Guidelines for red blood cell and plasma transfusion for adults and children

Expert Working Group*

Abstract

Objective: To provide broad guidelines and principles to help physicians, other health care workers and patients make decisions about the appropriateness of red blood cell and plasma transfusion.

Options: These guidelines are limited to red blood cell and plasma transfusion in adults and children over 4 months of age. Indications for specific clinical conditions and specialized blood components are not addressed. Options considered included appropriate use of allogeneic and autologous transfusion and substituting non-blood alternatives.

Outcomes: Patient well-being, avoidance of risk and appropriate use of the allogeneic blood supply.

Evidence: Existing practice guidelines and published research supporting clinical indications for transfusions; a review of the legal and ethical issues pertaining to transfusion practices; physician focus groups to assess current needs in the field of transfusion and counseling practices.

Values: Provision of optimum patient care and prudent clinical use of a precious resource, the allogeneic blood supply. Patients should be involved in transfusion decisions whenever possible.

Benefits, harms, costs: The risks and benefits of using allogeneic and autologous blood for transfusion were weighed and compared with those associated with non-blood alternatives. Costs, both monetary and non-monetary, were considered when known.

Recommendations: The recommendations relate to the dissemination of blood product information, the participatory process of informed consent and the clinical indications for blood product transfusion. Each recommendation was rated based on the strength of the supporting evidence. In brief, patients should be informed about transfusion. Accurate data regarding the risks of transfusion should be available to and used by physicians to inform patients effectively. Red blood cell transfusion, allogeneic or autologous, should be given to increase oxygen carriage in the blood in situations where this is likely to be inadequate. Plasma should be given primarily to support coagulation in the setting of multiple factor deficiencies or for therapeutic plasmapheresis for specific indications. Transfusion committees should function at a local level to assist in the dissemination of information and establishment of prudent transfusion practices.

Endorsement: The guidelines are endorsed by the following national associations: Aplastic Anemia Association of Canada, Canadian Anesthetists' Society, Canadian Association of Emergency Physicians, Canadian Association of General Surgeons, Canadian Association of Pathologists, Canadian Blood Agency, Canadian Cardiovascular Society, Canadian Critical Care Society, Canadian Healthcare Association, Canadian Hemophilia Society, Canadian Infectious Disease Society, Canadian Nurses Association, Canadian Orthopaedic Association, Canadian Paediatric Society, Canadian Red Cross Society, Canadian Society for Transfusion Medicine, Canadian Society of Internal Medicine, Canadian Society of Laboratory Technologists, Canadian Transplantation Society, College of Family Physicians of Canada, Patient Alumni Board of the Ottawa Heart Institute, Society of Obstetricians and Gynaecologists of Canada and Trauma Association of Canada.

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Special Supplement

Supplément spécial

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Ideally, practice guidelines are intended to assist practitioners and patients to make decisions about appropriate health care.[1] They are not intended to provide a rigid prescription for care. Guidelines should be discussed, adopted or modified according to local clinical needs and constraints.

Why do we need Canadian guidelines for red blood cell and plasma transfusion?

Many available guidelines are outdated, because the science and the blood system have changed dramatically in the last decade. Some guidelines reflect values that are not relevant to Canada; others rely heavily on "expert" opinions rather than critical review of evidence. Although in some areas of transfusion inadequate scientific evidence exists and "expert" opinions are necessary, in other areas sufficient evidence exists and should be used to generate recommendations. As well, some guidelines deal only with surgical populations; for other populations, patients with chronic anemia and, particularly, children, guidelines do not exist.

The great many publications on transfusion medicine in the last decade require synthesis and interpretation. New blood programs, such as autologous predeposit and intraoperative cell salvage, lack criteria for best integrating them into the predominantly allogeneic system. Critical evaluation of current transfusion practices in Canada may lead to new perspectives in clinical decision-making and applying new information and new choices.

Those generating guidelines have certain values that influence how the evidence is reviewed and the guidelines are elaborated. Two principles guided the Expert Working Group (EWG): the guidelines should permit optimal patient care while fostering prudent clinical use of the precious allogeneic blood supply. The EWG considered avoidance of transfusion to be ideal to the extent that avoidance was not likely to be a more serious risk than the transfusion. In addition, the members believe that, whenever possible, patients should be involved in transfusion decisions.

Informed consent and information disclosure

The EWG had some difficulty reaching consensus on some issues related to obtaining informed consent for red blood cell and plasma transfusion. Members agreed that health care workers should inform patients about the possibility and likelihood of blood transfusion, and solicit and answer any questions the patient might have. Beyond that point, members had difficulty providing guidelines for informed consent that reconcile requirements for full disclosure irrespective of the clinical scenario with a more pragmatic approach that considers disclosing transfusion-related information in light of the patient's clinical situation.

The EWG believes that the risk associated with red blood cell and plasma transfusion must be placed in the context of the overall risk associated with an illness or procedure. Blood transfusion is often given in situations, such as surgery, chemotherapy or critical illness, where the risk from transfusion is small compared with the overall risks. Undue emphasis on the risks from blood transfusion was thought by some to be both unreasonable and imprudent, as it could confuse patients about the absolute and relative risks they are facing. For example, coronary artery bypass grafting has an approximate composite risk of stroke, myocardial infarction and death of 1% to 2%. Is it then necessary or even appropriate to do more than advise patients that they have a 10% to 40% probability of receiving a blood transfusion, with which there are associated remote but real risks, then solicit the patient's response and questions.

The EWG agreed that, where clinically appropriate, patients should be advised that alternatives to allogeneic transfusion exist, but members could not reach consensus on the need to discuss them in detail, given their inconsistent availability and varying effectiveness in averting allogeneic exposure and preventing transmissible diseases.

Finally, the EWG agreed that patients should be informed that they have received red blood cells or plasma as soon as possible following transfusion, but could not reach consensus on who should inform them (e.g., treating physician, prescribing physician, blood bank, hospital administration) or how to ensure that they were informed.

Transfusion threshold

These guidelines differ from others in not explicitly recommending a threshold hemoglobin concentration or range of concentrations at which patients should be transfused. EWG members agreed that there was no evidence to support the generation of such thresholds. The EWG believes that the decision to transfuse should be made after review of the patient and the clinical situation; in addition, timely measurement of hemoglobin concentrations should be considered.

Volumes of plasma to be administered

These guidelines differ from others in not explicitly stating volumes of plasma to be administered. The EWG agreed that published practical guides for appropriate initial-dose volumes in given clinical situations are prudent.[2–5] It was recommended that plasma be given in

doses calculated to achieve a minimum of 30% of normal concentrations for most plasma factors (usually achieved with administration of 10–15 mL of plasma per kilogram body weight), except for urgent reversal of warfarin anticoagulation, for which 5–8 mL/kg will usually suffice.

However, these values are derived not from systematic assessments of therapy, but from synthesis of physiologic measurements of factor concentrations, hemostatic function and clinical observations of the effect of plasma administration on abnormal coagulation. Ongoing clinical and laboratory assessments are necessary to determine subsequent action.

Information about infectious risks of transfusion

In the past, physicians prescribing blood products have not had accurate and readily available information on the infectious risks of blood transfusion. No single national agency has assumed or been assigned to provide physicians or the community at large with this information. The EWG believes that a single agency should have the responsibility to provide this information, but could not reach a consensus about which agency should be delegated or whether the EWG had the mandate to make such a proclamation. However, the EWG believes that those who constitute the Canadian blood system have the responsibility to do this without delay.

Methods

These guidelines were developed according to the CMA's *Guidelines for Canadian Clinical Practice Guidelines*.[1] They cover red blood cell and plasma transfusions in adults and in children over 4 months of age. For infants under 4 months, the Canadian Paediatric Society has developed guidelines for transfusion of red blood cells.[6] Informed consent and the infectious risks related to the transfusion of these components are also addressed.

Broad guidelines and principles have been developed; specific clinical conditions or indications for specialized blood components, such as leuko-reduced or irradiated components or components at low risk of transmitting cytomegalovirus, are not addressed. The specific development process comprised 4 steps:

1. Background research

In this initial phase, consultants with the required expertise were commissioned to provide:

- a review of the scientific evidence supporting clinical indications for transfusion. For all sections, excluding that relating to autologous transfusion, a search of MEDLINE from January 1966 to July 1996 for all languages was constructed using the following medical subject headings: blood transfusion, erythrocyte transfusion and blood component transfusion. Manual searches of bibliographies of relevant reviews, guidelines and textbooks were also undertaken. During the search 1287 articles relevant to plasma or red blood cell transfusions for human adults or children over 4 months of age were found. For autologous transfusion, a recent meta-analysis was used as the evidence base (Andreas Laupacis, Phillip Wells, Dean Fergusson, Melissa Forgie, Ottawa Civic Hospital, Ottawa, Ont. 1997. A meta-analysis of the efficacy of preoperative autologous donation of blood [unpublished data]).
- a review of relevant ethical and legal issues
- an evaluation of physicians' current needs related to transfusion and counselling practices as expressed in 9 focus groups convened in Toronto, Vancouver, Ottawa, Montreal and Cornwall.

2. Guideline development

- *Expert Working Group:* Organizations representing various stakeholders (Appendix 1) were asked to suggest members for the EWG. All sponsors reviewed the curricula vitae of potential members. Criteria for selection included: credentials, practical experience, authorship of relevant works, fair representation of various specialties involved in transfusion medicine and the various regions of Canada. All short-listed candidates were asked to complete a conflict-of-interest evaluation form. By this process, 8 candidates were selected and appointed to the EWG by the CMA's Board of Directors.
- *Advisory Panel:* A larger group was convened to reflect the concerns of patients and practising providers and to provide feedback to the EWG. The 26 members of the Advisory Panel were appointed by their organizations (Appendix 1), to represent their stakeholder group on the panel.
- *Levels of evidence:* The definition of the levels of evidence used to grade the recommendations in these guidelines is a modified version of that used by the Canadian Task Force on the Periodic Health Examination:[7]

  Level I: Evidence obtained from at least one properly randomized controlled trial.

  Level II: Evidence obtained from well-designed controlled trials without randomization, cohort or case–control analytic studies, preferably from more than one centre, or research or evidence obtained from comparisons between times or places with or without the intervention.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Not applicable (N/A): opinions of the EWG about issues that cannot be evaluated using accepted study designs.

