCT may receive less benefit from a prophylactic transfusion strategy than do other patients with chemotherapy-induced thrombocytopenia, did not include any patients younger than 16 years of age. No comparable studies have been reported in pediatric patients. However, an analysis of patients younger than 18 years of age (n = 198) enrolled in the PLADO study (which evaluated bleeding using prophylactic platelet transfusions of various dosages) showed that children had a significantly higher risk of WHO grade 2 to 4 bleeding than did adults and that the effect of age was most pronounced among patients undergoing autologous HSCT. The reasons for this age effect are not known but may reflect differences in the nature and intensity of the chemotherapeutic regimens used in pediatric versus adult autologous HSCT patients and/or differences in vascular endothelial integrity.[110] These observations suggest that recommendations that consider decreasing the use of prophylactic platelet transfusions for adult patients undergoing autologous HSCT are not generalizable to pediatric patients.

Clinical Question 7

Is there a role for prophylactic platelet transfusion in patients with chronic, stable, severe thrombocytopenia who are not receiving active treatment?

Recommendation 7. Patients with chronic, stable, severe thrombocytopenia, such as individuals with myelodysplasia or aplastic anemia, who are not receiving active treatment may be observed without prophylactic transfusion, reserving platelet transfusions for episodes of hemorrhage or during times of active treatment (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. No new studies were identified.

Clinical interpretation. No randomized studies have been performed in patients with sustained, severe thrombocytopenia as can be seen in individuals with myelodysplasia, aplastic anemia, or congenital bone marrow failure syndromes. Many such patients have minimal or no significant bleeding for long periods of time despite low platelet counts. The recommendation was reworded for clarity but otherwise remains the same as in the previous version of the guideline.

Clinical Question 8

What is the appropriate threshold for prophylactic platelet transfusion in patients with solid tumors?

Recommendation 8. The risk of bleeding in patients with solid tumors during chemotherapy-induced thrombocytopenia is related to the depth and duration of the platelet nadir, although other factors contribute as well. The Panel recommends a threshold of $< 10 \times 10^9$/L for prophylactic platelet transfusion, based on extrapolation from studies in hematologic malignancies. Platelet transfusion at higher levels is appropriate in patients with active localized bleeding which can sometimes be seen in patients with necrotic tumors (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review update and analysis. Updates to the previous recommendation involve those patients for whom platelet transfusion at a higher level may be considered. The previous recommendation noted that transfusion at a higher level may be considered for patients receiving aggressive therapy for bladder tumors or for patients with necrotic tumors. No new relevant articles were identified.

Clinical interpretation. No prospective or controlled trials in this population have been reported, and it is difficult to recommend a single threshold below which prophylactic transfusion should be prescribed to all patients with solid tumors, except as an extrapolation from the experience in patients with hematologic malignancies. Although only a small minority of patients treated with conventional solid tumor regimens experience severe, sustained thrombocytopenia, platelet transfusions are sometimes a consideration after dose-intense chemotherapy and for patients who have had multiple courses of chemotherapy.

Because of the heterogeneity of this population, several subgroups may require special consideration. Because patients with gynecologic, colorectal, melanoma, or bladder tumors bleed from necrotic tumor sites, consideration should be given to transfusion at a higher threshold, perhaps 20×10^9/L. It should be noted, however, that because hemorrhage often occurs at much higher counts, it is unknown whether more liberal use of transfusions would decrease bleeding from such necrotic sites. Additional clinical research in this area is desirable.

Clinical Question 9

At what platelet count can surgical or invasive procedures be performed?

Recommendation 9. The Panel recommends a threshold of 40×10^9/L to 50×10^9/L for performing major invasive procedures in the absence of associated coagulation abnormalities. Certain procedures, such as bone marrow aspirations and biopsies, and insertion or removal of central venous catheters, can be performed safely at counts $\geq 20 \times 10^9$/L. There are sparse data, and no randomized trials, addressing the safety of other invasive procedures at much lower count levels. If platelet transfusions are administered before a procedure, it is critical that a post-transfusion platelet count be obtained to prove that the desired platelet count level has been reached. Platelet transfusions should also be available on short notice, in case intraoperative or postoperative bleeding occurs. For alloimmunized patients, histocompatible platelets must be available in these circumstances (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).

