Anesthesiology 2006; 105:198–208

Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies

An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies

PRACTICE guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to revision as warranted by the evolution of medical knowledge, technology, and practice. They provide basic recommendations that are supported by analysis of the current literature and by a synthesis of expert opinion, open forum commentary, and clinical feasibility data.

This update includes data published since the "Practice Guidelines for Blood Component Therapy" were adopted by the American Society of Anesthesiologists (ASA) in 1995; it also includes data and recommendations for a wider range of techniques than was previously addressed.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology.org, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the "ArticlePlus" link either in the Table of Contents or in the HTML version of the article.

Developed by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies: Gregory A. Nuttall, M.D. (Chair), Rochester, Minnesota; Brian C. Brost, M.D., Rochester, Minnesota; Richard T. Connis, Ph.D., Woodinville, Washington; James S. Gessner, M.D., Chestnut Hill, Massachusetts; Chantal R. Harrison M.D., San Antonio, Texas; Ronald D. Miller, M.D., San Francisco, California; David G. Nickinovich, Ph.D., Bellevue, Washington; Nancy A. Nussmeier, M.D., Houston, Texas; Andrew D. Rosenberg, M.D., Roslyn Heights, New York; Richard Spence, M.D., Baltimore, Maryland.

Submitted for publication November 2, 2005. Accepted for publication November 2, 2005. Supported by the American Society of Anesthesiologists under the direction of James F. Arens, M.D., Chair, Committee on Practice Parameters. Approved by the House of Delegates on October 25, 2005. A list of the references used to develop these Guidelines is available by writing to the American Society of Anesthesiologists.

Address reprint requests to the American Society of Anesthesiologists: 520 North Northwest Highway, Park Ridge, Illinois 60068-2573. Individual article reprints may be accessed at no charge through the Journal Web site, www.anesthesiology.org.

Methodology

A. Definition of Perioperative Blood Transfusion and Adjuvant Therapies

Blood transfusion refers to the perioperative administration of blood and blood components (*e.g.*, autologous blood, allogeneic whole blood, red blood cells, fresh frozen plasma [FFP], platelets, and cryoprecipitate). Adjuvant therapies refer to drugs and techniques to reduce or prevent blood loss and the need for transfusion of allogeneic blood.

B. Purpose of the Guidelines

The purposes of these Guidelines are to improve the perioperative management of blood transfusion and adjuvant therapies and to reduce the risk of adverse outcomes associated with transfusions, bleeding, or anemia. In addition, these Guidelines provide an update on the relative risks that cause morbidity and mortality associated with blood transfusion and adjuvant therapies.

C. Focus

These Guidelines focus on the perioperative management of patients undergoing surgery or other invasive procedures in which significant blood loss occurs or is expected. This includes but is not limited to (1) patients undergoing cardiopulmonary bypass or cardiac surgery, urgent or emergent procedures, obstetric procedures, organ transplantation, and major noncardiac surgery; (2) patients with preexisting blood disorders or acquired deficiency secondary to massive bleeding; (3) critically ill patients; and (4) patients who elect not to undergo transfusion. Excluded from the focus of these Guidelines are neonates, infants, children weighing less than 35 kg, and nonsurgical patients.

D. Application

These Guidelines apply to both inpatient and outpatient surgical settings and to procedures performed in operating rooms as well as in other locations (*e.g.*, interventional radiology, critical care units) where blood transfusion or other adjuvant therapy is indicated. They are directly applicable to care administered by anesthesiologists and individuals who deliver care under the medical direction or supervision of an anesthesiologist. They are also intended to serve as a resource for other

physicians and patient care personnel who are involved in the perioperative care of these patients.

E. Task Force Members and Consultants

The ASA appointed a Task Force of 10 members to (1) review the published evidence, (2) obtain the opinion of a panel of consultants including anesthesiologists and nonanesthesiologist physicians concerned with perioperative blood transfusion, and (3) obtain opinions from practitioners likely to be affected by the Guidelines. The Task Force included anesthesiologists in both private and academic practices from various geographic areas of the United States, a surgeon, a pathologist specializing in transfusion medicine, an obstetrician, and two consulting methodologists from the ASA Committee on Practice Parameters.

The Task Force developed the Guidelines by means of a seven-step process. First, they reached consensus on the criteria for evidence of effective blood transfusion and adjuvant therapies. Second, original published research studies from peer-reviewed journals relevant to the perioperative management of patients undergoing blood transfusions were reviewed. Third, the panel of expert consultants was asked to (1) participate in opinion surveys on the effectiveness of various perioperative management strategies and (2) review and comment on a draft of the Guidelines developed by the Task Force. Fourth, opinions about the Guideline recommendations were solicited from random samples of active members of the ASA. Fifth, the Task Force held open forums at two major national meetings to solicit input on its draft recommendations. National organizations representing specialties whose members typically care for patients undergoing perioperative transfusion were invited to participate in the open forums. Sixth, the consultants were surveyed to assess their opinions on the feasibility of implementing the Guidelines. Seventh, all available information was used to build consensus within the Task Force to finalize the Guidelines.

F. Availability and Strength of Evidence

Preparation of these Guidelines followed a rigorous methodologic process. To convey the findings in a concise and easy-to-understand fashion, these Guidelines use several descriptive terms.

When sufficient numbers of studies are available for evaluation, the following terms describe the strength of the findings.

Support: Meta-analysis of a sufficient number of randomized controlled trials* indicates a statistically significant relationship ($P < 0.01$) between a clinical intervention and a clinical outcome.

Suggest: Information from case reports and descriptive studies permits inference of a relationship between an intervention and an outcome. This type of qualitative information does not permit a statistical assessment of significance.

Equivocal: Qualitative data are not adequate to permit inference of a relationship between an intervention and an outcome and (1) there is insufficient quantitative information or (2) aggregated comparative studies have found no significant differences among groups or conditions.

The *lack* of scientific evidence in the literature is described by the following terms.

Silent: No identified studies address the relationship of interest.