- *Consensus:* The EWG reviewed both the background research identified above and additional articles retrieved by its members. The evidence was synthesized and draft positions were written, reviewed and revised during both face-to-face and teleconference meetings. A composite document was then constructed and presented at an assembly of the EWG and Advisory Panel. This document was further revised by the EWG, then circulated to the Advisory Panel, the participating organizations and the consultants for written commentary. This commentary was reviewed by the EWG in a series of teleconferences and the final document was prepared and submitted to the *Canadian Medical Association Journal* for peer review.

3. External review

Members of the EWG and the Advisory Panel suggested external reviewers who were members of medical organizations and other health professional associations, experts in the field and other interested parties. The comments of the external reviewers were considered by the EWG for incorporation into the final draft of the guidelines.

4. Endorsement

All organizations who appointed representatives to the Advisory Panel were contacted to obtain an official endorsement of the final draft of the guidelines.

Issues related to informed consent

The following is a general discussion of issues related to informed consent. For a more complete discussion, physicians are referred to *Consent: A Guide for Canadian Physicians*.[8]

What is informed consent?

Informed consent is undertaken by a patient and a physician to make a therapeutic decision; it allows the patient to preserve his or her primary role in making the decision to undergo a treatment or procedure.[8–12] As part of this process the physician must conform to a standard of disclosure about the risks and benefits of a particular therapy or procedure:[13] to disclose information that the physician knows or ought to know and a reasonable person in the patient's position would wish to know before making the decision.

When possible, discussions about transfusion should take place early enough to allow time to procure feasible alternatives such as autologous transfusion.[14] The language should be easily understood by the patient; a preprinted patient information sheet may be helpful but cannot supplant discussion. The discussion must include: description of the blood product or component to be transfused; the expected benefits, including possible consequences if transfusion is not given; the associated risks, including life-threatening risks; and appropriate alternatives. The patient must be given an opportunity to ask questions and the physician must ensure that the patient understands the explanation. Confirmation that the consent discussion has taken place is best noted in the patient's (hospital) chart. Signing a separate consent form for blood transfusion is of no particular advantage and cannot replace the discussion that must occur.[15]

Transfusion of blood products raises myriad ethical issues including: access to resources; access to alternative treatments; social, psychological, physical and emotional well-being of the patient; differing perceptions of risk; and potential conflicts of opinion and belief between the physician and the patient. The physician should be aware of these issues and the diverse cultural differences and beliefs in our society and act accordingly. A blood transfusion is often only part of a larger medical or surgical intervention, and the risks of the transfusion may be small compared with the total risk associated with the intervention. During the consent discussion, it may be appropriate that the emphasis placed on the various risks (i.e., that of the blood transfusion) reflect their relative magnitude in the whole process.

Special considerations: emergencies, children and incompetent adults

Emergencies

Physicians may treat a patient without consent when the treatment is necessary to preserve a patient's life or health and

- it is not possible to obtain consent because the patient is not mentally or physically capable of giving consent (either inherently or due to his or her medical condition);
- no substitute decision-maker is available;
- there is no evidence of advance directives.[10,12]

This also applies to emergencies involving children if their parents or guardians cannot be reached. If consent to treatment is refused, no treatment may be given, but

the physician should ensure that the patient is competent to refuse treatment.

Children and adolescents

The responsibility for making decisions on behalf of a minor normally rests with the parents or legal guardians. In the case of divorced parents, decision-making power rests with the parent who has legal custody. Decisions should be based on the best interests or welfare of the child rather than those of the parents. Canadian courts have not permitted parents to refuse life-saving transfusions (or any other life-saving treatment) for their children on religious grounds.[12] If a physician believes that refusal of a transfusion might endanger the child's life or health, and discussions with the parents or guardians fail to alter the decision, the physician is generally obliged, under provincial child protection laws, to notify and seek assistance from the appropriate authorities.

Generally, minors may consent to or refuse medical treatment if they are competent and capable of appreciating the full nature and consequences of the treatment or refusal of treatment. Although determination of capacity of a minor is the responsibility of the physician, the physician must be aware that provincial legislation may establish presumptive ages of capacity and specific conditions under which parents, guardians or child protection agencies must be notified.[16] In most provinces, child protection legislation requires that physicians notify authorities if, for example, they feel a child's life, health or safety is in danger. Some statutes make such reports mandatory for minors who are under a certain age even if the minor would otherwise be sufficiently mature to consent to or refuse treatment.

Incompetent adults

For adults who have never been competent, decisions must be in the patient's best interest. For adults who were once competent but have become temporarily or permanently incompetent, their prior wishes regarding treatment, to the extent that these are known or can be determined, should be respected. Some jurisdictions have passed legislation that provides for substitute consent and prior treatment directions (advance directives) and physicians should be aware of the provisions within their own jurisdiction. The provincial medical colleges and the Canadian Medical Protective Association are useful resources in these matters.

Informing transfusion recipients

Whenever possible, patients (or their guardians) should be informed that they have received a red blood cell or plasma transfusion. Providing this information respects the patient's autonomy and encourages more individual responsibility for health care.

Refusal of transfusion

A competent adult is entitled to refuse or cease any treatment for any reason. Refusal occurs most often among Jehovah's Witnesses, whose religion precludes receipt of blood products. The refusal is valid under any circumstances, even when it will result in the patient's death. Note that this does not apply to children (see *Children and adolescents*, above). The physician should ensure and, if possible, record that the patient's refusal is fully informed and that the patient is aware of the consequences of his or her decision. Exploration of issues such as depression, which may affect the patient's capacity and choice, should be undertaken. Although the physician who properly advises the patient is not liable for the consequences of a refusal,[12] physicians are advised to seek second opinions and legal advice if the refusal is likely to lead to serious morbidity or death.

Recommendations regarding informed consent

1. Patients should be informed that transfusion of red blood cells, plasma or both is a possible element of the planned medical or surgical intervention and provided with information about the risks, benefits and available alternatives. **Level of evidence: N/A**
2. When feasible, the patient's consent to a transfusion of red blood cells, plasma or both should be obtained and recorded in the patient's medical chart. **Level of evidence: N/A**
3. The physician overseeing the care of the patient should be responsible for obtaining informed consent for red blood cell or plasma administration. **Level of evidence: N/A**
4. Patients should be informed that they have received a red blood cell or plasma transfusion subsequent to its administration. **Level of evidence: N/A**

Allogeneic red blood cell transfusion

The standard unit of whole blood collected consists of approximately 450 mL of blood taken into 63 mL of anticoagulant.[17] Red blood cells are prepared by removing supernatant plasma from a whole blood donation after centrifugation. The characteristics of this component vary depending on the anticoagulant–preservative solution used (Table 1). In the average adult, each unit of blood should raise hemoglobin by 10–15 g/L.[17]

Oxygen transport and the physiologic responses to anemia

The simplest method of reducing the frequency of allogeneic blood transfusion is to withhold transfusion until more severe levels of anemia are reached. However, the optimum threshold for the initiation of transfusion therapy is not yet defined and, clearly, the level of anemia permitted cannot be such that tissue oxygen delivery (DO_2) or consumption are compromised. The oxygen carrying capacity of blood is measured either indirectly by measurement of the red blood cell concentration (the hematocrit) or directly by determining hemoglobin concentration ([Hb]). Although both measures are employed in research reports, [Hb] is more commonly used in the context of clinical medicine. (In this document, where authors report hematocrit, the original value is given and an approximate [Hb] provided.)

DO_2 is the product of tissue blood flow and arterial oxygen content; at the whole body level these factors are represented by the product of cardiac output (CO) and the arterial oxygen content (CaO_2).

$$DO_2 = CO \times CaO_2$$

CaO_2 depends on [Hb] and the percentage of Hb saturated with oxygen. CO is affected by both preload (venous return) and afterload. Blood flow is determined by resistance to flow in the vascular bed and the perfusion pressure driving flow through the bed. Blood is more viscous (inherently resistant to flow) at lower flow rates. Thus, viscosity is highest in venules and lowest in the aorta. Viscosity, independent of flow rate, is primarily a function of red blood cell concentration. Reduction in the red blood cell concentration lowers blood viscosity and reduces the resistance to flow. With progressive reduction there is an incremental rise in CO.[18] There is some inconsistency in reports as to the [Hb] at which CO begins to rise. In adults, the higher CO is initially a result of enhanced preload and a decreased afterload. The augmented venous return is a result of the profound reduction in viscosity and a passive increase in blood flow in the postcapillary venules. The decrease in afterload is produced by the reduction in the viscosity component of the systemic vascular resistance. In children, the increase in CO is more dependent on increased heart rate and less on enhanced stroke volume than in adults.

Blood with a low [Hb] has decreased oxygen carrying capacity. To compensate for this and to maintain oxygen delivery, tissues may augment blood flow, either by recruiting capillaries or by increasing flow through the existing capillary network. Tissues may also increase oxygen extraction ratios (ER). Enhanced oxygen extraction may occur particularly in tissue beds that normally consume a small proportion of the available oxygen. In supply-dependent beds, such as in the heart, higher ERs occur under normal conditions.[19,20] In these beds, to preserve oxygen consumption and aerobic metabolism, regional blood flow must increase proportionally more than the increment in CO. As [Hb] decreases to 50 g/L (hematocrit 0.15), there is evidence of decreased myocardial oxygen consumption, which may be due to impairment in myocardial oxygen extraction.[21] In animals, the onset of coronary lactate production (anaerobic metabolism) occurs at a [Hb] below 35 g/L (hematocrit 0.10).[22] In a model of coronary stenosis, this anaerobic state occurs at a [Hb] of 60–70 g/L.[23–25] These values also coincide with the onset of ventricular wall motion abnormalities.[25]

Tissue oxygenation may be improved with a shift to the right of the Hb-oxygen dissociation curve (to a higher P_{50}). This can be achieved through increased red blood cell levels of 2,3-diphosphoglycerate (2,3-DPG) and decreased pH, both of which facilitate oxygen unloading in the tissues. Changes in the Hb-oxygen dissociation curve resulting from changes in red blood cell 2,3-DPG levels take 12–36 hours to occur and increase with decreasing [Hb]. Because of these adaptations, in chronic anemia a 50% decrease in oxygen carrying capacity is accompanied by only a 25% decrease in oxygen availability.[26]

The physiologic compensations for a decreased [Hb] must be sufficient to balance the lower oxygen carrying capacity and maintain tissue oxygen delivery. The optimum [Hb] is the level that allows for the greatest oxygen delivery at the lowest energy cost to the organism. In terms of whole-body oxygen delivery, Messmer concluded that the optimum [Hb] was 100 g/L (hematocrit 0.30).[27,28] As [Hb] was decreased from 150 g/L to 100 g/L, while maintaining normal circulating blood volume, reduction in viscosity was sufficient to allow increased blood flow such that systemic oxygen transport capacity increased. With further reduction in [Hb], oxygen delivery declined so that, at [Hb] about 90 g/L, tissue oxygen delivery was at or below preanemic levels.[29]

Table 1: Characteristics of red blood cell components depending on anticoagulant used during collection

Characteristic	Anticoagulant–preservative solution	
	CPDA-1	CP2D
Additive (after plasma removed)	0	100 mL AS-3 (Nutricel)
Hematocrit	0.72–0.79	0.45–0.65
Red blood cell volume	Approx. 200 mL	Approx. 200 mL
Plasma volume	Approx. 90 mL	Approx. 60 mL
Shelf life	35 days	35 days*

Note: CPA-1 = citrate phosphate dextrose adenine; CP2D = citrate phosphate double dextrose.
*Currently licensed by the Bureau of Biologics for 35 days but has the potential for 42 days shelf life. The Canadian Red Cross Society is requesting that the shelf life be extended to 42 days.