Literature review update and analysis. **Central venous catheter placement.** A 2015 Cochrane review identified no completed RCTs on this question.[9] The 2015 review by the AABB identified eight observational studies of central venous catheter placement in the setting of thrombocytopenia and suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count $< 20 \times 10^9$L.[3,12] The quality of the evidence is labeled as low, and the strength of the recommendation is weak.

Lumbar puncture. A 2016 Cochrane review identified no completed RCTs on this question.[10] Based on observational data, the 2015 AABB guideline[3] and a 2010 pediatric platelet transfusion guideline by the C17 Guidelines Committee[7] each made recommendations regarding platelet transfusion thresholds for lumbar puncture. The AABB suggests prophylactic platelet transfusion for adult patients having elective diagnostic lumbar puncture with a platelet count $< 50 \times 10^9$ /L.[3] The quality of the evidence is labeled as very low, and the strength of the recommendation is weak. The C17 guideline recommends a transfusion at a threshold of 50×10^9/L for diagnostic lumbar punctures for newly diagnosed pediatric patients with leukemia and a threshold of 20×10^9/L for stable pediatric patients requiring a lumbar puncture, recognizing that transfusions at a higher level may be required for certain patients. The C17 recommendations were classified as weak, with moderate-quality evidence. No new relevant studies were identified by the updated ASCO review.

It should be noted that in many institutions, lumbar punctures are performed with fluoroscopic guidance, and it would be desirable to accumulate data using this technique in thrombocytopenic patients because it may be that the threshold could be lowered using this more directed technique.

Bronchoscopy. The updated ASCO review identified one observational study of bronchoscopy in patients with thrombocytopenia.[21] The study enrolled 150 patients who underwent bronchoscopy with or without bronchoalveolar lavage. All patients had a platelet count of $\leq 100 \times 10^9$/L, and 78% had an underlying malignancy. At the time of bronchoscopy, 72 patients had a platelet count $< 50 \times 10^9$/L, and 15 had a platelet count $< 20 \times 10^9$/L. There were 10 cases of bleeding in total, and nine of these cases were transient and defined as "no bleeding" by British Thoracic Society criteria. One patient experienced bleeding that required continuous suctioning but resolved spontaneously; this occurred at a platelet count of 61×10^9/L. The authors conclude that bronchoscopy can be performed safely even in patients with severe thrombocytopenia.

Liver biopsy. Three observational studies identified by the ASCO review evaluated bleeding by platelet count among patients undergoing liver biopsy. A retrospective analysis of 6,613 image-guided liver biopsies reported a higher frequency of hemorrhage among patients with a platelet count $\leq 50 \times 10^9$/L than among patients with a higher platelet count (2.2% *v* 0.5%, $P = .04$), although only 92 biopsies were performed at $\leq 50 \times 10^9$/L.[16] An analysis of 2,740 percutaneous liver biopsies in patients with hepatitis C–related fibrosis or cirrhosis also reported an increase in bleeding risk as platelet count declined.[23] Bleeding occurred in 5.3% of the biopsies performed at a platelet count of $\leq 60 \times 10^9$/L, compared with $< 1\%$ of biopsies performed at a higher platelet count. The third study evaluated transjugular liver biopsy in

50 patients with hematologic malignancies and severe thrombocytopenia (platelet count $\leq 30 \times 10^9$/L).[25] All patients received platelet transfusion. The post-biopsy platelet count remained $\leq 30 \times 10^9$/L in 24 patients. No hemorrhage-related complications were reported. Given the heterogeneity of these patient populations and the absence of systematic information about associated coagulopathy, it is not possible to identify a threshold for prophylactic platelet transfusion in these patients. The overall incidence of serious bleeding is low.

GI endoscopy. One observational study identified by the ASCO review evaluated the safety of GI endoscopy among adult oncology patients with a preprocedure platelet count of $\leq 75 \times 10^9$/L.[19] Standard forceps biopsy specimens were obtained in 398 procedures. Biopsy-related bleeding occurred in six cases, four of which occurred at a platelet count $< 50 \times 10^9$/L. Bleeding was managed with endoclip placement in five cases and with epinephrine in one case. Polypectomy was performed in 17 procedures, with two cases of bleeding. Bleeding caused by the biopsy or polypectomy was described as minor and easily controlled.