Insufficient: There are too few published studies to investigate a relationship between an intervention and outcome.

Inadequate: The available studies cannot be used to assess the relationship between an intervention and an outcome. These studies either do not meet the criteria for content as defined in the Focus of these Guidelines or do not permit a clear causal interpretation of findings due to methodologic concerns.

Formal survey information is collected from consultants and members of the ASA. The following terms describe survey responses for any specified issue. Responses are solicited on a five-point scale; ranging from 1 (strongly disagree) to 5 (strongly agree), with a score of 3 being equivocal. Survey responses are summarized based on median values as follows:

Strongly agree: Median score of 5 (at least 50% of the responses are 5).

Agree: Median score of 4 (at least 50% of the responses are 4 or 4 and 5).

Equivocal: Median score of 3 (at least 50% of the responses are 3, or no other response category or combination of similar categories contain at least 50% of the responses).

Disagree: Median score of 2 (at least 50% of responses are 2 or 1 and 2).

Strongly disagree: Median score of 1 (at least 50% of responses are 1).

Guidelines

I. Preoperative Evaluation

Preoperative evaluation of a patient for blood transfusion and adjuvant therapies includes (1) reviewing previous medical records, (2) conducting a patient or family interview, and (3) reviewing laboratory test results. Although comparative studies are insufficient to evaluate the perioperative impact of reviewing medical records

* A prospective nonrandomized controlled trial may be included in a meta-analysis under certain circumstances if specific statistical criteria are met.

or conducting a patient interview, the literature reports certain patient characteristics that may be associated with blood transfusion complications. These characteristics include, but are not limited to, congenital or acquired conditions such as factor VIII deficiency, sickle cell anemia, idiopathic thrombocytopenic purpura, and liver disease. In addition, the literature suggests that some preoperative laboratory tests (*e.g.*, hemoglobin, hematocrit, coagulation profile) may predict the need for blood transfusion or excessive blood loss. The consultants and ASA members strongly agree that reviewing previous medical records, interviewing the patient, and reviewing hemoglobin/hematocrit test results should be part of a preoperative evaluation.† The consultants strongly agree and the ASA members agree that a coagulation profile should be reviewed.

Recommendations. Preoperative evaluation should include reviewing previous medical records, conducting a physical examination of the patient, and an interview of the patient or family to identify risk factors for (1) organ ischemia (*e.g.*, cardiorespiratory disease), which may influence the ultimate transfusion trigger for red blood cells (*e.g.*, hemoglobin level), and (2) coagulopathy (*e.g.*, use of warfarin, clopidogrel, aspirin), which may influence transfusion of non–red blood cell components. In addition, a preoperative evaluation should include checking for the presence of congenital or acquired blood disorders, the use of vitamins or herbal supplements that may affect coagulation (appendix 2), or previous exposure to drugs (*e.g.*, aprotinin) that may, upon repeat exposure, cause an allergic reaction. Patients should be informed of the potential risks *versus* benefits of blood transfusion, and their preferences elicited. Available preoperative laboratory results including, but not limited to, hemoglobin, hematocrit, and coagulation profiles should be reviewed if they are appropriate and available. Additional laboratory tests should be ordered based on a patient's condition (*e.g.*, clinical coagulopathy) or institutional policy.

II. Preoperative Preparation

Preoperative patient preparation includes (1) discontinuation or modification of anticoagulation therapy, (2) the prophylactic administration of drugs to promote coagulation and minimize blood loss (*e.g.*, aprotinin, ε-aminocaproic acid, tranexamic acid), and (3) prevention or reduction of allogeneic transfusion requirements.

The impact of discontinuing anticoagulation therapy on blood loss has not been sufficiently addressed in the literature. In addition, the literature is insufficient to address the impact of delaying surgery until the effects of anticoagulation drugs have dissipated. The literature supports the use of aprotinin in reducing blood loss and in reducing the number of patients transfused in major surgical procedures (*e.g.*, selected cardiac and orthopedic procedures). In addition, the literature is supportive of the use of ε-aminocaproic acid and tranexamic acid in reducing blood loss; however, the impact of these drugs on reducing the number of patients transfused is equivocal. The literature is insufficient to evaluate the use of these drugs in a nonprophylactic manner. Some literature has reported adverse outcomes associated with the use of antifibrinolytic drugs such as graft thrombosis or closure and rare massive thrombosis. Severe anaphylactic reactions may occur with aprotinin reexposure.

The efficacy of erythropoietin in reducing the volume of allogeneic blood transfused per patient as well as reducing the number of patients requiring such transfusions is supported by the literature in select populations (*e.g.*, renal insufficiency, anemia of chronic disease, refusal of transfusion). The literature is insufficient to address the effects of vitamin K.

The efficacy of preadmission blood collection to reduce the volume of allogeneic blood transfused per patient and to reduce the number of patients requiring such transfusions is supported by the literature. However, the literature indicates that certain adverse outcomes (*e.g.*, transfusion reaction due to clerical errors, bacterial contamination) may still occur with the use of autologous blood.

The consultants agree and the ASA members strongly agree that anticoagulation drugs (*e.g.*, warfarin, clopidogrel, aspirin) should be discontinued before elective or nonemergent surgery, and both agree that such surgery should be delayed until the anticoagulation effects wear off. They agree that, when significant blood loss is expected, antifibrinolytics should be administered. In addition, the consultants and ASA members agree that erythropoietin may be used to reduce the use of allogeneic blood. They agree that vitamin K should be administered preoperatively for reversal of warfarin to potentially avoid transfusion of FFP. The ASA members agree and the consultants are equivocal that preadmission donation of blood should be offered to patients when transfusion of autologous blood is required or preferred. They disagree that autologous blood should be administered to the patient who donated it if his or her hemoglobin is greater than 10 g/dl.