Because oxygen delivery remained relatively constant between [Hb] 90 g/L and 150 g/L, there appeared to be little rationale for transfusing red blood cells to patients with [Hb] already in this range to increase oxygen delivery. Messmer's conclusion that systemic oxygen transport was optimum at [Hb] of 100 g/L was supported by whole-body physiologic measurements and cannot be extrapolated to support conclusions regarding regional circulations. Furthermore, although Messmer's assertions are widely acknowledged and help form the basis for current transfusion strategies, they disagree with the work of other investigators. Le Merre and co-workers[30] reported that systemic oxygen transport capacity decreased with even moderate hemodilution and argued that increased tissue extraction of oxygen was the major compensating factor.

Although the mechanisms for compensation remain to be clarified, clinical experience supports Messmer's conclusions; that is, there seems to be little clinical gain in transfusing most patients whose [Hb] is in the range 90–150 g/L.[31–33] The lack of measured benefit of transfusion is supported by the work of Hébert and colleagues,[34] who in a multicentred, randomized, controlled clinical trial, evaluated the effects of a restrictive transfusion threshold ([Hb] 70–90 g/L) compared with a more liberal one (100–120 g/L) in critically ill patients developing a [Hb] of less than 90 g/L in the first 72 hours after admission to an intensive care unit (ICU). The study groups were demographically similar. The number of units of blood administered was significantly smaller for the patients with the restrictive threshold; yet there was no difference noted in ICU 30-day and 120-day mortality. Although the findings are encouraging, this was a small study and confirmation following evaluation of larger groups is required.

Messmer's work provides a basis for estimating the optimum [Hb], but the experience of Jehovah's Witness patients provides data on the lowest tolerable concentration, perhaps a more appropriate marker to justify transfusion. Viele and Weiskopf[35] reviewed 54 publications involving 134 patients with moderate to severe anemia. The overall case fatality rate was 37%, and all patients whose deaths were attributed to anemia died with [Hb] less than 50 g/L. Considering only anemia-related deaths, the case fatality rate was 27% for patients who were under 50 years of age and 53% for patients over 50 years. No patients with a [Hb] of 50–80 g/L) died because of their anemia. Although these findings may reassure clinicians that very low [Hb] is tolerated in many younger patients and some older ones, there is a selection bias in these reports. Obviously, severely anemic survivors are more frequently reported than nonsurvivors, and the risk of severe anemia may thus be understated. Furthermore, mortality is not the only endpoint to be avoided with blood transfusion; these papers provide little information about morbidity-avoidance with transfusion.

Although there is little direct clinical evidence, much of the risk posed to the patient by a low [Hb] probably relates to the ability of the heart to tolerate anemia. Carson and co-workers[36] reported a retrospective cohort study of 1958 adults (over 18 yrs of age) who underwent surgery and refused blood transfusion between 1981 and 1994. There was an increase in the risk of death associated with a lower preoperative [Hb], and this risk was enhanced by the presence of cardiovascular disease. Mortality within 30 days was 1.3% in patients with [Hb] of 120g/L and increased in a roughly linear fashion to 33.3% in patients with [Hb] less than 60 g/L. In addition, the effect of blood loss on mortality was greater in patients with a lower preoperative [Hb]. The authors concluded that a low preoperative [Hb] or substantial blood loss during surgery increases the risk of death or perioperative morbidity and that this effect is larger in patients with cardiovascular disease.

Many physiologic mechanisms compensate for acute anemia and preserve tissue oxygen delivery. However, if these compensatory mechanisms are not intact, oxygen delivery may not be preserved and organ dysfunction may result. Older patients are less tolerant of low [Hb] levels; they are less able to increase heart rate and stroke volume (and hence CO) in response to exercise.[37] In elderly patients with low [Hb] but normal blood volume, oxygen delivery is decreased as a result of failure to increase CO. Oxygen consumption is maintained by increased extraction. This finding has been reported in healthy patients, patients with medical disease excluding patients with heart disease and patients with recognized coronary artery disease.[38–40] Although chronologic age does not necessarily parallel physiologic age, and there are wide individual differences in functional capability in a population, the compensatory mechanisms that preserve oxygen delivery generally are reduced in the elderly.

The perception that the elderly are at greater risk than younger cohorts if they become anemic presumably is related, not only to their reduced physiologic compensatory mechanisms, but also to the higher incidence of coronary artery disease and the resultant reduced capacity to increase coronary artery blood flow and, perhaps, CO.[41] This may limit the degree of hemodilution that will be tolerated by these patients because increased flow is an essential compensatory mechanism. Relatively modest hemodilution plus depleted or exhausted coronary vasodilator reserve may compromise ventricular metabolism and function.[41] Electrocardiographic evidence of ischemia was observed in 22% of patients with pre-existing impaired left ventricular function who were hemodi-

luted, but was not seen in patients with normal left ventricular function.[41] This report suggests that, in the presence of moderate coronary artery stenosis, flow may not increase sufficiently to offset the loss of oxygen carrying capacity caused by hemodilution, and ischemic cardiac dysfunction may result from even a modest reduction in [Hb]. Patients with critical vessel stenosis or pre-existing left ventricular dysfunction may not tolerate hemodilution to any degree. An association has been reported between low perioperative [Hb] levels and the occurrence of myocardial ischemia and infarction.[42] Finally, Carson and co-workers[36] concluded that patients with cardiovascular disease had a much greater risk of perioperative death than patients without cardiovascular disease when their preoperative [Hb] was 100 g/L or less. Coronary artery disease likely constitutes an important factor in determining a patient's tolerance of low [Hb].

Much of the information on tolerable levels of anemia comes from research in which anemia is the predominant physiologic stressor. In clinical medicine, the concurrent presence of underlying disease states, both acute and chronic, metabolic derangements or disturbances in oxygen transport may alter the patient's tolerance of anemia. However, there is insufficient explicit information to justify conclusions and meaningful comment in these specific situations.

For clinically stable patients who are not at risk for coronary artery disease, transfusion is more likely to be beneficial when [Hb] is less than 60 g/L, but not when [Hb] is greater than 80 g/L, as long as normal blood volume is maintained and patient assessment is ongoing. Critically ill patients and those at risk for coronary artery disease are less likely to be as tolerant of low [Hb] and will likely benefit from maintenance of a higher range of [Hb] than patients not at risk.

Indices of oxygen delivery and tissue oxygenation may accurately indicate the need to transfuse red blood cells; however invasive monitoring is required to generate these indices. Thus, decisions about transfusion must often be made on the basis of available but less informative data, including patient characteristics (i.e., age, presence of heart disease), the clinical context (i.e., stable with no ongoing bleeding versus ongoing blood loss), measured vital signs and the patient's tolerance of the situation. In some situations, particularly in the perioperative period and also in critically ill, sedated and ventilated patients, medications may further mask the expected hemodynamic indices, and patient characteristics and the clinical context may have a greater role in the decision to transfuse red blood cells.

In some situations, transfusion of multiple units is appropriate — typically during resuscitation from a major hemorrhage. However, the routine transfusion of multiple units in less urgent situations appears to be common and should be re-evaluated. Instead, physicians should consider transfusing one unit at a time with assessment after each unit to avoid unnecessary exposure.

Principles specific to acute blood loss

When blood loss is acute, initial reductions in total arterial oxygen content are usually well tolerated because of compensatory increases in CO. Although determined by the rate of blood loss, the lower limit of human tolerance to acute anemia has not been established, but oxygen delivery will probably be adequate in most people with a [Hb] above 70 g/L,[2,43] assuming that oxygen delivery is not compromised by other physiologic disturbances. However this is not always a valid assumption. The effects of medications, pre-existing disease and hypothermia have been described well and must be considered when assessing an individual patient's response to acute blood loss.[43–45] Barring such other factors, tissue oxygenation appears to be maintained and anemia well tolerated at a hematocrit as low as 0.18–0.25 ([Hb] of 60–80 g/L).[46]

Measured [Hb] will frequently be misleading during acute blood loss because it depends on the rapidity and degree of blood loss and the effects of fluid resuscitation (acute hemodilution). With ongoing blood loss, by the time a [Hb] is reported (from a sample drawn earlier), the actual oxygen carrying capacity may have changed.

There is currently no evidence to support a threshold value for initiating blood transfusion in the case of acute blood loss. All recent reviews have refuted the concept of a transfusion threshold, most concluding that insufficient evidence exists to support a single hemoglobin requirement.[46,47] The decision to administer red blood cell transfusions should be determined by evaluating the rate of ongoing blood loss, evidence of end-organ compromise and the risk or presence of coronary artery disease.

Acute blood loss may occur in a variety of clinical situations. The most important clinical features are the amount of blood loss and the likelihood of continuing losses. The primary treatment goals in this setting are to restore intravascular volume, to ensure sufficient oxygen carrying capacity and to stop the blood loss as soon as possible. Management of a patient with acute blood loss should also include other measures to maximize the oxygenation of circulating blood (such as airway management, administration of oxygen and treatment of pulmonary injuries). The principles of management of hypovolemic shock are reviewed in the manual for the American College of Surgeons' advanced trauma life support course.[43]

In cases of acute hemorrhage related to elective

surgery, the availability of predeposited autologous blood units and measures to decrease blood loss (intraoperative and postoperative blood salvage, acute normovolemic hemodilution) may reduce the requirement for allogeneic blood cell transfusion (Andreas Laupacis et al. See citation on page S3).