Clinical interpretation. Thrombocytopenic patients frequently require invasive diagnostic or therapeutic procedures. Common procedures include placement of permanent or temporary central venous catheters, transbronchial and esophageal endoscopic biopsies, lumbar puncture, paranasal sinus aspirations, bone marrow biopsies, and occasionally even major surgery.

A platelet count of 50×10^9/L is often stated as a standard for the level at which major surgery can be performed safely. Although strong opinions abound, it is difficult to draw firm data-driven conclusions as to the lower level of platelet count that is safe for these various procedures, and more systematic research in this area is clearly needed.[111] It must be emphasized that it is critical to determine the post-transfusion platelet count in patients about to undergo invasive procedures. It is inappropriate to assume that a hemostatic platelet count level has been achieved simply because a platelet transfusion was administered recently. Post-transfusion counts obtained 10 minutes after transfusion can be helpful in this regard.[112,113] The platelet transfusion must therefore be closely coordinated with the timing of the planned surgical intervention.

Clinical Question 10

When and how should patients be monitored for refractoriness to platelet transfusion?

Recommendation 10. Although there are no empirical data to suggest that monitoring and acting on the post–platelet-transfusion count decreases the incidence of hemorrhagic events, the Panel consensus is that platelet counts performed 10 to 60 minutes after transfusion should be obtained after all transfusions, when refractoriness is suspected. Because patients may have a poor increment to a single transfusion, yet have excellent platelet increments with subsequent transfusions, a diagnosis of refractoriness to platelet transfusion should be made only when at least two transfusions of ABO-compatible units, stored for < 72 hours, result in poor increments, as defined in the supporting text of the recommendation (Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review update and analysis. The updated recommendation specifies a time frame for post-transfusion platelet counts.

The frequency and predictors of platelet refractoriness and alloimmunization were evaluated in a subset of the participants in the PLADO trial.[27] The analysis was restricted to patients who had a starting HLA class 1 panel-reactive antibody score $< 20\%$ as well as a panel-reactive antibody measure at the end of the study, received all of their transfused platelets as either leukoreduced apheresis or filter-leukoreduced whole-blood–derived PCs, and (for the refractoriness analysis) received at least two transfusions. Platelet refractoriness was defined as two consecutive platelet transfusions, both of which had $\leq$ 4-hour corrected count increments (CCIs) of $<$ 5,000. Fourteen percent of patients (102 of 734) were platelet refractory by this definition. Alloimmunization was detected in only 8% of the refractory cases, further substantiating the low rate of alloantibody formation using leukocyte-reduced blood products.

Clinical interpretation. No formal study has been performed to document the effectiveness of monitoring and acting on post-transfusion platelet counts. However, it is the consensus of the Panel that patients remain at risk of hemorrhagic events if the post-transfusion counts are still at or below the platelet value used to trigger the initial transfusion, and, therefore, monitoring the post-transfusion count allows the practitioner to determine the adequacy of platelet transfusion therapy. If patients fail to achieve an adequate platelet increment after transfusion, investigations as to the cause of platelet transfusion refractoriness should be initiated. The practitioner should then work with the blood bank to determine a rational transfusion program for such patients.

The platelet increment is determined by subtracting the pretransfusion platelet count from the count determined approximately 1 hour after transfusion. Identical results are obtained using a 10-minute post-transfusion count, which is simple to obtain because the patient must be seen when the transfusion is completed to switch the IV bags.[112] Although it would be desirable to obtain immediate post-transfusion increments after all platelet transfusions, it is reasonable to obtain such increments after all transfusions to outpatients and in nonbleeding hospitalized patients if the day-to-day increments are not satisfactory.

The percentage of platelet recovery, or the CCI, is determined using a formula based on the estimated blood volume or size of the patient as well as the number of platelets in the infused product. Although different values of the CCI have been used to define an adequate transfusion response, the TRAP study used a CCI of $\geq$ 5,000 to define a satisfactory response, and this definition is endorsed by the Panel.[82] The CCI = absolute increment $\times$ body-surface area (m^2)/number of platelets transfused $\times 10^{11}$. Thus, if transfusion of 4×10^{11} platelets produced an increment of 40,000/μL in a 2-m^2 recipient, the CCI = 40,000 $\times$ 2/4 = 20,000.