Recommendations. If possible, the preoperative evaluation should be done well enough in advance to correct or plan for the management of risk factors associated with transfusions. For elective surgery, patient preparation should include discontinuing anticoagulation therapy for a sufficient time in advance of surgery, if clinically possible. If sufficient time has not elapsed, surgery should be delayed until the effects of these drugs dissipate. The Task Force notes that the effect of clopidogrel may last for approximately a week, and the effects of warfarin may last for several days depending on patient

† Refer to appendix 1 for complete results of the consultant and ASA membership surveys.

response and the administration of reversal agents (*e.g.*, vitamin K, prothrombin complex concentrate, recombinant activated factor VII, or FFP). The risk of thrombosis *versus* the risk of increased bleeding should be considered when altering anticoagulation status. Assure that blood and blood components are available for patients when significant blood loss or transfusion is expected.

Antifibrinolytic therapy should not be routinely administered. However, such therapy may be used for reducing the volume of allogeneic blood transfused for patients at high risk of excessive bleeding (*e.g.*, repeat cardiac surgery). The risks and benefits of instituting antifibrinolytic therapy should be assessed on a case-by-case basis.

Erythropoietin should be administered when possible to reduce the need for allogeneic blood in certain selected patient populations (*e.g.*, renal insufficiency, anemia of chronic disease, refusal of transfusion). The Task Force recognizes that erythropoietin administration is perceived as being expensive and requires time (in weeks) to induce a significant increase in hemoglobin concentration. Vitamin K or another warfarin antagonist should be used for reversal of warfarin to potentially avoid transfusion of FFP.

Where autologous blood is required or preferred, the patient may be offered the opportunity to donate blood before admission. However, the Task Force cautions that preoperative anemia may be induced in addition to an increase in total intraoperative autologous or allogeneic transfusions, as well as costs.

III. Intraoperative and Postoperative Management of Blood Loss and Transfusions

Intraoperative and postoperative interventions include (A) red blood cell transfusion, (B) management of coagulopathy, and (C) monitoring and treatment of adverse effects of transfusion.

A. Red Blood Cell Transfusion. Intraoperative and postoperative management of potential or actual blood loss includes (1) monitoring the amount of blood loss, (2) monitoring hemoglobin or hematocrit, (3) monitoring for the presence of inadequate perfusion and oxygenation of vital organs (*e.g.*, blood pressure, heart rate, temperature, blood oxygen saturation), and (4) transfusion of allogeneic red blood cells or autologous blood (*i.e.*, normovolemic hemodilution and intraoperative red blood cell recovery).

The literature is insufficient to evaluate the efficacy of specific intraoperative or postoperative monitoring techniques for detecting the presence of inadequate perfusion or oxygenation of vital organs, or as indicators for the transfusion of red blood cells. The literature supports the efficacy of acute normovolemic hemodilution as well as intraoperative red blood cell recovery in reducing the number of allogeneic units transfused per patient in certain appropriate surgical procedures (*e.g.*, cardiac surgery, liver surgery, large orthopedic surgeries). However, the literature is equivocal regarding the ability of either technique to reduce the number of patients transfused. Although the practice is uncommon in the United States, the literature suggests that postoperative red blood cell recovery will reduce the number of patients transfused.

Despite a large volume of work that has been published since the last practice guidelines, the information needed to define precisely when a blood transfusion should be given is not available in the literature. Although multiple trials have evaluated transfusion thresholds on patient outcome, the literature is insufficient to define a transfusion trigger in surgical patients with substantial blood loss.

The consultants and ASA members strongly agree that a periodic visual assessment of the surgical field and communication with the surgical team should be done to assess the presence of excessive microvascular bleeding (*i.e.*, coagulopathy). The consultants and ASA members strongly agree that monitoring for the presence of inadequate perfusion and oxygenation of vital organs should be continuous. They strongly agree that red blood cells should usually be administered when the hemoglobin level is less than 6 g/dl and strongly agree that red blood cells are usually unnecessary when the level is more than 10 g/dl. In addition, the consultants and ASA members agree that, when autologous blood is required or preferred, acute normovolemic hemodilution and intraoperative or postoperative red blood cell recovery are viable options. The consultants are equivocal and the ASA members agree that postoperative red blood cell recovery is a viable option in avoiding or minimizing allogeneic transfusion. Finally, they agree that frequent postoperative point-of-care sampling and other laboratory testing may be a source of significant ongoing blood loss.

Recommendations.

1. Monitoring for blood loss. A visual assessment of the surgical field should be periodically conducted to assess the presence of excessive microvascular bleeding (*i.e.*, coagulopathy). Standard methods for quantitative measurement of blood loss (*e.g.*, suction and sponge) should be used.

2. Monitoring for inadequate perfusion and oxygenation of vital organs. Conventional monitoring systems (*e.g.*, blood pressure, heart rate, oxygen saturation, urine output, electrocardiography) should be used to assess the adequacy of perfusion and oxygenation of vital organs. Special monitoring systems should be used when appropriate (*e.g.*, echocardiography, mixed venous oxygen saturation, blood gasses).

3. Monitoring for transfusion indications. Measure hemoglobin or hematocrit when substantial blood loss or any indication of organ ischemia occurs. Red blood cells should usually be administered when the hemoglobin concentration is low (*e.g.*, less than 6 g/dl in a young, healthy patient), especially when the anemia is

acute. Red blood cells are usually unnecessary when the hemoglobin concentration is more than 10 g/dl. These conclusions may be altered in the presence of anticipated blood loss. The determination of whether intermediate hemoglobin concentrations (*i.e.*, 6–10 g/dl) justify or require red blood cell transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.

4. Transfusion of allogeneic red blood cells or autologous blood. Maintain adequate intravascular volume and blood pressure with crystalloids or colloids until the criteria for red blood cell transfusion listed above are met. Adequate quantities of red blood cells should be transfused to maintain organ perfusion. When appropriate, intraoperative or postoperative blood recovery and other means to decrease blood loss (*e.g.*, deliberate hypotension) may be beneficial. Acute normovolemic hemodilution, although rarely used, may also be considered.