Principles specific to chronic anemia

In determining the need for red blood cell transfusion, it is important to consider the differences between acute and chronic anemia. Acute anemia is often accompanied by hypovolemia which, at least initially, is often the major physiologic problem. The patient with chronic anemia is normovolemic or even hypervolemic. Also, in the case of chronic anemia, decisions usually need not be made rapidly; there is time to consider and discuss the role of transfusion therapy, and its benefits and risks with the patient. It is an ideal situation for involving a competent patient in the treatment plan.

Evaluating the symptoms of chronic anemia is not a simple process. In a study[48] of adult patients with iron-deficiency anemia and [Hb] of 80–120 g/L, there was no correlation between the degree of anemia and the intensity of any of the symptoms of fatigue, irritability, palpitations, dizziness, breathlessness and headache. Furthermore, treatment with iron in amounts sufficient to increase [Hb] an average of 23 g/L resulted in no greater improvement in any of the symptoms than did treatment with a placebo.

The relationship between the degree of anemia and functional status in patients with chronic renal failure was studied by the Canadian Erythropoietin Study Group.[49] In a randomized, placebo-controlled study of 118 dialysis patients, investigators examined the effect on quality of life and exercise capacity of 3 levels of anemia: mean [Hb] of 70 g/L (placebo group); mean [Hb] of 100 g/L (low-dose erythropoietin group); and mean [Hb] of 120 g/L (high-dose erythropoietin group). Quality of life, in global terms, was similar in all 3 groups. However, treated patients experienced significant improvement in symptoms (fatigue, depression, physical symptoms), although no difference was noted between the low- and high-dose treatment groups.

In general, otherwise healthy people display few symptoms or signs of anemia at rest when [Hb] is greater than 70–80 g/L, although they often show dyspnea with exertion; at 60 g/L most patients will complain of some weakness; at 30 g/L patients will complain of dyspnea at rest; and at [Hb] of 20–25 g/L congestive heart failure frequently occurs.[50] Children are amazingly tolerant of chronic anemia and may remain asymptomatic even when [Hb] is less than 50 g/L.

Before considering transfusion of red blood cells for the treatment of chronic anemia, it is essential to determine the cause of the anemia so that, where appropriate, treatment other than red blood cell transfusion may be used. Classic examples of anemias that may be severe but correctable by alternative therapies are iron-deficiency anemia in childhood and pernicious anemia in adults.

If red blood cell transfusion is considered necessary for the immediate treatment of a chronic anemia, the goal need not be to attain a normal [Hb] but rather to attain a [Hb] that will avert the danger of inadequate tissue oxygenation or cardiac failure. When red blood cell transfusion is considered for the long-term treatment of chronic anemia, treatment goals (other than to maintain a certain [Hb]) should be determined in advance and assessment of success should be done at an interval (or intervals) appropriate to the underlying condition. In this setting, the physician and the patient must consider such questions as: What symptoms and signs are caused or aggravated by the anemia? Can these symptoms and signs be alleviated by red blood cell transfusions? What is the minimum level of hemoglobin at which the patient can function satisfactorily? Do the potential benefits of red blood cell transfusion outweigh the risks (and possibly the inconveniences) for this patient? In determining the risk–benefit ratio for a given patient, such factors as lifestyle, the presence of other medical disorders, the likely duration of the anemia and the patient's overall prognosis must be considered. For example, a patient may be willing to tolerate a very limited capacity for exertion if the anemia is likely to be temporary, but not if the anemia will be permanent.

In general, the risks per unit of red blood cell transfusion are the same in any setting. However, with the presence of severe chronic anemia, transfusion may lead to congestive heart failure, particularly in the elderly. In such cases, red blood cell transfusions must be administered very slowly and, in some patients, partial exchange transfusion may be performed. The administration of many red blood cell transfusions over a prolonged period will eventually lead to iron overload.

Issues specific to red blood cell transfusion in children

Principles guiding the decision to administer red blood cell transfusions to infants over 4 months of age and children are for the most part the same as for adults. Young children have lower [Hb] than adults — from 95–115 g/L at 6 months of age to 115–125 g/L at 2 years. These lower levels are thought to be due to the higher intra-erythrocyte levels of 2,3-DPG found in children.[51]

The physiologic responses to anemia in childhood and

the [Hb] at which transfusion becomes necessary have not been well studied. Two studies in Africa attempted to identify when transfusions should be given to prevent death in children with anemia and malaria. One[52] involved 116 children under 5 years of age with mean hematocrit on admission of 0.14 ([Hb] of 47 g/L). Children were randomly chosen to receive or not receive a transfusion of whole blood. There was no difference in hospital admissions and deaths in the "no transfusion" group versus the "transfusion" group. The second was a surveillance study[53] in which data were collected over about 12 months on all children under 12 years of age (n = 2433) admitted to the pediatric ward of a Kenyan hospital. Transfusions (with whole blood) were administered according to routine practice and availability. Based on laboratory and clinical criteria, children with clinical signs of respiratory distress and [Hb] of less than 47 g/L who were transfused had a lower fatality rate than those who were not. Among children without respiratory distress there was no association between receipt of blood transfusion and death, irrespective of [Hb] on admission. Although these studies are not definitive, they do support the clinical impression that asymptomatic children without underlying cardiorespiratory disease are able to tolerate very low [Hb] (40–50 g/L) provided the anemia has developed slowly.

There are reports of successful outcomes of surgical procedures without the use of blood transfusion in the children of Jehovah's Witnesses. These procedures include open heart surgery in selected patients weighing less than 20 kg.[54,55]

For acute nonsurgical bleeding, the principles of resuscitation of a child are generally the same as for an adult. However, young infants are less able to tolerate rapid blood loss because of their limited ability to increase myocardial contractility in response to hypovolemia. Young infants rely primarily on increases in heart rate rather than contractility to increase CO. In addition, an apparently small amount of lost blood may be significant in a small child, because it may represent an important fraction of total blood volume (80–90 mL/kg). Therefore, young infants, particularly those under 6 months of age, require earlier and more vigorous volume replacement and possibly earlier red blood cell replacement (e.g., after losses of 20–25% of total blood volume versus 30–35% in the older infant and child).[56]

Pediatric patients are more likely than many adults to be long-term survivors; thus, in determining the balance between benefits and risks of transfusion, greater consideration must be given to long-term complications. For example, the transmission of viruses with long incubation periods (e.g., hepatitis C virus) and, for girls, the potential for hemolytic disease of the newborn in future pregnancies should they become alloimmunized to red blood cell antigens are considerations. Nevertheless, untreated chronic and severe anemia can lead to growth retardation in childhood.

Recommendations regarding the transfusion of red blood cells

5. A physician prescribing transfusion of red blood cells or plasma should be familiar with the indications for and the benefits and risk from the use of these fractions. **Level of evidence: N/A**
6. Documentation that supports the administration of the red blood cells or plasma should be found in the patient's chart. **Level of evidence: N/A**
7. Red blood cell transfusions should be administered primarily to prevent or alleviate symptoms, signs or morbidity due to inadequate tissue oxygen delivery (resulting from a low red blood cell mass). **Level of evidence: II**
8. There is no single value of hemoglobin concentration that justifies or requires transfusion; an evaluation of the patient's clinical situation should also be a factor in the decision. **Level of evidence: II**
9. In the setting of acute blood loss, red blood cell transfusion should not be used to expand vascular volume when oxygen carrying capacity is adequate. **Level of evidence II**
10. Anemia should not be treated with red blood cell transfusions if alternative therapies with fewer potential risks are available and appropriate. **Level of evidence: II**

Autologous blood transfusion

Autologous blood transfusion is a general term used to describe a procedure by which previously donated (or shed) blood is transfused (or re-infused) into the same donor or patient. Autologous blood can be obtained by

- predonation (predeposit) of blood
- perioperative normovolemic hemodilution (withdrawal of blood immediately before surgery, with volume replacement by crystalloid solutions) and subsequent reinfusion of the removed blood
- intraoperative blood salvage
- postoperative blood salvage.

The EWG considered only predonation.

A substantial proportion of patients who require blood are not candidates for autologous blood donation; for example, those with acute or chronic anemia; those with active infection; those requiring urgent surgery; small children; and some patients who require cancer surgery.[57,58] Use of autologous blood reduces the likeli-

hood that allogeneic blood will be used (Andreas Laupacis et al. See citation on page S3.), and thus would be expected to reduce certain risks associated with blood transfusion — for example, the risk of exposure to transmissible infections such as HIV and hepatitis C; alloimmune hemolysis; allergic reactions; immunization to foreign antigens; graft-versus-host disease; and, possibly, immunosuppression. There is conflicting evidence as to whether predonation of autologous blood reduces postoperative infection because of avoidance of transfusion-associated immunosuppression.[59,60] Also, of autologous blood transfusion does not prevent other adverse effects: septicemia from bacterial contamination;[61–64] nonhemolytic (febrile) transfusion reactions caused by plasma factors generated during blood storage; clerical or laboratory error leading to transfusion of the wrong blood unit[65]; and circulatory overload. Because these risks remain, autologous blood should not be routinely reinfused to patients in the absence of an indication.

The risks associated with allogeneic blood that can be avoided by using autologous blood are rare. Furthermore, specific risks are associated with autologous blood. The risks from predeposited autologous blood include a higher likelihood of receiving blood in the postoperative period (Andreas Laupacis et al. See citation on page S3.) and adverse events associated with blood donation, particularly in cardiac patients.[66,67] In addition, surgery may have to be rescheduled to avoid wastage of blood already collected.

There is insufficient evidence to indicate overall whether using autologous blood is more, equally or less safe than using allogeneic blood. Nevertheless, other considerations support the use of autologous blood for transfusion. First, it would theoretically prevent exposure to new infectious or other noxious agents that might contaminate the blood supply in the future. Second, there is a widespread perception among patients and health care workers that autologous blood is likely to be safer. Third, the interim report of the Commission of Inquiry on the Blood System in Canada[14] has made several recommendations in favour of wider availability and use of autologous blood. Fourth, use of autologous blood reduces demand for banked allogeneic blood and thus helps alleviate blood shortages. (Note: At present, unused autologous blood units do not meet Canadian Red Cross donor criteria and, therefore, cannot be added to the general blood supply.) Fifth, autologous donation is helpful for elective surgical patients with rare blood groups or antibodies to multiple or high-incidence alloantigens.