As an alternative, because most centers do not routinely provide platelet counts of the infused product, the Panel suggests using a rough estimate of an absolute increment of 2,000/unit of PC or 10,000/transfusion of apheresis platelets to be equivalent to a CCI of 5,000. This is based on the assumption that an average-sized adult has a body surface area of 1.76 m^2 and the average platelet count in a unit of PC is 0.7×10^{11}. For children, an approximate equivalent calculation for the absolute increment is 3,500/m^2/unit.

Because patients may have a poor increment to a single transfusion, yet have adequate platelet increments with subsequent transfusions, refractoriness to platelet transfusion should be diagnosed only when at least two ABO-compatible transfusions, stored for < 72 hours, result in poor increments as defined previously.[82] It is suggested that the transfusions be ABO compatible because of evidence that ABO incompatibility (eg, A platelets to group O recipients) can sometimes compromise post-transfusion increments.[4] Once these criteria are fulfilled, alloimmunization should be suspected, although immune platelet destruction as a result of drug-related antibodies, as well as clinical factors such as hypersplenism, severe disseminated intravascular coagulation, shock, and massive hemorrhage, may also result in poor platelet increments.[114] Therefore, it is critical to first document that the patient is, in fact, alloimmunized, because such patients are managed differently from those with other causes of refractoriness to transfusion. Approximately 90% of patients who are alloimmunized will have alloantibody to HLA antigens detectable by lymphocytotoxicity assays or platelet antibody testing.[82,115,116] It is the consensus of the Panel that all patients who are refractory to platelet transfusions as defined previously have such antibody studies performed to confirm a diagnosis of alloimmunity.

Clinical Question 11

How should refractoriness to platelet transfusion be managed?

Recommendation 11. Alloimmunization is usually due to antibody against HLA antigens and only rarely to platelet-specific antigens. Patients with alloimmune-refractory thrombocytopenia, as defined previously, are best managed with platelet transfusions from histocompatible donors matched for HLA-A and HLA-B antigens. Many blood suppliers have access to computerized lists of such donors. For patients (1) whose HLA type cannot be determined, (2) who have uncommon HLA types for whom suitable donors cannot be identified, or (3) who do not respond to HLA-matched platelets, histocompatible platelet donors can often be identified using platelet cross-matching techniques. In many patients, these two techniques are complementary (Type of recommendations: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. The ICTMG conducted systematic reviews of HLA-matched[13] and cross-matched[15] platelet transfusion. The HLA-matched review included 29 nonrandomized studies and one RCT. The cross-match review included 31 nonrandomized studies. Based on this body of evidence, the ICTMG made the following weak recommendations for patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusion: patients who have class 1 HLA antibodies should probably receive class 1 HLA-selected or crossmatch-selected platelet transfusion; patients who have HPA antibodies should probably receive HPA-selected or crossmatch-selected platelet transfusion; and patients who are refractory due solely to nonimmune factors should probably not receive HLA-selected or crossmatch-selected platelets.[4]

The ASCO literature review included one additional observational study of cross-match–selected platelets in refractory patients. Jia et al[18] conducted a retrospective evaluation of 193 patients who were refractory to random single-donor apheresis platelets. Fifty-six (29%) were HLA and/or HPA antibody positive. In these patients, cross-match–compatible platelets resulted in higher 1-hour CCIs than did random platelet units (8,700 ± 4,500 *v* 3,600 ± 2,400; $P < .001$).

Clinical interpretation. The transfusion of HLA-matched platelets results in adequate increments in approximately 50% to 60% of transfusion events and, if available, HLA-matched platelets are generally used in the initial management of patients with alloimmune refractory thrombocytopenia.[85,114] When choosing HLA-matched products, one should also consider that HLA antigens can have variable expression on leukocytes (used to determine the HLA type of the patient/donor pair) and platelets. For example, platelets mismatched for HLA B44 or B45 can still produce satisfactory increments approximately 75% of the time.[116] Other single-antigen mismatched platelets can also produce adequate increments in many patients.[117]