B. Management of Coagulopathy. Intraoperative and postoperative management of potential or actual coagulopathy includes (1) visual assessment of the surgical field and laboratory monitoring for coagulopathy, (2) transfusion of platelets, (3) transfusion of FFP, (4) transfusion of cryoprecipitate, (5) administration of drugs to treat excessive bleeding (*e.g.*, desmopressin, topical hemostatics), and (6) recombinant activated factor VII.

Visual assessment of the surgical field is standard practice and entails assessments of the presence of microvascular bleeding and the extent of blood present. Laboratory monitoring includes point-of-care intraoperative or postoperative assessments. In a bleeding patient, obtaining coagulation tests is also standard practice, and the literature suggests that coagulation test results correlate with perioperative blood loss, depending on the type of fluid used for intravascular volume replacement. The literature supports the use of desmopressin and topical hemostatics to treat excessive bleeding. Although there are insufficient numbers of published clinical trials assessing the efficacy of recombinant activated factor VII in treating excessive microvascular bleeding (*i.e.*, coagulopathy), multiple case reports indicate its efficacy as a rescue drug when standard therapy has failed.

Despite a large volume of work that has been published since the last practice guidelines, the information needed to define precisely when transfusion of a blood component should occur is not available in the literature. Although multiple trials have evaluated transfusion algorithms on patient and transfusion outcome, especially in cardiac surgery, the literature is insufficient to define specific transfusion algorithms for coagulopathy in surgical patients with substantial blood loss.

The consultants and ASA members strongly agree that, in addition to a periodic visual assessment of the surgical field, communication with the surgical team should include an assessment of the presence of microvascular bleeding. The consultants and ASA members agree that, in a bleeding patient, platelets should be administered when the count is below 50,000 cells/mm^3. They also agree that, in a bleeding patient, FFP should be administered when international normalized ratio (INR) or activated partial thromboplastin time (aPTT) is elevated and that cryoprecipitate should be given when fibrinogen concentrations are less than 80 mg/dl. The consultants agree and the ASA members are equivocal that recombinant activated factor VII is an appropriate rescue drug when traditional, well-tested options have been exhausted. The ASA members agree and the consultants are equivocal that desmopressin should be administered when excessive microvascular bleeding occurs. Finally, the consultants and ASA members agree that topical hemostatics (*e.g.*, fibrin glue or thrombin gel) should be administered for the control of excessive bleeding.

Recommendations.

1. Visual assessment of the surgical field and laboratory monitoring for coagulopathy. A visual assessment of the surgical field should be jointly conducted by the anesthesiologist and surgeon to determine whether excessive microvascular bleeding (*i.e.*, coagulopathy) is occurring. Visual assessment for excessive blood loss should also include checking suction canisters, surgical sponges, and surgical drains. Laboratory monitoring for coagulopathy should include determination of platelet count, prothrombin time (PT) or INR, and aPTT. Other tests may include fibrinogen level, assessment of platelet function, thromboelastogram, d-dimers, and thrombin time.

2. Transfusion of platelets. If possible, a platelet count should be obtained before transfusion of platelets in a bleeding patient, and a test of platelet function should be done in patients with suspected or drug-induced platelet dysfunction (*e.g.*, clopidogrel). In surgical or obstetric patients with normal platelet function, platelet transfusion is rarely indicated if the platelet count is known to be greater than 100×10^9/l and is usually indicated when the count is below 50×10^9/l in the presence of excessive bleeding. Vaginal deliveries or operative procedures ordinarily associated with limited blood loss may be performed in patients with platelet counts less than 50×10^9/l. Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known or suspected platelet dysfunction (*e.g.*,

the presence of potent antiplatelet agents, cardiopulmonary bypass) and microvascular bleeding.‡

The determination of whether patients with platelet counts between 50 and 100 $\times$ 10^9/l require therapy, including prophylactic therapy, should be based on the potential for platelet dysfunction, anticipated or ongoing bleeding, and the risk of bleeding into a confined space (*e.g.*, brain or eye). When the platelet count cannot be done in a timely fashion in the presence of excessive microvascular bleeding (*i.e.*, coagulopathy), platelets may be given when thrombocytopenia is suspected. When thrombocytopenia is due to increased platelet destruction (*e.g.*, heparin-induced thrombocytopenia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura), prophylactic platelet transfusion is ineffective and rarely indicated.

3. Transfusion of fresh frozen plasma. If possible, coagulation tests (*i.e.*, PT or INR and aPTT) should be obtained before the administration of FFP in a bleeding patient. Transfusion of FFP is not indicated if PT, INR, and aPTT are normal. FFP transfusion is indicated for (1) correction of excessive microvascular bleeding (*i.e.*, coagulopathy) in the presence of a PT greater than 1.5 times normal or INR greater than 2.0, or an aPTT greater than 2 times normal; (2) correction of excessive microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume (approximately 70 ml/kg) and when PT or INR and aPTT cannot be obtained in a timely fashion; (3) urgent reversal of warfarin therapy; (4) correction of known coagulation factor deficiencies for which specific concentrates are unavailable; or (5) heparin resistance (antithrombin III deficiency) in a patient requiring heparin. FFP is not indicated solely for augmentation of plasma volume or albumin concentration.

Fresh frozen plasma should be given in doses calculated to achieve a minimum of 30% of plasma factor concentration (usually achieved with administration of 10–15 ml/kg FFP), except for urgent reversal of warfarin anticoagulation, for which 5–8 ml/kg FFP usually will suffice. Four to five platelet concentrates, 1 unit single-donor apheresis platelets, or 1 unit fresh whole blood§ provide a quantity of coagulation factors similar to that contained in 1 unit FFP.