The cost of providing autologous blood is higher than for providing allogeneic blood.[68] Minimizing the waste of autologous units by focusing on patients who are most likely to use blood is important in improving the cost-effectiveness of autologous blood.[69,70]

A recent meta-analysis provides insight into the potential benefits and risks of a program for the predeposit of autologous blood (Table 2). This review of 6 randomized, controlled trials and 9 nonrandomized comparator-controlled studies revealed that the predeposit of autologous blood reduced the amount of allogeneic blood transfused (the odds ratio [OR] for the randomized, controlled trials was 0.17, 95% confidence interval [CI] 0.08–0.32) (Andreas Laupacis et al. See citation on page S3.). There was a direct relation between the proportion of patients transfused in the control group and the absolute benefit of predeposited autologous blood for reducing exposure to allogeneic blood (i.e., the benefit is greatest when the expected use of blood is highest). Interestingly, this meta-analysis also showed that patients who predeposit autologous blood were significantly more likely to receive any blood product (including their own) than control patients (OR 6.69, 95% CI 3.63–12.32). The authors offered 2 reasons for this observation: lower

Table 2: Advantages and disadvantages of autologous blood transfusion

Advantages	Disadvantages
Reduces exposure to allogeneic blood	Blood loss must be anticipated and a program established to allow for blood predeposit or salvage
Reduces risk of • transmissible viral infections • alloimmune hemolysis • allergic reactions • immunization to foreign antigens • graft-versus-host disease • transfusion-induced immunosuppression	Does not prevent adverse effects such as • septicemia from bacterially contaminated unit • nonhemolytic transfusion reactions caused by plasma factors generated during blood storage • clerical or laboratory error leading to transfusion of the wrong unit • circulatory overload
Averts exposure to new or unknown infectious or other noxious agents that might contaminate the blood supply	Increased likelihood of receiving blood in the postoperative period Cost is higher than with existing allogeneic program
Reduces demand for banked allogeneic blood, thus can help alleviate blood shortages	Adds risk for adverse events associated with blood donation
Satisfies public demand and patients' desires that their own blood be used.	Scheduling of surgery may have to be altered to permit autologous blood donation or to avoid wasting blood already collected

preoperative [Hb] and a more liberal transfusion policy for patients who had predeposited their own blood. This analysis suggests that patients who predeposit autologous blood may be at greater risk for certain complications associated with transfusion (e.g., septicemia from contaminated blood units, transfusion of the wrong blood unit due to laboratory or clerical error).

Recommendations regarding the use of autologous blood

11. Predonation of autologous blood should be considered a therapeutic option for adolescents and adults undergoing elective surgery in which the likelihood of transfusion is substantial (i.e., 10% or more).
Level of evidence: III
12. Indications for the transfusion of autologous blood should be the same as those for allogeneic blood.
Level of evidence: III

Plasma transfusion

Plasma for transfusion is prepared by centrifuging anticoagulated whole blood from a single donor followed by storage at or below –18°C. Larger volumes of plasma may be collected using automated apheresis units and similarly stored. A typical unit of plasma has a volume of 200–250 mL if obtained from a whole blood donation or 400–600 mL when obtained by plasmapheresis. Plasma frozen within 8 hours of donation contains at least 0.70 U/mL of factor VIII:C and is referred to as fresh-frozen plasma (FFP). In plasma frozen 8 to 72 hours after collection the concentration of coagulation factors V and VIII:C may be reduced as much as 15%; it is usually referred to as frozen plasma (FP). In Canada, there is some regional variation as to which plasma products (FP and FFP) are available. However, in most therapeutic applications, there is little reason to choose one over the other, and the generic term plasma is used in this document. Cryosupernatant or cryo-poor plasma is the supernatant fluid obtained after preparation of a factor-VIII:C cryoprecipitate from plasma. It contains greatly reduced concentrations of factors V and VIII:C and other large-molecular-weight proteins such as fibrinogen, fibronectin and von Willebrand factor.

Excluding viruses such as human cytomegalovirus (CMV) and human T-cell lymphotropic virus type II (HTLV-II), which are transmitted only by infected leukocytes in cellular blood products, plasma carries the same risk of viral transmission per donor exposure as that of red blood cells.[71] Virus-inactivated purified or recombinant concentrates of many physiologically important plasma proteins are now commercially available. These products have been shown to be safer and more effective than plasma in correcting specific protein or coagulation factor deficiencies. Hence, the consensus in published guidelines[2,5,72–75] is that plasma transfusion should be avoided when a safer and more effective product can be used to achieve the same therapeutic goal (Table 3). This applies specifically to

- intravascular volume expansion or repletion where crystalloids, synthetic colloids or purified human albumin solutions are preferred (including therapeutic plasmapheresis where plasma should not be used as routine replacement fluid)
- the correction of hypoalbuminemia or protein malnutrition, where purified human albumin or synthetic amino acid solutions are preferred
- the correction of hypogammaglobulinemia, where purified human immunoglobulin concentrates are preferred
- the treatment of hemophilia and von Willebrand's disease where desmopressin (DDAVP) or existing virus-free factor concentrates are preferred
- the treatment of any other isolated congenital procoagulant or anticoagulant factor deficiency, where virus-inactivated or recombinant factor concentrates are preferred if they exist.

Table 3: Alternatives to plasma

Type of product	Product
Purified human plasma-derived concentrates*	Purified human albumin* Purified human immunoglobulin (IVIg)* Purified human fibrinogen* Purified human factor VII* Purified human factor VIII:C* Purified human von Willebrand factor* Partly purified prothrombin complex (FEIBA)* Partly purified human factor IX* Highly purified human factor IX* Purified human factor XI* Purified human factor XIII* Purified Human protein C* Purified human antithrombin III* Purified human C1 esterase inhibitor* Fibrin glue (Tisseel)
Purified animal plasma-derived concentrates*	Purified porcine factor VIII:C
Recombinant proteins	Human factor VIII:C* Human factor VIIa
Synthetic replacement molecules	Amino acids (Aminosyn) Pentastarch (Pentaspan)*
Pharmacologic agents	Desmopressin (DDAVP) Aminocaproic acid (Amicar) Tranexamic acid (Cyclokapron) Aprotinin (Trasylol)

*Available from the Canadian Red Cross Society according to a list distributed September 1996, subject to modifications as new preoducts become available or existing products are deleted.

In the past, plasma has been used for life-threatening complications of hereditary angioneurotic edema due to deficiency of C1 esterase inhibitor. A concentrate in which viruses have been inactivated now also exists for the treatment of this disorder.[76]

Plasma transfusion is often used to prevent or stop bleeding in patients with acquired multiple coagulation factor deficiencies, which may occur in the conditions described below.

Vitamin K deficiency and warfarin effect

When severe bleeding occurs in patients with laboratory evidence of a deficiency of vitamin K-dependent factor (usually a prolonged prothrombin time [PT] or increased international normalized ratio [INR]) or is expected to occur from an emergency surgery or invasive procedure, correction of the hemostatic defect may be obtained by administration of plasma. There is evidence that prothrombin complex concentrates can achieve a more rapid or complete reversal of oral anticoagulation than plasma alone.[77] Accordingly, some physicians advocate such concentrates as primary therapy for patients with life or limb-threatening hemorrhagic complications associated with warfarin therapy. In addition, parenteral administration of vitamin K is advised in these circumstances. In nonurgent situations, parenteral administration of synthetic vitamin K alone is usually recommended but may require up to 6 hours to bring about significant correction of the hemostatic defect.[78]

Severe liver disease

Elevated PT, INR or partial thromboplastin time (aPTT) in patients with liver disease is a cause for concern when surgery or percutaneous liver biopsy must be undertaken. Studies[79,80] attempting to demonstrate the efficacy of plasma have shown that its ability to correct abnormal coagulation in these patients is often poor or quite variable. Although it is generally agreed that people who are not bleeding or do not face an invasive procedure should not receive plasma merely to correct abnormal coagulation tests, guidelines have recommended the use of plasma in bleeding patients with liver disease.[2,73] The addition of partly purified prothrombin complex concentrates has been shown to be more effective than plasma alone,[80] but the use of these products as the first-line therapy is usually not recommended because of their associated risk of causing thrombosis and disseminated intravascular coagulation (DIC), particularly in liver disease. Although a threshold PT, INR or aPTT value of 1.5 times normal has been suggested in other guidelines to indicate a need for plasma administration before hemostatic challenges, a clear correlation has not been demonstrated between the occurrence of bleeding and the actual results of coagulation tests obtained prior to surgery or liver biopsy.[81,82]

Three retrospective studies[81,83,84] found that patients with liver disease and mild coagulopathy did not have excess bleeding with invasive procedures (liver biopsy, paracentesis, thoracentesis). These studies reported PT, rather than INR, values. The relation between PT and INR is

$$INR = (PT_{patient}/PT_{mean})^{ISI}$$

where $PT_{patient}$ is the patient's PT, PT_{mean} is the mean of the normal range for PT (measured in a laboratory) and ISI (international sensitivity index) is the measure of the responsiveness of the thromboplastin used to measure the PT to a reduction in vitamin-K dependent coagulation factors. The higher the ISI, the less responsive the thromboplastin and the smaller the increase in PT when testing plasma from patients receiving oral anticoagulants. Using relatively insensitive rabbit thromboplastins (ISI values about 2.0[81,83] and 2.5[84]), these studies reported no increased bleeding in patients whose PTs were as high as 1.5 times the mean of the normal range, corresponding to INR values of approximately 2.2 and 2.7 respectively (i.e., $1.5^{2.0}$ and $1.5^{2.5}$).

In formulating our recommendation, we chose the lower value (2.2) as a preliminary basis. However, it should be noted that although INR values are comparable among different thromboplastins when used to test patients receiving oral anticoagulants, they are not comparable in patients with liver disease.[85] Moreover, in Canada, most laboratories use relatively sensitive (low ISI) thromboplastins. To determine an appropriate INR recommendation for patients with liver disease, we took into account a Canadian study [85] that compared INR values using different thromboplastins for patients with liver disease. It suggested that for patients with liver disease, an INR of 2.2 derived using a rabbit thromboplastin corresponded to an INR of 2.0 derived using a human placental thomboplastin (Thromborel S [Behring Diagnostics, Kanata, Ont.; ISI about 1.09], widely used in Canada) and to an INR of 1.8 obtained using a recombinant human thromboplastin (Innovin [Dade Diagnostics, Mississauga, Ont.; ISI about 0.86]). Therefore, we adopted a value of 2.0 as the threshold INR in the final formulation of our recommendation for patients with liver disease who will undergo certain invasive procedures (see recommendation 13b).