There is no evidence that alloimmunized patients benefit from nonmatched prophylactic platelet transfusions that do not produce post-transfusion increments, and the Panel recommends that such patients be transfused for hemorrhagic events only. There is anecdotal evidence that if HLA or cross-matched platelets are not available, repeated transfusions of large numbers of pooled random-donor platelets may benefit alloimmunized patients with active bleeding. This may be related to a transient decrease in the alloantibody titer or to the possibility that such random-donor platelet products may fortuitously include some histocompatible units.[118,119] Therapies used for the treatment of idiopathic thrombocytopenic purpura have been tried for patients with alloimmune refractory thrombocytopenia, with little success. Perhaps the best studied is IV gamma globulin (IVIG). Most nonrandomized studies fail to show a benefit of IVIG for patients with alloimmune-refractory thrombocytopenia.[120,121] In addition, a small randomized placebo-controlled study failed to show a significant benefit of IVIG for such patients.[122] Corticosteroids and splenectomy,[123] the mainstays of treatment of ITP, have also not been shown to be of benefit for patients with alloimmune thrombocytopenia, nor has the use of plasma exchange.[124]

EXTERNAL REVIEW

The draft was submitted to two external reviewers with content expertise. Review comments were reviewed by the Expert Panel and were integrated into the final manuscript before approval by the CPGC.

PATIENT AND CLINICIAN COMMUNICATION

Treatment decision making should be a process that is shared between clinicians and their patients. Clinicians must communicate evidence-based options for treatment, inclusive of their benefits and risks, and patients must be allowed to express their goals and preferences. It is important to recognize that patients are no longer reliant solely on their medical team for information and often access other sources online, in print, or through social media and support groups.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[125-128] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform the treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations in developing specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups when making recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCC, any treatment plan must take into account the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Implementation requires increasing awareness of the guideline recommendations among front-line practitioners, patients, and caregivers and providing adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate the implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and are most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

As noted, there are relatively few compelling studies addressing thresholds for prophylactic platelet transfusions in patients with solid tumors. Similarly, the paucity of information about the safety of certain invasive procedures in thrombocytopenic patients is disappointing. It is difficult to conduct randomized trials in these populations, in part because the incidence of serious bleeding is so low and hence the numbers of patients to be included would be large. Nonetheless, careful assessment of the incidence of bleeding in a series of markedly thrombocytopenic patients undergoing different procedures can be informative, and such research should be encouraged.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

Related ASCO Guidelines

- Integration of Palliative Care into Standard Oncology Care[129] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[130] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Platelet Transfusion for Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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Patents, Royalties, Other Intellectual Property: Patent on platelet lysate (Inst)
Travel, Accommodations, Expenses: Terumo BCT

Scott D. Rowley
Stock or Other Ownership: GlaxoSmithKline, Express Scripts, McKesson, AmerisourceBergen,
Consulting or Advisory Role: Chimerix, Mesoblast, FATE
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Travel, Accommodations, Expenses: Chimerix

Michael B. Troner
No relationship to disclose

Kenneth C. Anderson
Consulting or Advisory Role: Celgene, Millennium Pharmaceuticals, Gilead Sciences, Bristol-Myers Squibb
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Appendix

Table A1. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update, Expert Panel Membership

Member	Affiliation
Charles A. Schiffer, MD, Co-chair	Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI
Kenneth C. Anderson, MD, Co-chair	Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
Meghan Delaney, DO, MPH	University of Washington, Seattle Children's Hospital, Seattle, WA
Heather Hume, MD	CHU Sainte-Justine, University of Montreal, Quebec, Canada
Anthony J. Magdalinski, DO, PGIN representative	Alliance Cancer Specialists, Sellersville, PA
Jeffrey J. McCullough, MD	University of Minnesota, Minneapolis, MN
James L. Omel, MD, patient representative	Grand Island, NE
John M. Rainey, MD	University Health Center, Lafayette, LA
Paolo Rebulla, MD	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
Scott D. Rowley, MD	Hackensack University Medical Center, Hackensack, NJ
Michael B. Troner, MD	Miami Cancer Institute, Miami, FL

NOTE. ASCO staff: Kari Bohlke, ScD, health research methodologist.
Abbreviations: CHU, Centre Hospitalier Universitaire; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico; PGIN, Practice Guideline Implementation Network.