4. Transfusion of cryoprecipitate. If possible, a fibrinogen concentration should be obtained before the administration of cryoprecipitate in a bleeding patient. Transfusion of cryoprecipitate is rarely indicated if fibrinogen concentration is greater than 150 mg/dl. Transfusion of cryoprecipitate is usually indicated (1) when the fibrinogen concentration is less than 80–100 mg/dl in the presence of excessive microvascular bleeding, (2) to correct excessive microvascular bleeding in massively transfused patients when fibrinogen concentrations cannot be measured in a timely fashion, and (3) for patients with congenital fibrinogen deficiencies. Whenever possible, decisions regarding patients with congenital fibrinogen deficiencies should be made in consultation with the patient's hematologist. The determination of whether patients with fibrinogen concentration between 100 and 150 mg/dl require therapy should be based on the potential for anticipated or ongoing bleeding and the risk of bleeding into a confined space (*e.g.*, brain or eye). Bleeding patients with von Willebrand disease should be treated with specific concentrates if available. If concentrates are not available, cryoprecipitate is indicated. Each unit of cryoprecipitate contains 150–250 mg fibrinogen. Each unit of FFP contains 2–4 mg fibrinogen/ml. Therefore, it should be noted that each unit of FFP delivers the equivalent amount of fibrinogen as 2 units cryoprecipitate.‖

5. Drugs to treat excessive bleeding. Desmopressin or topical hemostatics such as fibrin glue or thrombin gel should be considered when excessive bleeding occurs.

6. Recombinant activated factor VII. When traditional well-tested options for treating excessive microvascular bleeding (*i.e.*, coagulopathy) have been exhausted, recombinant activated factor VII should be considered.

C. Monitoring and Treatment of Adverse Effects of Transfusions. Adverse effects of transfusions include, but are not limited to, bacterial contamination, transfusion-related acute lung injury (TRALI), transmission of infectious diseases, and transfusion reaction.

Bacterial contamination: Bacterial contamination of blood products, most frequently platelets, is the leading cause of death from blood transfusions. The increased risk of bacterial overgrowth is related to a storage temperature of above 20–24° centigrade. Many blood banks are now culturing their platelet concentrates. If a patient develops a fever within 6 h after receiving platelets, sepsis from contaminated platelets may be a possibility.

TRALI: Transfusion-related acute lung injury is noncardiogenic pulmonary edema resulting from immune reactivity of certain leukocyte antibodies a few hours after transfusion. Signs and symptoms will appear 1–2 h after transfusion and are in maximum force within 6 h. Hypoxia, fever, dyspnea, and even fluid in the endotracheal tube may occur. There is no specific therapy other than stopping transfusion and instituting critical care supportive measures. Most patients recover in 96 h, although TRALI is one of the top three most common causes of transfusion related deaths.

Infectious diseases: Another major adverse effect of transfusion therapy is the transmission of infectious agents. For the past 20 yr, transfusion-induced hepatitis and autoimmune deficiency syndrome were dominant concerns regarding allogeneic blood administration.

‡ The proper dose of platelets should be based on recommendations of the local institutional transfusion committee.

§ Many institutions in the United States no longer have fresh whole blood available from the blood bank.

‖ American Association of Blood Banks, American National Red Cross, and America's Blood Centers: Circular of information for the use of human blood components. Bethesda, Maryland, American Association of Blood Banks, 2002.

These infectious risks are now rare. One of the major reasons for the decrease in blood-borne infections has been the use of nucleic acid technology. The human immunodeficiency virus, hepatitis C virus, and West Nile virus can now be detected by this technology. To date, malaria, Chagas disease, severe acute respiratory syndrome, and variant Creutzfeldt-Jakob disease cannot be detected.

Transfusion reaction: General anesthesia may mask the symptoms of both hemolytic and nonhemolytic transfusion reactions. Signs of hemolytic reactions include hypotension, tachycardia, hemoglobinuria, and microvascular bleeding, but these may be erroneously attributed to other causes in the anesthetized patient. The most common signs of a nonhemolytic transfusion reaction in awake patients include fever, chills, or urticaria. However, these signs may not be detectable during anesthesia.

The consultants and ASA members strongly agree that checking for signs and symptoms of a transfusion reaction should periodically be done in the anesthetized patient. The consultants agree and the ASA members strongly agree that urine output and color should be assessed. Both the consultants and ASA members agree that peak airway pressure should be assessed to monitor for transfusion reactions.

Recommendations. Periodically check for signs and symptoms of bacterial contamination, TRALI, and hemolytic transfusion reactions, including urticaria, hypotension, tachycardia, increased peak airway pressure, hyperthermia, decreased urine output, hemoglobinuria, and microvascular bleeding. Before instituting therapy for transfusion reactions, stop the blood transfusion and order appropriate diagnostic testing.

Appendix 1. Methods and Analyses

The scientific assessment of these Guidelines was based on evidence linkages or statements regarding potential relationships between clinical interventions and outcomes. The interventions listed below were examined to assess their impact on a variety of outcomes related to perioperative blood transfusion and adjuvant therapies.

1. Preoperative evaluation
   a. Focused history
      (i) Reviewing medical records
      (ii) Conducting a patient interview
      (iii) Patient condition
   b. Laboratory tests
      (i) Hemoglobin or hematocrit
      (ii) Coagulation profile (PT, aPTT, activated coagulation time, thromboelastogram)

2. Preoperative patient preparation
   a. Interventions to prevent blood loss
      (i) Discontinuation of anticoagulation
      (ii) Delay of surgery until drug effects (*e.g.*, warfarin, clopidogrel, aspirin) dissipate
   b. Prevention/reduction of allogeneic transfusion requirements
      (i) Drugs to prevent or reduce perioperative anemia
         Erythropoietin
         Vitamin K
      (ii) Autologous blood collection
         Preadmission autologous blood donation *versus* no autologous blood collection or conventional transfusion
         Preadmission autologous blood donation *versus* intra or postoperative blood collection
      (iii) Drugs to promote coagulation and minimize blood loss
         Aprotinin
         ε-Aminocaproic acid
         Tranexamic acid