Current evidence neither proves nor disproves the efficacy of plasma transfusion in preventing bleeding during surgery or liver biopsy in patients with liver disease. Finally, it should be recognized that the coagulopathy of liver disease is often complex and may include specific

defects that are not reflected by the INR value alone (i.e., coexisting thrombocytopenia or dysfibrinogenemia).

Disseminated intravascular coagulation

Acute DIC is characterized by the abnormal consumption of coagulation factors and platelets and may lead to thrombocytopenia, hypofibrinogenemia and increased PT, INR or aPTT with uncontrollable bleeding from wound and puncture sites. Retrospective and uncontrolled evidence suggests that the transfusion of plasma, along with other blood components, may be useful in limiting hemorrhage, provided aggressive measures are simultaneously undertaken to overcome the triggering disease.[85,86] Plasma transfusion is generally not recommended in the absence of bleeding or in chronic DIC, where it is believed to be ineffective.[5]

Massive transfusion

Massive blood transfusion is defined as the transfusion of more than 10 units of packed red blood cells in adults or the replacement of more than 1 blood volume in 24 hours. The degree and rapidity of blood loss necessitating massive transfusion can be markedly variable; the requirement for blood components and complications of massive transfusion are more likely with greater and more rapid blood loss. Massive blood transfusion may be associated with a number of complications that are usually related to the underlying condition as well as to the large volumes of crystalloid and blood components administered. Some of the adverse effects of massive transfusion may be ameliorated by using blood warming devices and filters and by closely monitoring the patient using clinical, laboratory and hemodynamic measurements.[43,44,46,87]

Abnormal hemostasis can occur in association with massive transfusion.[88–90] A reduction in platelet count after transfusion may occur with the decrease proportional to the number of units of blood transfused. Thrombocytopenia is an important factor linked with microvascular bleeding in this setting. In addition, coagulation factors in the recipient may be both consumed and diluted as a result of the underlying process and the resuscitation, resulting in coagulopathy.[91] Abnormal tests of coagulation are common in this setting, but unless they are more than 1.5 times the normal, they are not likely to be associated with microvascular bleeding.[92] However, most authors have noted that, as coagulation measures become more abnormal, the occurrence of microvascular bleeding is more likely.[92,93]

Past recommendations advocated routine transfusion of plasma (i.e., administer 2 units of plasma for every 5 units of red blood cells transfused) to reduce the risk of abnormal bleeding due to factor depletion during massive transfusion.[94] However, there is no evidence to support the routine or prophylactic administration of plasma in this scenario.[88,94] Several groups[90,94] found that prophylactic administration of plasma did not reduce the incidence of hemostatic disorders following massive transfusion.

Cardiopulmonary bypass

Open heart surgery using cardiopulmonary bypass (CPB) is frequently complicated by postoperative bleeding.[95,96] Approximately 3–5% of patients undergo a second operation for excessive bleeding that, at least half the time, is caused by inadequate surgical hemostasis; the remainder are presumed to be the result of a poorly defined defect in hemostasis.[95] Acquired platelet dysfunction has historically been considered the major hemostatic defect following CPB.[96] It is now also recognized that despite the use of high doses of heparin, there is progressive activation of the coagulation pathway during CPB, as shown by markers of thrombin generation, and concurrent activation of the fibrinolytic system.[97–99] Several randomized, double-blind clinical trials have shown that prophylactic use of antifibrinolytic agents, such as aprotinin,[100–102] ε-aminocaproic acid[103] or tranexamic acid,[104] significantly reduces bleeding in adults undergoing heart surgery. There is some evidence that these agents can also be effective for patients who bleed during the postoperative period.[105,106]

Despite adequate protamine reversal of heparin after surgery involving CPB, routine coagulation tests (INR, aPTT, thrombin clotting times) usually show above-normal values, primarily because of hemodilution. These abnormal values are commonly used to justify giving plasma to patients who are bleeding following cardiac surgery; unfortunately, there is no correlation between the abnormal values and clinical bleeding.[106] Moreover, the concentration of coagulation factors is generally thought to be adequate for hemostasis,[95,106,107] and are not raised significantly by plasma transfusion.[106] (These routine coagulation tests do not reflect activation of the fibrinolytic system, which occurs to a variable extent among post-CPB patients.[108]) No studies indicate that prophylactic or therapeutic plasma administration improves hemostasis after CPB. Martinowitz and colleagues[109] randomly selected 40 post-CPB patients to receive either the plasma or cell fraction of whole blood; the cell fraction led to higher platelet counts and a decrease in bleeding time, whereas the plasma fraction did not cause any improvement. Evidence[110] suggests, but has not been established in comparative clinical trials

that antifibrinolytic agents such as ε-aminocaproic acid, rather than plasma, are reasonable first-line therapy for nonsurgical bleeding after CPB.

Thrombotic thrombocytopenic purpura

The fatal course of thrombotic thrombocytopenic purpura (TTP) has been dramatically altered since the first report of the empirical use of plasma in a small series of patients in 1977.[111] Other uncontrolled studies have confirmed the benefit of plasma therapy in TTP and the closely related adult hemolytic–uremic syndrome. Two well-designed prospective, randomized studies[112,113] have shown that plasma exchange is better than plasma infusion in the treatment of TTP. Why plasma works in TTP is not known; however, large multimers of von Willebrand factor are known to contribute to the pathogenesis of TTP.[114,115] Unlike plasma, cryosupernatant is devoid of any von Willebrand factor multimers and is effective treatment in patients unresponsive to standard plasma therapy.[116,117]

Issues specific to plasma transfusion in children

Although very few studies address the use of plasma in childhood, experts generally recommend applying the same principles as for adults to guide transfusion decisions for children. This approach seems reasonable for children 6 or more months old because, by 6 months, the concentration of coagulation factors and natural inhibitors of coagulation generally approach adult levels.[118] Infants under 6 months of age have relatively lower levels of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX), the 4 contact factors and the vitamin K-dependent inhibitors of coagulation.[118] (PT and aPTT values are correspondingly greater.[118]) Thus, these factors likely are more rapidly depleted in situations such as acute hemorrhage or DIC, and it may be reasonable to administer plasma to infants less than 6 months old relatively sooner than for older children and adults. Where feasible, transfusion decisions should be guided both by the clinical situation and appropriate laboratory monitoring, although the results of coagulation tests may be more difficult to interpret in young infants.

Plasma has long been used to treat congenital deficiencies of hemostatic or anticoagulant proteins; however, more appropriate alternatives now exist for most disorders and, as new treatments are rapidly becoming available, recommendations for treatment are changing. Physicians with special expertise in pediatric hemostasis or thrombosis should supervise the care of children with these disorders. The available alternatives to plasma include:

- specific factor concentrates, recombinant or derived from human plasma
- factor concentrates, containing multiple coagulation factors (e.g., prothrombin complex concentrates for the treatment of FII or FX deficiencies)
- other medical treatments such as synthetic desmopressin (DDAVP) for the most common form of von Willebrand disease (Table 3).

Treatment with plasma may occasionally be necessary for deficiencies for which an alternative does not exist. Plasma has also been used to treat severe thrombotic complications in patients with congenital deficiencies of the anticoagulant proteins antithrombin III and protein C, but has now been replaced by diverse protein concentrates.

Observational reports and 2 randomized trials[119,120] have addressed the role of plasma in treatment of hemolytic–uremic syndrome (HUS) in childhood. Experts have reached consensus that plasma is not indicated for classic childhood HUS, i.e., the syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure following diarrhea associated with enterohemorragic *E. coli* infection. HUS and TTP may be indistinguishable pathologically, and the clinical manifestations of HUS occasionally approach those of TTP. In the absence of definitive studies, and in light of the adult TTP studies,[112,113] plasma exchange seems a reasonable consideration in treating children with unusually complicated HUS, particularly those with neurologic complications.

Recommendations regarding plasma transfusion

13. Plasma transfusion should be considered for patients with acquired multiple coagulation-factor deficiencies under the following circumstances.
    a. Plasma is recommended when serious bleeding has occurred or when preparing for an emergency surgical or invasive procedures in patients with vitamin K deficiency or on warfarin therapy with significantly increased PT, INR or aPTT.
    Level of evidence: III
    b. Plasma is recommended when there is actual bleeding in patients with liver disease and increased PT, INR or aPTT. Plasma may be administered to prepare for surgery or liver biopsy when the results of PT, INR, aPTT or other appropriate coagulation assay are deemed sufficiently abnormal. Prophylactic plasma transfusion is not indicated for certain invasive procedures (e.g., percutaneous liver biopsy, paracentesis, thoracentesis) in patients with liver disease if their INR is 2.0 or less.
    Level of evidence: II

c. Plasma is recommended in patients with acute disseminated intravascular coagulation with active bleeding associated with increased PT, INR or aPTT, provided that the triggering condition can also be treated effectively. **Level of evidence: II**
d. Plasma should be administered in the context of massive transfusion (more than 1 blood volume) if there is microvascular bleeding associated with a significantly increased PT, INR or aPTT. If PT, INR or aPTT cannot be measured quickly, plasma may be transfused in an attempt to stop diffuse nonsurgical bleeding. **Level of evidence: II**

14. Plasma should be used in the treatment of TTP or adult HUS, followed as soon as possible by daily plasmapheresis with either cryosupernatant or plasma as replacement fluid. Plasma transfusion or exchange is not recommended in the classic form of pediatric HUS. **Level of evidence: I**
15. Plasma should be used in patients with acquired deficiencies of a single coagulation factor only when DDAVP or appropriate factor concentrates are ineffective or unavailable. Plasma should be used in these patients only when bleeding has occurred or is reasonably expected to occur from surgery or other invasive procedures. Plasma may be used depending on the specific factor involved. **Level of evidence: III**

The risks of blood transfusion

The noninfectious risks

Physicians generally have better access to information on the noninfectious risks of blood transfusion than to that on the infectious risks. Therefore, noninfectious risks will be covered only briefly (Table 4).