3. Intraoperative and postoperative interventions
   a. Red blood cell transfusion
      (i) Monitoring for inadequate perfusion and oxygenation (blood pressure, heart rate, temperature, oxygen saturation)
      (ii) Monitoring for transfusion indications
         Cardiac monitoring for ischemia
         Hemoglobin or hematocrit threshold values
         Coagulation profile
      (iii) Transfusion of allogeneic erythrocytes
      (iv) Transfusion of autologous blood
         Acute normovolemic hemodilution *versus* no acute normovolemic hemodilution
         Acute normovolemic hemodilution combined with intraoperative red blood cell recovery
         Intraoperative red blood cell recovery
         Postoperative red blood cell recovery
         Cell salvage *versus* other retransfusion techniques (*e.g.*, blood filtering)
   b. Management of coagulopathy
      (i) Platelet transfusion
      (ii) FFP transfusion
      (iii) Cryoprecipitate transfusion
      (iv) Drugs to treat excessive bleeding
         Desmopressin
         Topical hemostatics (fibrin glue, thrombin gel)
   c. Monitoring and laboratory testing for transfusion reactions
      (i) Urine output and color
      (ii) Peak airway pressure

Although they are not included in the focus of these guidelines, promising areas of ongoing research include (1) the use of algorithms to improve decision making and reduce transfusion requirements and (2) hemoglobin-based oxygen carriers or other synthetic blood substitutes to reduce transfusion requirements. Scientific evidence was derived from aggregated research literature, and opinion-based evidence was obtained from surveys, open presentations, and other activities (*e.g.*, Internet posting). For purposes of literature aggregation, potentially relevant clinical studies were identified *via* electronic and manual searches of the literature. The electronic and manual searches covered a 12-yr period from 1994 through 2005. More than 3,000 citations were initially identified, yielding a total of 878 nonoverlapping articles that addressed topics related to the evidence linkages. After review of the articles, 566 studies did not provide direct evidence and were subsequently eliminated. A total of 312 articles contained direct linkage-related evidence. Initially, each pertinent outcome reported in a study was classified as supporting an evidence linkage, refuting a linkage, or equivocal. The results were then summarized to obtain a directional assessment for each evidence linkage before conducting a formal meta-analysis. Literature pertaining to five evidence linkages contained enough studies with well-defined experimental designs and statistical information sufficient for meta-analyses. These linkages were (1) erythropoietin *versus* placebo, (2) preadmission blood donation *versus* no autologous blood collection, (3) antifibrinolytics (aprotinin *vs.* placebo; ε-aminocaproic acid *vs.* placebo; tranexamic acid *vs.* placebo), (4) transfusion of autologous blood (acute normovolemic hemodilution *vs.* no acute normovolemic hemodilution; intraoperative red blood cell recovery *vs.* no recovery), and (5) desmopressin *versus* no desmopressin.

Table 1. Meta-analysis Summary

Linkages	n	Fisher Chi-square	*P* Value	Weighted Stouffer Zc	*P* Value	Effect Size	Mantel-Haenszel OR	CI	Heterogeneity: Significance	Heterogeneity: Effect Size
Preoperative preparation										
Prevention/reduction of allogenic transfusion requirements										
Drugs										
Erythropoietin vs. no erythropoietin										
Allogeneic units*	7	41.50	0.001	4.15	0.001	0.14	—	—	0.005	0.030
Allogeneic patients transfused*	13	—	—	—	—	—	0.46	0.33–0.65	—	0.450
Autologous blood collection										
Preadmission donation *vs.* conventional transfusion										
Allogeneic units†	5	58.30	0.001	5.97	0.001	0.18	—	—	0.600	0.020
Allogeneic patients transfused†‡	7	—	—	—	—	—	0.24	0.11–0.49	—	0.009
Intraoperative and postoperative interventions										
Reduction/minimization of bleeding										
Drugs to promote coagulation and minimize blood loss										
Aprotinin vs. placebo										
Total blood loss*	8	115.02	0.001	10.37	0.001	0.77	—	—	0.001	0.001
Patients transfused*	13	—	—	—	—	—	0.43	0.33–0.56	—	0.030
ε-Aminocaproic acid *vs.* saline										
Postoperative/total blood loss*	5	42.60	0.001	3.62	0.001	0.28	—	—	0.250	0.300
Patients transfused*	5	—	—	—	—	—	0.58	0.31–1.11	—	0.700
Tranexamic acid *vs.* saline										
Total blood loss*	9	124.88	0.001	18.01	0.001	0.96	—	—	0.001	0.001
Patients transfused*‡	12	—	—	—	—	—	0.28	0.12–1.06	—	0.001
Drugs to treat excessive bleeding										
Desmopressin *vs.* saline										
Total blood loss*	7	61.25	0.001	3.86	0.001	0.20	—	—	0.001	0.001
Blood transfusion										
Transfusion of autologous blood and components										
Acute normovolemic hemodilution vs. conventional transfusion										
Allogeneic units	7	48.39	0.001	3.40	0.001	0.42	—	—	0.001	0.001
Allogeneic patients transfused	8	—	—	—	—	—	0.82	0.53–1.25	—	0.600
Intraoperative red blood cell recovery *vs.* conventional transfusion										
Allogeneic units†	7	66.88	0.001	5.41	0.001	0.15	—	—	0.001	0.001

* Double-blind studies only. † Combined randomized and nonrandomized studies. ‡ DerSimonian-Laird random effects odds ratio.
CI = confidence interval; OR = odds ratio.