Most acute hemolytic reactions due to ABO incompatibility can be avoided by appropriate testing before transfusion and use of procedures to prevent errors. Of 158 transfusion-related fatalities due to acute hemolysis reported to the US Federal Drug Administration in

Table 4: Summary of the nature and frequency of noninfectious risks associated with red blood cell and plasma transfusion

Complication	Usual cause	Frequency
Acute hemolytic reaction[121,122,123]	ABO incompatability	1 per 25 000 RBC units
Delayed hemolytic reaction[122,123–126]	Hemolysis due to minor blood group incompatability	1 per 2500–9000 RBC units
RBC alloimmunization[127]	Recipient antibody response to donor antigen	About 8% of patients transfused with RBCs
Nonimmune hemolytic reaction[122,128]	Physical or chemical degradation of RBCs (freezing, heating or addition of a hemolytic drug or solution)	Unknown
Febrile, nonhemolytic reaction or chills without fever[122,123,129]	Recipient antibody to donor WBC or platelet antigen or accumulation of cytokines in blood units during storage or both	1 per 100 RBC units
Anaphylaxis[122,123,128]	Complement activation	1 per 20 000–50 000 units (RBC or plasma)
Urticarial reactions[122,123]	Antibody-mediated response to donor plasma proteins	1 per 100–300 plasma transfusions (probably similar with RBC transfusions)
Transfusion-related acute lung injury[122,123]	Complement-mediated pulmonary edema	Unknown
Graft-versus-host disease[79,130,123,131,132]	Engraftment of immunocompetent donor lymphocytes in host	Unknown
Postransfusion purpura[122,133,134]	Recipient develops antibodies against donor and recipient platelets	Unknown
Passive alloimmune thrombocytopenia[135,136]	Donor blood contains platelet-specific alloantibody that results in abrupt thrombocytopenia in the recipient	Rare
Circulatory overload[122,131]	Excess intravascular volume	1% of transfused patients
Hypothermia, coagulopathy, acid–base disturbances, hypocalcemia, electrolyte abnormalities and citrate toxicity associated with massive transfusion[88,90,94,137–140]	Loss, consumption or dilution of blood elements	Related to volume transfused, unlikely to be seen when < 1.5 blood volumes replaced
Iron overload	Chronic RBC transfusion therapy (each unit contains 200 mg of iron)	Variable, according to number of RBC units transfused; begins after the tranfusion of > 20 RBC units

1976–85, at least 86% were the result of process errors.[141]

In an analysis of fatal and nonfatal blood transfusion errors (transfusion of blood to other than the intended recipient or release of blood of an incorrect group) reported to the New York State Health Department from January 1990 to October 1991, 22% of errors occurred in phlebotomy and ordering, 32% within the blood bank and 46% during transfusion administration.[121] The authors estimated a transfusion error rate of 1 in 12 000 transfusions and the death rate due to transfusion error was 1 in 600 000 units transfused. Further discussion of these potential adverse events is beyond the scope of this document; however, it is important to remember that several complications, in addition to acute hemolysis, may be fatal: delayed hemolysis, anaphylaxis, transfusion-related acute lung injury, graft-versus-host disease, post-transfusion purpura and iron overload. The interested reader is referred to recent excellent references.[122,141]

Furthermore, recent studies in animals and humans suggest that blood transfusions may cause immunosuppression.[142,143]

The infectious risks

The infectious risks described in this section apply only to nonfractionated blood components. Human blood can never be guaranteed to be completely free from infectious agents. However, risks change constantly over time, and the prevalence of the known infectious agents in collected blood has been decreasing as a result of more stringent donor-selection requirements and improved laboratory testing procedures.

The most reliable sources of data on the risk of infectious diseases related to blood transfusion are large, multicentre, prospective studies measuring seroconversion rates among repeat blood donors and the number of acquired infections in a large cohort of red-blood-cell recipients. There is relatively little information about infectious risks from blood collected in Canada; therefore, we have relied largely on data from the United States. The risks in Canada may be smaller because of a lower incidence of some blood-transmissible viruses in our donor population.[144]

When obtaining informed consent for blood transfusion, physicians may find that a comparison of the residual risks of infection from transfusion with the risks of death from various causes may be useful (Table 5). Similarly, estimates of risks related to the planned interventions (i.e., major cardiovascular surgery, general anesthesia) may help to put the risk of transfusion in perspective. Commenting on a report of transfusion-transmitted viral infections,[145] Holland[146] states, "Today, the serious risks from the blood components given to patients in transfusion are smaller than those from the underlying disease or the primary therapy."

Although responsibility for providing information to health professionals about the current risks of infection associated with transfusion of blood components probably lies with the blood collection and distribution agency, a hospital transfusion committee or equivalent body should assist in disseminating this information to health professionals and patients.

Viral contamination

Viral contamination of blood can occur only if the donor has viremia when the blood was being collected. In Canada, all units of collected blood are tested for serologic evidence of infection with human immunodeficiency viruses types 1 and 2 (HIV-1 and HIV-2), human T-cell lymphotropic virus type I (HTLV-I), hepatitis B virus (HBV) and hepatitis C virus (HCV). The HTLV-I assay will also detect most infections caused by HTLV-II.[150] The residual risk of transfusion-associated infection (the likelihood of a screening test failing to identify the blood as infected) with one of the above viruses can be determined based on estimates of the number of donors giving blood during the infectious "window." The infectious window extends from a few days after the virus infects a

Table 5: Risk of selected causes of death in Canada and the United States

Cause of death	Risk in Canada (1994)[147]	Risk in United States
All causes, infants <1 yr	1:159 live births	
Motor vehicle accident, 15–19 year olds	1:4 763*	
Motor vehicle accident, all ages	1:9 594*	
Accidental fall	1:12 463*	1:20 000[148]*
Childbirth	1:27 508 live births	
Hit by a car while walking		1:40 000[148]*
Drowning	1:91 985*	1:50 000[148]*
Fire	1:97 830*	1:50 000[148]*
General anesthesia during surgery		1:65 000 (1987)[149]
Airplane crash	1:471 795*	1:250 000[148]*

*Annual risk.

person, during which there is rapid viral multiplication, until the earliest time that the screening test can detect its presence; if blood is collected during this period, it is presumed to be infectious to others through transfusion. The Retrovirus Epidemiology Donor Study (REDS),[145] in the United States, of approximately 590 000 repeat donors who made 2.3 million donations from January 1991 to December 1993 has provided the following estimates of the chance of a unit of virus-contaminated blood remaining undetected: HIV, 1 in 676 000; HTLV (I and II), 1 in 641 000; HCV, 1 in 103 000; and HBV, 1 in 63 000.

The original HIV estimate of 1 in 493 000 in the REDS[145] was based on current generation antibody tests, but did not include HIV-1 p24 antigen testing, which was introduced into routine blood donor screening in Canada and the United States in March 1996. The p24 antigen test was calculated to reduce the HIV window by 27.3% to about 19 days, which lessens the risk of an undetected but contaminated unit entering the supply to about 1 in 676 000 units. The REDS estimate is close to the upper limit of a range of 1 in 450 000 to 660 000 units reported in a study from the US Centers for Disease Control and Prevention and the American Red Cross.[151] From a study conducted between April 1989 and March 1993, Remis and co-workers[144] estimated an HIV risk of 1 in 913 000 units (95% CI, 1 in 507 000 to 1 in 2 050 000) for blood collected in Canada.

The REDS[145] risk estimate for HBV infection of 1 in 63 000 is appreciably higher than the 1 in 200 000 cited by Dodd[152]; the lower rate was based on earlier information provided by the US Public Health Service.[153]

As many as 35% to 50% of Canadian blood donors test seropositive for CMV.[154] Risk of serious outcome from transfusion-transmitted CMV infection is largely restricted to infants with very low birth weight (less than 1200 g); immunocompromised hosts, especially patients receiving bone-marrow transplants; and seronegative women in early stages of pregnancy where there is a risk of infection of the fetus. Recipients of solid-organ transplants, who received blood products not screened to eliminate units collected from CMV-positive donors, appeared to have little increased risk of CMV infection.[154] The Canadian Red Cross blood centres have identified a group of CMV-seronegative blood donors who can supply blood components for at-risk patients on request. CMV is transmitted only by infected leukocytes; therefore, techniques that reduce the number of leukocytes in the transfused product, including use of a leukoreduction blood filter, will reduce the risk of CMV infection.[155] Units of very fresh blood components carry a higher risk of CMV infection than products stored for several days.[156]

Hepatitis G virus (HGV) is considered to be the same virus as hepatitis GB virus, type C (HGBV-C), previously derived from another source. HGV RNA has been detected by polymerase chain reaction technology in 1% to 2% of volunteer blood donors in the United States. The virus is transmitted parenterally and has been found in people who have received a transfusion. Many people with serologic evidence of HGV are also infected with HCV and would be excluded as donors by laboratory assays for the latter. Although HGV infection may result in a chronic carrier state, there is no conclusive evidence that HGV causes acute or chronic hepatitis.[130] Reports of a causal association between HGV infection and aplastic anemia in 2 patients have been challenged by Kao and colleagues,[157] and the possible etiologic role of some strains of the virus in a few cases of fulminant hepatitis requires further clarification.[158] Large-scale epidemiologic studies to define the epidemiology and natural history of HGV infection must await development of new laboratory technology.[130]

Infections caused by contamination of blood components with other organisms such as hepatitis A virus and parvovirus B19, for which blood donors are not serologically screened, have been documented but estimates of rates of transfusion-associated infections are not available. The risk of serious clinical consequences of parvovirus B19 infection is greatest for patients with anemia that results in increased red blood cell production (e.g., sickle-cell disease) and possible development of transient aplastic crisis; for people with immunodeficiencies who may develop severe, chronic anemia; and for nonimmune pregnant women, in whom the outcome may be intrauterine death associated with hydrops fetalis. The risk of fetal death is less than 10% after proven maternal infection in the first half of pregnancy and may be negligible in the second half. Congenital anomalies have not been reported among newborn infants in association with parvovirus B19 infection.[159]

Bacterial contamination

Bacterial contamination of blood donor products may result from exposure to skin bacteria introduced through venipuncture when blood collection is started; use of blood collection and administration apparatus contaminated at source by the manufacturer; manipulation of the blood product by blood bank or hospital staff administering the transfusion; or by bacteremia, usually asymptomatic, in the donor at the time of blood collection (e.g., *Yersinia enterocolitica*).

The number of contaminating bacteria increases with the duration of storage of red blood cells or plasma before transfusion, thus increasing the possibility of clinical signs of infection in the recipient. Storage at room temperature enhances the growth of most bacterial

pathogens, but *Yersinia* multiplies readily at storage temperatures as low as 4°C.

Clinically significant bacterial contamination of red blood cells is less than 1 in a million units transfused.[160] The risk of death from bacterial sepsis has been estimated at 1 in 9 million units of red blood cells transfused.[161] Bacterial contamination of blood components accounted for 16% of transfusion-associated fatalities reported in the United States between 1986 and 1991; 28% of these were associated with transfusion of red blood cells. The risk of bacterial contamination is not reduced by the use of autologous blood transfusion.[162]

Transmission of syphilis by transfusion in Canada has been virtually eliminated by careful donor selection and serologic testing of each unit for markers of syphilis infection.