General variance-based effect-size estimates or combined probability tests were obtained for continuous outcome measures, and Mantel-Haenszel odds ratios were obtained for dichotomous outcome measures. Two combined probability tests were employed as follows: (1) the Fisher combined test, producing chi-square values based on logarithmic transformations of the reported *P* values from the independent studies, and (2) the Stouffer combined test, providing weighted representation of the studies by weighting each of the standard normal deviates by the size of the sample. An odds ratio procedure based on the Mantel-Haenszel method for combining study results using 2×2 tables was used with outcome frequency information. An acceptable significance level was set at $P < 0.01$ (one tailed). Tests for heterogeneity of the independent studies were conducted to assure consistency among the study results. DerSimonian-Laird random-effects odds ratios were obtained when significant heterogeneity was found ($P < 0.01$). To control for potential publishing bias, a "fail-safe n" value was calculated. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Meta-analytic results are reported in table 1. To be accepted as significant findings, Mantel-Haenszel odds ratios must agree with combined test results whenever both types of data are assessed. In the absence of Mantel-Haenszel odds ratios, findings from both the Fisher and weighted Stouffer combined tests must agree with each other to be acceptable as significant. Interobserver agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a kappa (κ) statistic for two-rater agreement pairs were as follows: (1) type of study design, $\kappa = 0.72–0.93$; (2) type of analysis, $\kappa = 0.63–0.92$; (3) evidence linkage assignment, $\kappa = 0.84–1.00$; and (4) literature inclusion for database, $\kappa = 0.49–1.00$. Three-rater chance-corrected agreement values were (1) study design, Sav = 0.81, Var (Sav) = 0.008; (2) type of analysis, Sav = 0.78, Var (Sav) = 0.008; (3) linkage assignment, Sav = 0.90, Var (Sav) = 0.003; and (4) literature database inclusion, Sav = 0.67, Var (Sav) = 0.037. These values represent moderate to high levels of agreement.

Consensus was obtained from multiple sources, including (1) survey opinion from consultants who were selected based on their knowledge or expertise in perioperative blood transfusion and adjuvant therapies, (2) survey opinions from a randomly selected sample of active members of the ASA, (3) testimony from attendees of two publicly held open forums at two national anesthesia meetings,# (4) Internet commentary, and (5) Task Force opinion and interpretation. The survey

79th Clinical and Scientific Congress of the International Anesthesia Research Society, March 12, 2005, Honolulu, Hawaii; and 27th Annual Meeting of the Society of Cardiovascular Anesthesiologists, May 14, 2005, Baltimore, Maryland.

Table 2. Consultant Survey Responses

	n	Percent Responding to Each Item				
		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
1. Preoperative evaluation						
Review medical records	26	69.2*	26.9	3.8	0.0	0.0
Interview the patient and family	25	60.0*	32.0	8.0	0.0	0.0
Review hemoglobin/hematocrit test results	26	76.9*	23.1	0.0	0.0	0.0
Review coagulation profile	26	53.8*	30.8	7.7	7.7	0.0
2. Preoperative preparation						
Discontinue anticoagulation drugs	26	42.3	30.8*	19.2	7.7	0.0
In elective cases, surgery should be delayed until the effects of anticoagulation drugs have dissipated	26	34.6	42.3*	11.5	11.5	0.0
When significant blood loss is expected, administer antifibrinolytics (*e.g.*, aprotinin, ε-aminocaproic acid or tranexamic acid)	26	38.5	42.3*	15.4	3.8	0.0
Administer erythropoietin to select patients (*e.g.*, renal insufficiency, anemia, chronic disease, or transfusion refusal)	25	40.0	52.0*	0.0	8.0	0.0
Administration of vitamin K for reversal of warfarin to potentially avoid transfusion of FFP	26	38.5	30.8*	15.4	15.4	0.0
Preadmission donation of autologous blood should be done to avoid or minimize allogeneic transfusion	26	15.4	23.1	26.9*	26.9	7.7
If available, autologous blood should be administered to the patient who donated it if the hemoglobin is greater than 10 g/dl	26	0.0	3.8	7.7	42.3*	46.2
3. Intraoperative and postoperative management						
Visual assessment of the surgical field should be periodically conducted to assess the presence of excessive microvascular bleeding	26	53.8*	42.3	3.8	0.0	0.0
Periodically communicate with the surgical team to assess the presence of excessive microvascular bleeding	26	50.0*	38.5	7.7	3.8	0.0
Continuous monitoring for inadequate perfusion and oxygenation	26	57.7*	38.5	3.8	0.0	0.0
Usually administer red blood cells when the hemoglobin level is less than 6 g/dl	26	61.5*	30.8	3.8	3.8	0.0
Red blood cells are usually unnecessary when the hemoglobin level is greater than 10 g/dl	26	61.5*	34.6	3.8	0.0	0.0
Use normovolemic hemodilution or acute normovolemic hemodilution to reduce transfusion requirements when autologous blood is required or preferred	26	15.4	38.5*	30.8	11.5	3.8
Intraoperative red blood cell recovery is a viable option to avoid or minimize allogeneic transfusion	26	38.5	53.8*	3.8	3.8	0.0
Postoperative red blood cell recovery is a viable option to avoid or minimize allogeneic transfusion	26	3.8	38.5	34.6*	23.1	0.0
Frequent postoperative sampling of point-of-care and other intraoperative laboratory tests may be associated with significant ongoing blood loss	24	12.5	45.8*	16.7	20.8	4.2
In a bleeding patient, administer platelets when the platelet count is less than 50,000 cells/mm^3	26	42.3	34.6*	7.7	15.4	0.0
In a bleeding patient, administer FFP when INR (PT) or aPTT is elevated	26	11.5	69.2*	0.0	19.2	0.0
In a bleeding patient, administer cryoprecipitate when fibrinogen concentrations are $<$ 80 mg/dl	26	26.9	65.4*	3.8	3.8	0.0
When excessive microvascular bleeding (coagulopathy) occurs, administer:						
Desmopressin (DDAVP)	25	4.0	36.0	40.0*	16.0	4.0
Fibrin glue	25	20.0	40.0*	28.0	12.0	0.0
Thrombin gel	23	17.4	34.8*	34.8	13.0	0.0
Recombinant activated factor VII is an appropriate rescue drug when traditional, well-tested options have been exhausted	26	23.1	42.3*	34.6	0.0	0.0
To monitor for transfusion reactions:						
Periodically check for signs and symptoms	26	69.2*	30.8	0.0	0.0	0.0
Assess urine output and color	26	42.3	46.2*	7.7	3.8	0.0
Assess peak airway pressure	26	30.8	38.5*	26.9	3.8	0.0

* Median.

aPPT = activated partial thromboplastin time; FFP = fresh frozen plasma; INR = international normalized ratio; n = number of consultants who responded to each item; PT = prothrombin time.

rate of return was 31% (n = 21 of 67) for consultants, and 29% (n = 87 of 300) for membership respondents. Results of the surveys are reported in tables 2 and 3 and in the text of the Guidelines.

The consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the Guidelines were instituted. The rate of return was 24% (n = 16 of 67). The percent of responding consultants expecting *no change* associated with each linkage were as follows: preoperative evaluation—75%; discontinuation of anticoagulation and delay of surgery—94%; drugs to manage perioperative anemia—75%; drugs to promote coagula-

Table 3. ASA Membership Survey Responses

	n	Percent Responding to Each Item				
		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
1. Preoperative evaluation						
Review medical records	94	85.1*	12.8	1.1	1.1	0.0
Interview the patient and family	94	87.2*	12.8	0.0	0.0	0.0
Review hemoglobin/hematocrit test results	94	66.0*	24.5	8.5	1.1	0.0
Review coagulation profile	92	46.7	27.2*	16.3	9.8	0.0
2. Preoperative preparation						
Discontinue anticoagulation drugs	94	56.4*	34.0	6.4	3.2	0.0
In elective cases, surgery should be delayed until the effects of anticoagulation drugs have dissipated	94	40.4	43.6*	10.6	5.3	0.0
When significant blood loss is expected, administer antifibrinolytics (*e.g.*, aprotinin, ε-aminocaproic acid or tranexamic acid)	92	25.0	41.3*	32.6	1.1	0.0
Administer erythropoietin to select patients (e.g., renal insufficiency, anemia, chronic disease, or transfusion refusal)	93	20.4	52.7*	22.6	4.3	0.0
Administration of vitamin K for reversal of warfarin to potentially avoid transfusion of FFP	93	29.0	46.2*	15.1	9.7	0.0
Preadmission donation of autologous blood should be done to avoid or minimize allogeneic transfusion	94	24.5	43.6*	22.3	9.6	0.0
If available, autologous blood should be administered to the patient who donated it if the hemoglobin is greater than 10 g/dl	94	6.4	12.8	18.1	46.8*	16.0
3. Intraoperative and postoperative management						
Visual assessment of the surgical field should be periodically conducted to assess the presence of excessive microvascular bleeding	91	73.6*	26.4	0.0	0.0	0.0
Periodically communicate with the surgical team to assess the presence of excessive microvascular bleeding	91	67.0*	31.9	1.1	0.0	0.0
Continuous monitoring for inadequate perfusion and oxygenation	88	73.9*	22.7	2.3	1.1	0.0
Usually administer red blood cells when the hemoglobin level is less than 6 g/dl	91	73.6*	16.5	6.6	3.3	0.0
Red blood cells are usually unnecessary when the hemoglobin level is greater than 10 g/dl	91	51.6*	40.7	4.4	3.3	0.0
Use normovolemic hemodilution or acute normovolemic hemodilution to reduce transfusion requirements when autologous blood is required or preferred	90	17.8	48.9*	25.6	6.7	1.1
Intraoperative red blood cell recovery is a viable option to avoid or minimize allogeneic transfusion	91	44.0	48.4*	5.5	2.2	0.0
Postoperative red blood cell recovery is a viable option to avoid or minimize allogeneic transfusion	91	19.8	41.9*	29.7	6.6	2.2
Frequent postoperative sampling of point-of-care and other intraoperative laboratory tests may be associated with significant ongoing blood loss	88	9.1	44.3*	26.1	19.3	1.1
In a bleeding patient, administer platelets when the platelet count is less than 50,000 cells/mm^3	91	44.0	39.6*	9.9	6.6	0.0
In a bleeding patient, administer FFP when INR (PT) or aPTT is elevated	91	23.1	59.3*	9.9	5.5	2.2
In a bleeding patient, administer cryoprecipitate when fibrinogen concentrations are $<$ 80 mg/dl	91	16.5	56.0*	23.1	4.4	0.0
When excessive microvascular bleeding (coagulopathy) occurs, administer:						
Desmopressin (DDAVP)	91	11.0	42.9*	38.5	7.7	0.0
Fibrin glue	89	12.4	43.8*	40.4	3.4	0.0
Thrombin gel	89	12.4	48.3*	36.0	3.4	0.0
Recombinant activated factor VII is an appropriate rescue drug when traditional, well-tested options have been exhausted	91	3.3	26.4	62.6*	6.6	1.1
To monitor for transfusion reactions:						
Periodically check for signs and symptoms	90	65.6*	34.4	0.0	0.0	0.0
Assess urine output and color	91	52.7*	46.2	1.1	0.0	0.0
Assess peak airway pressure	91	36.3	54.9*	6.6	2.2	0.0

* Median.

aPPT = activated partial thromboplastin time; ASA = American Society of Anesthesiologists; FFP = fresh frozen plasma; INR = international normalized ratio; n = number of members who responded to each item; PT = prothrombin time.

tion and minimize blood loss—81%; preoperative autologous blood collection—88%; monitoring for inadequate perfusion and oxygenation—94%; monitoring for transfusion indications—88%; transfusion of allogeneic red blood cells—94%, transfusion of autologous blood—100%; transfusion of platelets—88%; transfusion of FFP—88%; transfusion of cryoprecipitate—94%; treatment of excessive bleeding—88%; and monitoring and laboratory testing for transfusion reactions—88%. Eighty-eight percent of the respondents indicated that the Guidelines would have *no effect* on the amount of time spent on a typical case. Two respondents (12%) indicated that there would be an increase in the amount of time they would spend on a typical case with the implementation of these Guidelines. The

amount of increased time anticipated by these respondents ranged from 5 to 10 min.

Appendix 2. Vitamin and Herbal Supplements That May Affect Blood Loss

Herbal Supplements That Decrease Platelet Aggregation

Bilberry
Bromelain
Dong quoi
Feverfew
Fish oil
Flax seed oil
Garlic
Ginger
Gingko biloba
Grape seed extract
Saw palmetto

Herbs That Inhibit Clotting

Chamomile
Dandelion root
Dong quoi
Horse chestnut

Vitamins That Affect Coagulation

Vitamin K
Vitamin E