Parasitic contamination

Parasitic contamination of blood can occur only if the donor has a parasitemia, usually asymptomatic, at the time of blood collection. Donor selection criteria based on a history of recent travel to, or former residence in, endemic areas greatly reduce the possibility of collecting blood from those capable of transmitting malaria, Chagas' disease or leishmaniasis. Reported cases of transfusion-associated Chagas' disease are extremely rare in the United States and Canada. Transfusion-associated cases of malaria have occurred in recent years in Canada, and the residual risk of receiving a unit of red blood cell concentrate contaminated with malaria parasites is estimated at 1 in 400 000 units (Anthony Giulivi, MD, FRCPC, Canadian Red Cross Society, Ottawa: personal communication, 1996).

Creutzfeldt-Jakob disease

This rapidly progressive, fatal, degenerative neurologic disease is believed to be caused by an infectious protein agent called a prion. People considered to be at risk of Creutzfeldt-Jakob disease (CJD) as a result of past corneal or dura mater grafts, injections with growth hormone or gonadotropins derived from human brain extracts or having a history of CJD in a first-degree blood relative are permanently excluded from blood donation. Blood components and plasma derivatives from a person subsequently found to be at risk of CJD or subsequently diagnosed to have CJD are immediately withdrawn from further distribution. These precautions have been undertaken even though a case of transfusion-related CJD has never been confirmed in humans.[163]

A definite history of blood transfusion was found in 16 of 202 patients with CJD; this rate was similar to that in a matched control group.[164] An analysis of multiple-cause-of-death mortality data for 1979–94 in the United States revealed 3642 death certificates on which CJD was listed as a cause of death; none listed thalassemia, sickle-cell disease or hemophilia — diseases associated with high exposure to blood products. A 1995 US study uncovered no hemophilia patients with CJD.[165] The growing epidemiologic data in the United States strengthen the conclusion that the risk, if any, for transmission of CJD by blood products is extremely small and, at present, appropriately regarded as theoretical.[165] The Laboratory Centre for Disease Control, Health Canada, has launched an active surveillance program of CJD and is undertaking extensive epidemiologic studies to monitor any possible relation between transfusion and CJD.

Recommendations regarding the infectious risks of blood and plasma

16. Current, accurate information pertaining to the infectious risks of red blood cells and plasma should be accessible to physicians, other health care providers and consumers. **Level of evidence: N/A**
17. Local committees responsible for blood transfusions for an institution or a regional health authority should ensure that accurate information about the infectious risks of blood transfusion are disseminated to health care providers. **Level of evidence: N/A**

Addendum: Alternatives to allogeneic transfusions in surgical settings

Although not part of the EWG's mandate, this topic warrants a brief review. Several strategies are employed or advocated to reduce the requirement for allogeneic blood transfusion. Most of these focus on the perioperative period, and supplement surgical hemostatic techniques promoted to minimize shed blood. They can be broadly divided into 3 categories:

- creation of sources of autologous blood to be administered in the perioperative period;
- substitution of allogeneic blood with nonblood alternatives (crystalloids, colloids, oxygen-carrying solutions);
- use of pharmacologic agents to reduce blood loss.

The value of these strategies is limited by the paucity of sufficiently large randomized, controlled trials. Furthermore, most studies of pharmacologic agents focus on cardiac surgery and have limited applicability to general surgery.

Strategies to create sources of autologous blood include autologous predeposit, which has been reviewed elsewhere in this document, normovolemic hemodilu-

tion and perioperative cell salvage. Normovolemic hemodilution (NVH) has been advocated for decades.[166] The principle is simple: blood is drawn from the patient and replaced with colloid and crystalloid combinations to maintain intravascular volume. When indicated, the collected blood is transfused back to the patient. Diluting the circulating volume reduces the number of red blood cells lost per unit volume of blood shed[166] thereby reducing the need for allogeneic blood.

There is little evidence that the strategy is effective in many current applications.[167] Goodnough and colleagues[168] used NVH in patients undergoing radical prostate surgery. One litre of blood was withdrawn before the start of surgery. The net benefit was estimated to be 95 mL (range 25–204 mL) of red blood cell volume saved, that is, less than 10% of the volume lost perioperatively. Mathematical modeling of NVH suggests that the allogeneic blood-sparing benefit is more likely to be clinically relevant when more than 1 L of blood is withdrawn before surgical blood loss occurs.[167] Modeling consistently finds a ratio of 4–5 units withdrawn for each unit of allogeneic blood saved.[167,169,170] Although greater degrees of hemodilution are more sparing, the volume of blood that must be removed to achieve the necessary hemodilution is rarely achieved.[168] Furthermore, the surgical subpopulations that would tolerate such aggressive hemodilution have not been well defined.[45]

Perioperative salvage and retransfusion of washed or unwashed shed blood is being increasingly promoted to reduce allogeneic blood requirements. The underlying principle is simple: shed blood is collected and returned to the patient, either washed or unwashed. The equipment and process are expensive and are warranted primarily when major hemorrhage is expected. With smaller shed volumes, the acquisition cost per unit is high, and there is generally no indication to return the small volumes collected to the patient. Existing programs are being reviewed and restructured to accommodate these facts.

Perioperative administration of a number of medications has been advocated to reduce allogeneic blood needs. A large proportion of the published trials are small; however, meta-analysis of these studies has allowed some conclusions to be drawn.[171]

Aprotinin attenuates fibrinolysis, thereby diminishing clot degradation, and helps preserve platelet function after CPB. It has been used predominantly in patients undergoing cardiac surgery with CPB and been found to decrease intraoperative and postoperative blood loss and reduce the number of transfusion events, volumes transfused and use of other blood components. Because of its prothrombotic activities, concern has been expressed about the potential for increased coronary artery graft occlusion and perioperative myocardial infarction in treated patients. No convincing evidence has been presented to justify these concerns or to allay them.

Tranexamic acid and ε-aminocaproic acid inhibit fibrinolysis. Again, their use has been predominantly assessed in cardiac surgery populations. Both effectively decrease blood loss and volumes of blood transfused.[171]

Desmopressin (DDAVP) stimulates the release of von Willebrand factor and factor VIII:C from vascular endothelium, enhancing platelet–subendothelial interaction. However, meta-analysis of available evidence has failed to demonstrate a benefit with respect to reducing surgical blood losses.[171]

Recombinant human erythropoietin has recently been approved for perioperative use. It enhances erythropoiesis in both anemic and nonanemic patients, facilitates autologous predeposit and increases and maintains [Hb] perioperatively. However, allogeneic blood exposure is reduced only in selected patients.[172–174] Hypertension and thrombotic events have been reported during perioperative erthropoietin therapy. Thrombotic events occur overall at rates similar to those in patients not treated with erythropoietin.[175]

The use of nonblood alternatives to replace shed blood is a useful, although limited, strategy. With the acceptance of low and sometimes, very low hematocrits, it has become accepted clinical practice to replace very large volumes of shed blood with crystalloid and colloid solutions. The risk of avoidance of blood transfusion in these situations is not known and may, in some instances, be higher than the risk of transfusion. Research into oxygen-carrying solutions containing either fluorocarbons or hemoglobin compounds continues. As yet, no oxygen carriers with proven utility and safety comparable to those of blood are commercially available.[176]

Many alternative strategies may reduce allogeneic blood requirements. Two elements are common to all. First, the additional costs are not well defined, but are partly offset by the reduced need for allogeneic blood; typically, the party carrying the cost of the new strategies is not the same as the one benefitting from the reduction in allogeneic blood costs. Second, the risks of implementing alternative strategies measured against the benefits of avoiding allogeneic transfusion have not been adequately assessed. For example, with respect to the drug therapy, 1 drug-related death in 200 000–500 000 would be sufficient to negate the risk reduction achieved with their allogeneic blood-sparing action (Andreas Laupacis, MD: unpublished data). The value of autologous predonation in reducing allogeneic exposure for patients undergoing coronary artery bypass grafting is negated if 1 patient in 101 000 has a stroke, infarction or dies as a result of the donation process.[177] Reactions to autologous

donations occur in about 4% of patients who would not normally meet donation criteria for medical reasons, and in about 1% of these patients the reactions are severe.[178,179] In one study,[67] about 1 in 17 000 autologous blood donors developed a sufficiently severe reaction to require hospitalization.

Clearly, when recommending alternatives to allogeneic transfusion to patients, physicians must consider the overall risk of the alternative. In many instances, it is not evident that alternative strategies pose fewer potential risks to the patient than allogeneic transfusion.

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Appendix 1. Participant organizations (and their representatives)

Aplastic Anemia Association of Canada (Ms. Jennifer Johnstone)
Canadian Anaesthetist's Society (Dr. James Robblee)
Canadian Association of Emergency Physicians (Dr. Garth Dickenson)
Canadian Association of General Surgeons (Dr. John Marshall)
Canadian Association of Pathologists (Dr. Lois Shepherd)
Canadian Blood Agency (Dr. Gershon Growe)
Canadian Bone Marrow Foundation (Ms. Susan Beechinor-Carter)
Canadian Cardiovascular Society (Dr. Fraser Rubens)
Canadian Critical Care Society (Dr. Hugh Devitt)
Canadian Healthcare Association (Ms. Michelle Albagli)
Canadian Hematology Society (Dr. Robert Barr)
Canadian Hemophilia Society (Dr. Irwin Walker)
Canadian Infectious Disease Society (Dr. Gilles Delage)
Canadian Medical Association (Dr. Anne Carter)
Canadian Medical Protective Association (Dr. Robert Robson)
Canadian Nurses Association (Ms. Vija Hay)
Canadian Orthopaedic Association (Dr. Robert Hollinshead)
Canadian Paediatric Society (Dr. Charles Morin)
Canadian Red Cross Society (Dr. Tony Giulivi)
Canadian Society of Internal Medicine (Dr. Howie Abrams)
Canadian Society of Laboratory Technologists (Mrs. Nancy Heddle)
Canadian Society for Transfusion Medicine (Dr. Bernard Fernandes)
Canadian Transplantation Society (Dr. Cathy Tang)
College of Family Physicians of Canada (Dr. Gary Viner)
Federation of Medical Licensing Authorities of Canada (Dr. Bryan Ward)
Health Canada (Dr. Paul Gully)
Patient Alumni Board of the Ottawa Heart Institute (Mr. Len Demille)
Society of Obstetricians & Gynaecologists of Canada (Dr. Robert Kinch)
Trauma Association of Canada (Dr. Bernie Boulanger)